Assessment of short stature in children : auxological screening and diagnostic work-up

Grote, F.K.

Assessment of short stature in children

Auxological screening and diagnostic work-up

The publications of this thesis and the studies discribed were supported by an educational grant from Pfizer bv.

Printed by: Ponsen en Looijen B.V., Wageningen
Cover photo: F.J. Willemse
Lay-out: Ponsen en Looijen B.V., Wageningen

ISBN: 978-90-6464-083-4

Assessment of short stature in children

Auxological screening and diagnostic work-up

Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van de Rector Magnificus Dr. D.D. Breimer,
hoogleraar in de faculteit der Wiskunde en
Natuurwetenschappen en die der Geneeskunde,
volgens besluit van het College voor Promoties
te verdedigen op 1 maart 2007
klokke 16.15 uur
door

Floor Katelijn Grote

geboren te Bemmel
in 1972

Promotiecommissie

Promotor:	Prof. dr. J.M.Wit
Co-promotores:	Dr. W. Oostdijk Dr. S.M.P. F de Muinck Keizer-Schrama (ErasmusMC - Sophia, Rotterdam)
Referent:	Prof. dr. S.P. Verloove-Vanhorick
Overige leden:	Prof. dr. W.J.J. Assendelft Prof. dr. A.C. Hokken-Koelega (ErasmusMC - Sophia, Rotterdam) Prof. dr. R.A. Hira Sing (VUMC, Amsterdam) Dr. H.A. Moll (ErasmusMC - Sophia, Rotterdam)

Table of contents

Chapter 1

General introduction and outline of this thesis

General introduction

Growth impairment is considered a relatively early sign of poor health in children. Depending on its setting and the age of the child the impairment is expressed in several ways. Failure to thrive is a term often used in the first years of life and is either defined as poor weight for age, poor weight for length or poor length for age.[1,2] In older children one speaks more of growth retardation or short stature. Other definitions of growth impairment are stunting (low height for age) or a decline in height velocity.

In developing countries the principal cause of growth failure is malnutrition. In industrialized countries a great diversity of congenital or acquired conditions, such as Turner syndrome, Growth Hormone Deficiency (GHD), can underlie growth failure (see table 1). Here the largest and most important groups to be detected are GHD, Turner syndrome and celiac disease, as others are either rare or accompanied by other symptoms. Whatever the cause of the restricted growth is, an early diagnosis and treatment is important not only to prevent further health damage, but also to create an optimal effect on adult height and an extension of the period of a better quality of life of those who are treated.

A proper treatment of children with abnormal growth depends both on the early identification of these children in the community (by growth monitoring) and on an accurate diagnostic work-up in the hospital after referral.

Table 1. Causes of short stature:

1. Primary growth disorders:	2. Secondary growth disorders:	3. Idiopathic short stature:
a. Skeletal dysplasias	a. Disorders in specific systems:	a. Familial short stature
	Cardiac disease	
	Pulmonary disorder	
	Liver disorder	
	Intestinal disorder	
	Renal disorder	
	Chronic anemia	
	Chronic inflammatory disorder	
	Malnutrition disorders	
b. Clinically defined syndromes with chromosomal aberrations	b. Endocrine disorders	b. Non-familial short stature
Turner syndrome	*Growth hormone deficiency*	
Mixed gonadal dysgenesis	*Thyroid disorders*	
Down syndrome	*Adrenal disorders*	
Other	*Gonadal disorder*	
	Diabetes mellitus	
	Precocious Puberty	

c. Clinically defined syndromes without chromosomal aberrations	c. Metabolic disorder
Noonan syndrome	*Disorder of carbohydrate metabolism*
Silver-Russel syndrome	*Disorder of lipid metabolism*
Von Recklinhausen syndrome	*Disorder of amino acids*
Cornelia de Lange syndrome	*Disorder of calcium and phosphate metabolism*
Prader-Labhardt-Willi syndrome	*Disorder of bone metabolism*
Williams syndrome	
Bloom syndrome	
Rubinstein syndrome	
Other	
d. Small for gestational age (SGA) with persisting short stature	d. Iatrogenic short stature
	Medication
	Total body irradiation
	e. Psychogenic short stature
	Psychosocial short stature
	Anorexia nervosa

History of growth monitoring

To facilitate the detection of growth disorders, growth monitoring, implying regular measurements of weight and length, is essential. Nowadays growth monitoring is widely accepted and almost every child is measured regularly during childhood. The earliest citation of growth dates from the sixth century B.C. It was mentioned in a poem by the Greek Solon the Athenian.[3] The poem deals with the division of human lifespan into ten successive seven-year periods ("hebdomads"). The translation by Tanner of the first four hebdomads is at follows:[3]

A young boy acquires his first ring of teeth
as an infant [literally while unable to speak] and
sheds them before he reaches the age of 7 years.
When the god brings to an end the next seven-year period,
the boy shows the signs of beginning puberty [or: of beginning pubic hair].
In the third hebdomad, the body enlarges,
the chin becomes bearded and the bloom of the boy's complexion is lost.
In the fourth hebdomad physical strength is at its
peak and is regarded as the criterion of manliness.

It took until the 18th century before the first growth studies took place. Initially these studies were done for military purposes as the body size of guards and soldiers was of interest. During that century other individual growth studies, like the study of P.G de Montbeillard´s son (1759 - 1777) and the study on the pupils of the Carlschule in Stuttgart (1772 – 1777) were performed. With the increasing interest in public health in the nineteenth century there was a change towards general growth studies.

The relationship between political state and health had become stronger since the decline of mortality due to epidemics and increasing wealth in industrialized countries in the 18th century. The most important influence on this relation was however "the declaration of health as a right of democratic citizenship", first declared by revolutionaries in 1791 in France.[4] Disease prevention became politically and economically a major subject and by the end of the nineteenth century one began to understand the importance of child health care for the general welfare. As a result the 20th century was declared as "the century of the child", in which child health and welfare was not only medicalized but was also serving as a powerful tool for the state to expand its power in health and welfare in general.[5] This resulted in the establishment of compulsory school systems and abandonment of child labor in the western world. With this development, children turned into attractive research subjects and children have been measured regularly in schools and infant welfare clinics ever since. At the same time the recurrence of wars played an important role in the development of growth monitoring, for it led to concerns about the quality of the health status of populations, and brought as a consequence the mathematical basis for growth studies.[3]

In the Netherlands growth studies were performed since 1850, but it took until 1955 for these studies to become nationally representative and to cover the complete age group of childhood (0-18 years). The first well baby clinic was established in 1901 by the paediatrician B.P.B. Plantenga in The Hague.[6] In the beginning children were only weighed but since 1972 nearly every child is monitored for length (measured in supine position, usually below 2 years of age), height (measured in standing position, usually from 2 years onwards) and weight from birth till the age of 16-18 years. Since 1978 these measurements are registered in a "book of growth" (Groeiboek).

During the 1970s several health organizations, including the World Health Organization and UNICEF, promoted the monitoring of growth worldwide as part of the "Child Survival and Development Revolution".[7] Since then growth monitoring, even in underdeveloped countries, has become a central activity in child health care, but its effectiveness and its performance remain subject of debate.[8]

In this discussion it is important to realize that there is a difference in purposes and objectives of growth monitoring programs depending on its setting. In developing countries the principal aim of growth monitoring is to detect malnutrition. In industrialized countries, where there is much less malnutrition, growth monitoring is aimed at detecting other acquired or congenital causes of growth retardation, and is increasingly used to detect overweight.

The effect of routine growth monitoring in developing countries has recently been questioned.[9] The efficacy and efficiency of height monitoring in developed countries has hardly been studied.

Auxological screening

Auxology comes from the greek word Auxē –logiā and means the science or study of growth. Auxological screening is therefore often used to describe growth monitoring and implies regular height and weight measurements.

After height and weight measurements are taken they should be plotted on a growth chart for the child's growth to be monitored over time. Many different growth charts are being used around the world, not only different in reference population but also in parameters and units (percentiles or SD-scores). In developing countries weight for age is the usual parameter, whereas in industrialized countries growth monitoring may be conducted less frequently and the preferred parameter is height for age.[10, 11] Many charts are expressed in percentiles but more and more charts have turned to standard deviation scores (SDS) ((Height – mean height for the same age and sex) / (SD for the same age and sex). Using SD scores has several advantages: 1) It is easier to express measurements far below P3 as SDS than as a percentile; 2) The distance between SD scores is equal, whereas the distance between the usual percentiles differs; 3) percentiles cannot be used to compare growth between subpopulations or between different international populations, as they are unsuitable for statistical purposes. Percentiles can however easily be transformed into SD scores and the other way around, if the measurements have a Gaussian distribution.

Other parameters that are directly involved in growth monitoring are target height, bone age and stages of puberty. After the age of approximately 3 years, target height SDS is strongly correlated with the child's height SDS. It is a mathematical approach of the estimated final height of a boy or a girl on the basis of their genetic potential. Using the Dutch reference growth data, target height and target height SDS can be calculated with the following formulas: [12]

1) for males: TH (cm) = [(Height $_{\text{Father}}$ + Height $_{\text{Mother}}$ +13)/2] +4.5;
   TH SDS= (TH-184.0)/7.1
2) for females TH = [(Height $_{\text{Father}}$ + Height $_{\text{Mother}}$ -13)/2] +4.5;
   TH SDS= (TH-170.6)/6.5.

The term 13 cm represents the difference between male and female final height,[13] , whereas the term 4.5 cm represents the height difference per generation (30 years).[14] Bone age in combination with height can be used to predict final height, using various methods.[15,16] Puberty is assessed using the stages of Tanner and Whitehouse.[17] As short children with a body proportion outside the normal range, are prone to have a primary growth disorder, body proportions are indirectly involved in growth monitoring, especially in industrialized countries where the aim of growth monitoring is the detection of growth disorders. The most suitable parameter for body proportions is the sitting height/ height ratio.[18]

For an early identification of children with abnormal growth it is important to have correct and well-defined referral criteria next to a good growth monitoring system, with accurate growth charts. In the literature, however, mainly arbitrary referral criteria are used to express growth failure in experimental studies on growth monitoring.[19-21] For failure to thrive, often used in infancy and early childhood to describe growth impairment, there

is even no consensus on the choice of anthropometric indicators or their criteria for abnormality.[1,2]

Only a few guidelines have been published on referral criteria for children with impaired growth.[22,23] One of those guidelines, the UK-consensus, concentrates on the referral of children with short stature after a single height measurement at school entrance (a height < P 0.4 (-2.66 SDS) at 5 years of age).[22] According to the other guideline, the Dutch Consensus Guideline, seven referral criteria should be used (see paragraph on growth monitoring in the Netherlands).[23] Both guidelines are however based on consensus meetings rather than on experimental evidence, and specific information on their sensitivity and specificity to detect growth disorders is lacking. Although the authors of the Dutch Consensus guideline had aimed at promoting early diagnosis of aberrant growth as well as at preventing unnecessary referral and interventions, it was shown later that if this guideline would be followed, an unacceptable percentage of healthy children would be referred.[24] This high percentage seems mainly due to the rule based on height deflection. The United Kingdom guideline must lead to a better specificity, as it has only one strict referral criterion and does not use deflection. However, it has an unknown sensitivity to detect disorders timely.[22,25]

Diagnostic work-up in children with short stature

A diagnostic work-up is a thorough medical examination for diagnostic purposes and in case of short stature consists of several components, i.e. medical history, physical examination, laboratory investigations, radiographic investigations, specific tests for suspected diseases and genetic analyses.

As the outcome of the assessment of short stature is very heterogeneous, a good routine diagnostic work up for screening purposes depends on the frequency of the underlying medical disorder, the severity of the disease, its clinical presentation - including symptoms and signs other than auxological ones-, and the invasiveness and costs of the tests to be used.

Aside from the scarce evidence on referral criteria there is little experimental evidence on the diagnostic work-up in secondary health care for children with poor growth. Although there are a number of consensus guidelines on the diagnosis of GHD,[26-30] and some articles on the analysis of short stature in general,[31-38] these articles are primarily expert-based reviews on how to deal with short stature rather than experimental studies about the outcome of laboratory investigations. One study evaluated the outcome of the analysis of short stature in a growth clinic, but did not use a standard protocol for the diagnostic work-up.[39] The only guideline reported so far which addresses the diagnostic work-up for short stature in general is the Dutch Consensus Guideline (see paragraph on growth monitoring in the Netherlands).[23] But again, this guideline is based on consensus rather than on experimental evidence.

Growth monitoring in the Netherlands

To promote early diagnosis and treatment of aberrant growth and to prevent unnecessary referral and interventions, a consensus meeting was held on "Diagnosis of short stature in childhood" in 1996 by general practitioners, well-baby clinic doctors, school doctors, paediatricians and paediatric endocrinologists.[40] Consensus was achieved on referral and diagnostic work-up of children with short stature. This Dutch consensus guideline (DCG) was then published in a Dutch medical journal and a book.[23,40]

In the analysis of short stature the DCG addresses five stages. First of all it focuses on seven auxological referral criteria (table 2 and appendix for further explanation). When a child is referred according to these criteria, the pediatrician is subsequently advised to follow four diagnostic steps:

- The patient's history, the physical examination, growth data and a hand radiograph should be collected to determine signs or symptoms that may indicate a specific disease.
- In the presence of specific clinical clues, appropriate further specific investigations are done. When there are no signs or symptoms leading to the suspicion of a certain disease, a list of laboratory investigations is advised for screening of several pathological conditions (table 3).
- Dependent on the abnormalities in the screening laboratory investigations further, more specific tests can be performed to establish the final diagnosis.
- If there is no indication of a certain disease after the preceding procedures the three following tests should still be considered: chromosomal analysis for Turner syndrome in girls, a biopsy to prove or rule out celiac disease and the determination of zinc to investigate zinc deficiency in children with failure to thrive.[41]

However, it is not known how many doctors are aware of the guideline and whether or not it changed medical practice, as the implementation was limited to a single publication in a medical journal, a book and a couple of postgraduate courses.[23,40] Moreover the guideline is based on consensus and lacks experimental evidence. Van Buuren et al showed that if the guideline would be followed, an unacceptable percentage of healthy children would be referred,[24] and specific information on the sensitivity is not available.

Table 2. Seven auxological referral criteria taken from the Dutch Consensus Guidelines.[23]

Description rule		Criteria	Rule nr.
Absolute height		HSDS* < -2.5	1
Clinical symptoms		HSDS* < -1.3 AND (dysmorphic features OR disproportions)	2
Persistent short stature after born SGA**		SGA** AND HSDS* < -1.88 after the age of 2 years	3
$HSDS_{cor}$†	♂: < 10 yr and > 13.4 yr; ♀: < 9 yr and > 12.3 yr	HSDS* < -1.3 AND HSDS-THSDS < -1.3	4
	Pubertal age■:	HSDS* < -1.3 AND HSDS-THSDS§ < -1.3	5
	♂: 10 – 13.4 yr; ♀: 9 – 12.3 yr	With pubertal signs	

Deflection‡	♂: < 10 yr and > 13.4 yr;	T2 – T1 > 1(1)	6a
	♀: < 9 yr and > 12.3 yr	(SDS1 – SDS2)/(T2-T1) < -0.25	
		T2 – T1 > 1	6b
		(SDS1 – SDS2)< -1	
	Pubertal age■:	T2 – T1 > 1(1)	7a
	♂: 10 – 13.4 yr;	(SDS1 – SDS2)/(T2-T1) < -0.25	
	♀: 9 – 12.3 yr	With pubertal signs	
		T2 – T1 > 1	7b
		(SDS1 – SDS2)< -1	
		With pubertal signs	

* HSDS= Height Standard Deviation Score (Height – mean height for the same age and sex / SD for the same age and sex (see appendix)).

** SGA = Small for Gestational Age

§ THSDS= Target Height Standard Deviation Score (Target height = (height of mother (+height of father +13) + 4.5) / 2 (see appendix))

† $HSDS_{cor}$= HSDS corrected for parental height (see appendix)

‡ Deflection: Deflection is either expressed as an SDS decrease (SDS1-SDS2) per year (T1-T2) (7a), or as a cumulative deflection over an unspecified time interval (7b). In the categories 3-10 and 10-18, T1 >= 3 years, in the other categories T1> 0. (see appendix)

■ Pubertal age: When a child does not show any pubertal signs (♂: genital stage >= Tanner stage 2 OR testis volume >= 4 ml; ♀: breast>= Tanner stage 2) at this age referral is not necessary.

Table 3. Laboratory investigations in the diagnostic work up according the DCG

Laboratory investigations	In order to diagnose	Category
Blood		
Hb, Ht, Leukocytes, Cellindices, Leukocyte differentiation, ESR (Ferritin)	Anemia / infections (and celiac disease and cystic fibrosis)	I
ALAT, ASAT, y GT	Liver diseases	II
Albumin, Creatinine, Sodium, Potassium, Calcium, Phosphate, Alkaline phosphatase, acid-base equilibrium	Renal diseases	III
IgA-anti endomysium, IgA- antigliadin, Anti-tissue glutaminase*, Total IgA	Celiac disease	IV
TSH, FT4	Hypothyroidism	V
IGF-I	Growth hormone deficiency	VI
FSH**	Turner's syndrome	VII
Urine		
pH, glucose, protein, blood and sedimentation	Renal diseases	VIII

* At the moment the consensus meeting took place, anti tissue glutaminase as a diagnostic tool for celiac disease was not yet introduced nation wide.

** Only in girls.

Aim of this thesis

The aim of this thesis is to collect evidence and create new guidelines for the assessment of short stature in children, including both referral criteria and diagnostic procedures.

Outline this thesis

In this ***first chapter*** we have explored the definition of impaired growth in the literature, given an overview of the history of growth monitoring, explained the importance of auxological screening and diagnostic work up in the assessment of short stature and set out some general principles of these two processes.
In the remainder of the thesis we have gathered the evidence needed for a new guideline for the assessment of short stature in children.

Part A reviews the importance of testing for two growth related diseases (Celiac Disease or Cystic Fibrosis) in the routine diagnostic work up for short stature. Starting off from these diseases the literature is searched for evidence for the disease to be taken into account in the screening of short stature. In ***chapter two*** we study the prevalence of celiac disease in children with short stature and no gastrointestinal symptoms and in ***chapter 3*** the prior-probability of CF in infants and children with short stature and/or poor weight gain.

In ***Part B*** the current practice of growth monitoring and diagnostic work-up of short stature in practice are described. ***Chapter 4*** describes the results of an inquiry among pediatric endocrinologists in Europe and most industrialized countries around the world about the referral criteria advised for growth monitoring in primary care, and about diagnostic procedures for short stature in secondary care. ***Chapter 5*** aims at getting more information on the current policy of growth monitoring, the definition of failure to thrive and the use of guidelines (especially the DCG) among well-baby-clinic doctors and school doctors (doctors of Primary Health Care 0-19 years) and general practioners in the Netherlands.

Part C is concerned with an evaluation of existing guidelines. ***Chapter 6*** is an evaluation of the referral pattern of short stature in primary health care using the Dutch Consensus guidelines and the consensus guidelines from the UK, comparing it with cut-off values mentioned in the WHO Global Database on Child growth and Malnutrition.[42] ***Chapter 7*** contains the results of a study in two hospitals, in which we investigated how many children were correctly referred to secondary health care according to existing consensus guidelines; evaluated the diagnostic work-up in secondary health care; and assessed the frequency of underlying medical disorders. As the Dutch Consensus Guideline (DCG) is the only guideline addressing referral criteria as well as diagnostic work-up, the analyses are based on its seven auxological referral criteria to determine whether children are correctly referred or not and on all elements of the diagnostic work up.

Part D contains biometrical studies to determine cut-off points of auxological criteria to be used in the decision whether growth-retarded children should be referred for further investigations. First, insight is gained into the diagnostic performance of a broad set of referral criteria for auxological screening for Turner syndrome in the open population in ***chapter 8***. Thereafter optimal auxological referral criteria for detecting celiac disease are determined in ***chapter 9***. Thirdly, the diagnostic efficiency of several auxological criteria (including both weight and length) for the detection of children with cystic fibrosis are explored in ***chapter 10***.

Part E consist of ***chapter 11*** and describes the radiographic evaluation in literature of children with growth problems.

New evidence-based guidelines for growth monitoring on a population basis are presented in ***Part F (chapter 12)***.

Finally, we discuss in ***chapter 13*** the evidence collected for the algorithm for referral of children with short stature and the collected evidence for the diagnostic work up. We also make recommendations for the diagnostic work up after referral, discuss the implementation process of the new guideline in the Netherlands, and offer some proposals for future research.

References

1. Wright CM: Identification and management of failure to thrive: a community perspective. Arch Dis Child 2000, 82:5-9.
2. Jolley CD: Failure to thrive. Curr Probl Pediatr Adolesc Health Care 2003, 33:183-206.
3. Tanner JM: A history of the study of human growth. London: Cambridge University Press; 1981.
4. Porter D: Health, civilization and the state: a history of public health from ancient to modern times. London: Routledge; 1999.
5. Cooter R: In the name of the child: health and welfare: 1880-1940. London: Routledge; 1992.
6. Prof.Dr.M.J.van Lieburg: Een eeuw consultatiebureau in Nederland 1901-2001. 2001.
7. Nabarro D, Chinnock P: Growth monitoring--inappropriate promotion of an appropriate technology. Soc Sci Med 1988, 26:941-948.
8. Morley D: Growth monitoring. Arch Dis Child 2001, 84:90.
9. Garner P, Panpanich R, Logan S: Is routine growth monitoring effective? A systematic review of trials. Arch Dis Child 2000, 82:197-201.
10. Onis de M, Wijnhoven TM, Onyango AW: Worldwide practices in child growth monitoring. J Pediatr 2004, 144:461-465.
11. Panpanich R, Garner P: Growth monitoring in children. Cochrane Database Syst Rev 2000,CD001443.
12. Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E, Roede MJ, Verloove-Vanhorick SP, Wit JM: Continuing positive secular growth change in The Netherlands 1955-1997. Pediatr Res 2000, 47:316-323.
13. Tanner JM, Goldstein H, Whitehouse RH: Standards for children's height at ages 2-9 years allowing for heights of parents. Arch Dis Child 1970, 45:755-762.
14. Fredriks A.M.: Growth Diagrams 1997: Fourth Dutch Nation-wide Survey. PhD≈Thesis. Leids University Medical Center; 2004.
15. Bayley N, Pinneau SR: Tables for predicting adult height from skeletal age: revised for use with the Greulich-Pyle hand standards. J Pediatr 1952, 40:423-441.
16. Tanner JM, Landt KW, Cameron N, Carter BS, Patel J: Prediction of adult height from height and bone age in childhood. A new system of equations (TW Mark II) based on a sample including very tall and very short children. Arch Dis Child 1983, 58:767-776.
17. Tanner JM, Whitehouse RH: Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. Arch Dis Child 1976, 51:170-179.
18. Fredriks AM, van Buuren S, van Heel WJ, Dijkman-Neerincx RH, Verloove-Vanhorick SP, Wit JM: Nationwide age references for sitting height, leg length, and sitting height/height ratio, and their diagnostic value for disproportionate growth disorders. Arch Dis Child 2005, 90:807-812.
19. Ahmed ML, Allen AD, Sharma A, Macfarlane JA, Dunger DB: Evaluation of a district growth screening programme: the Oxford Growth Study. Arch Dis Child 1993, 69:361-365.
20. Frindik JP, Kemp SF, Kearns FS, Hale B: Growth screening. A positive medical experience. Clin Pediatr (Phila) 1992, 31:497-500.
21. Voss LD, Mulligan J, Betts PR, Wilkin TJ: Poor growth in school entrants as an index of organic disease: the Wessex growth study. BMJ 1992, 305:1400-1402.
22. Hall DM: Growth monitoring. Arch Dis Child 2000, 82:10-15.
23. de Muinck Keizer-Schrama SM: [Consensus 'diagnosis of short stature in children.' National Organization for Quality Assurance in Hospitals]. Ned Tijdschr Geneeskd 1998, 142:2519-2525.
24. Van Buuren, S, Bonnemaijer-Kerckhoffs DJ, Grote FK, Wit JM, Verkerk PH: Many referrals under Dutch short stature guidelines. Arch Dis Child 2004, 89:351-352.
25. Hindmarsh PC: Monitoring children's growth. Abnormal growth should also be defined by the crossing of height centiles. BMJ 1996, 312:122.

26. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. GH Research Society. J Clin Endocrinol Metab 2000, 85:3990-3993.
27. Hilken J: Uk audit of childhood growth hormone prescription, 1998. Arch Dis Child 2001, 84:387-389.
28. Juul A, Bernasconi S, Chatelain P, Hindmarsh P, Hochberg Z, Hokken-Koelega A, de Muinck Keizer-Schrama SM, Kiess W, Oberfield S, Parks J et al.: Diagnosis of growth hormone (GH) deficiency and the use of GH in children with growth disorders. Horm Res 1999, 51:284-299.
29. Juul A, Bernasconi S, Clayton PE, Kiess W, DeMuinck-Keizer SS: European audit of current practice in diagnosis and treatment of childhood growth hormone deficiency. Horm Res 2002, 58:233-241.
30. Wilson TA, Rose SR, Cohen P, Rogol AD, Backeljauw P, Brown R, Hardin DS, Kemp SF, Lawson M, Radovick S et al.: Update of guidelines for the use of growth hormone in children: the Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee. J Pediatr 2003, 143:415-421.
31. Cappa M, Loche S: Evaluation of growth disorders in the paediatric clinic. J Endocrinol Invest 2003, 26:54-63.
32. Duck SC: Identification and assessment of the slowly growing child. Am Fam Physician 1996, 53:2305-2312.
33. Fox LA, Zeller WP: Evaluation of short stature. Compr Ther 1995, 21:115-121.
34. Goldberg MJ, Yassir W, Sadeghi-Nejad A, Stanitski CL: Clinical analysis of short stature. J Pediatr Orthop 2002, 22:690-696.
35. Halac I, Zimmerman D: Evaluating short stature in children. Pediatr Ann 2004, 33:170-176.
36. Hermanussen M: The analysis of short-term growth. Horm Res 1998, 49:53-64.
37. Hindmarsh PC, Brook CG: Auxological and biochemical assessment of short stature. Acta Paediatr Scand Suppl 1988, 343:73-76.
38. Rosenfield RL: Essentials of growth diagnosis. Endocrinol Metab Clin North Am 1996, 25:743-758.
39. Green AA, Macfarlane JA: Method for the earlier recognition of abnormal stature. Arch Dis Child 1983, 58:535-537.
40. Consensus Diagnostiek kleine lichaamslengte bij kinderen. Centraal Begeleidingsorgaan voor de Intercollegiale Toetsing (CBO); 1996.
41. Kaji M., Nishi Y.: Growth and minerals: Zinc. Growth, Genetics & Hormones 2006, 22:1-7.
42. An evaluation of infant growth: the use and interpretation of anthropometry in infants. WHO Working Group on Infant Growth. Bull World Health Organ 1995, 73:165-174.

Part A

Review on the importance of testing for specific diseases in the routine diagnostic work up for short stature

Chapter 2

Short stature and the probability of coeliac disease, in the absence of gastro-intestinal symptoms

Jeroen C.W. van Rijn, Floor K. Grote*, Wilma Oostdijk*, Jan-Maarten Wit*.*

* Department of Paediatrics, Leiden University Medical Center, Leiden, The Netherlands

Arch Dis Child 2004;89:882-3.

Clinical scenario

An 8-year old girl is referred to the paediatrician because of her stunted growth. Her height SDS is –2.3 (≈0.4%ile), her weight for height ratio is + 0.9 SDS (≈75%ile). At the age of 3 years, her height SDS was + 0.3 (just over 50%ile). Her weight for height ratio had not changed considerably. At the age of four to five years, she had several episodes of constipation and anaemia. There were no other complaints. A diagnostic work-up was performed: IgA anti-endomysium (IgA EmA) antibodies were positive. A small intestinal biopsy (gold standard) showed total villous atrophy, consistent with coeliac disease. During follow-up, she fulfilled the ESPGAN criteria for coeliac disease (finding of characteristic small bowel mucosa abnormalities in a small bowel biopsy, and a clinical remission when placed on a gluten free diet).

Structured clinical question

What is the prevalence of coeliac disease [outcome] in children with short stature and no gastrointestinal symptoms [patients]?

Search strategy and outcome

Pubmed – (body height AND (short OR little OR small OR abnormal) OR short stature OR dwarfism) OR failure to thrive AND coeliac disease (limited by: Ages: All child 0-18 year, Language: English) – 120 references of which 11 relevant and of sufficient quality (see table).
Embase – same search strategy – no additional relevant references
Cochrane database – same search strategy – none relevant
The way study groups were selected varied. Articles with the least selective study groups are reported higher in the table than studies with a more selective study group.

Citation, country	Study group	Study Type (Level of evidence)	Outcome	Key Results	Comments
Knudtzon J, et al (1991), Norway[1]	168 children (50 girls; 93 boys; age 0.5 – 17.2 years) with short stature without significant abdominal symptoms.	Prospective cohort study (level 2b)	Proportion of coeliac disease in the study group	2.9% (5/168) of the children with short stature were diagnosed as having coeliac disease.	'Short stature' was not defined. Results are not internally consistent. Diagnosis was not based on ESPGAN-criteria.

Stenhammer L, et al. (1986), Sweden[2]	87 children (32 girls, 55 boys; age 1.0-16.5 years) with short stature (height more than 2SD below the mean for age and sex) and no gastrointestinal symptoms, signs of systemic disease or malabsorption	Prospective cohort-study (level 1b)	Proportion of coeliac disease in the study group	5% (4/87) children with short stature were diagnosed as having coeliac disease. There is an overrepresentation of coeliac disease among short children admitted to hospital for examination.	Diagnosis was made based on ESPGAN-criteria Gold standard was applied to all children. Results are not fully described.
Cacciari E, et al. (1985), Italy[3]	108 patients (30 girls, 78 boys; age 2.8 – 16.7 years) with short stature (height below third centile) and no gastrointestinal symptoms	Prospective cohort study (level 1b/2b)	Proportion of coeliac disease in study group	8.3% (9/108) patients with short stature were diagnosed as having coeliac disease.	Gold standard was applied to all patients. Diagnosis of coeliac disease was not according to ESPGAN-criteria. Possible overlap in patients in the two studies of Cacciari?
Cacciari E, et al. (1983), Italy[4]	60 children (21 girls, 39 boys) with short stature (height below third centile) and no gastrointestinal symptoms	Prospective cohort study (level 1b/2b)	Proportion of coeliac disease in study group	8.3% (5/60) patients with short stature were diagnosed as having coeliac disease.	Gold standard applied to all patients. Diagnosis of coeliac disease was not according to ESPGAN-criteria.
Rossi TM, et al. (1993), USA[5]	117 children (age: 2 – 17 years) with height more than 2SD below the mean for age. Of these children, 57 were diagnosed with GH-deficiency. All children were clinically and chemically euthyroid.	Prospective cohort study (level 2b)	Proportion of coeliac disease in a group of children with short stature	1.7% (2/117) of children with short stature had biopsy proven coeliac disease. There is an association between idiopathic short stature and coeliac disease.	Basic data are not adequately described (no sex differentiation) Gold standard was not applied to all patients. Diagnosis of coeliac disease was not according to ESPGAN-criteria

Bonamico M, et al. (1992), Italy[7]	49 children (27 girls, 22 boys; mean age 112 months (SD: 39)) with short stature (height below the third centile) and no gastrointestinal symptoms. None of the 49 patients showed somatic, cardiac, renal or chromosomal disorders	Prospective cohort study (level 1b)	Proportion of coeliac disease in the study group	59.1% (29/49) children with short stature were diagnosed as having coeliac disease.	Gold standard was applied to all patients. Diagnosis of coeliac disease was made according to ESPGAN-criteria.
Groll A, et al. (1980), United Kingdom[8]	34 children (16 girls, 18 boys; age 2.5 – 17.0 years) with short stature (more than 2SD below the mean for age) and no gastrointestinal symptoms. There were no dysmorphic features, and endocrine investigations were normal.	Prospective cohort study (level 1b/2b)	Proportion of coeliac disease in the study group	21% (8/34) children with short stature were diagnosed as having coeliac disease	Diagnosis was not according to ESPGAN-criteria.
Rosenbach Y, et al. (1986), Israel[9]	23 children (12 girls, 11 boys; age 6-16 years) below third centile for age and a bone age delay of at least 25%. Extensive preliminary work up (including hypothalamic, pituitary, adrenal, and gonadal functions, sweat test, stool examination for ova and parasites) was found to be negative.	Prospective cohort study (level 2b)	Proportion of coeliac disease in the study group	48.7% (11/23) of the patients with short stature were diagnosed as having coeliac disease.	Gold standard was applied to all patients. Diagnosis was not according to the ESPGAN-criteria.

Lecea A de, et al. (1996), Spain[10]	118 children (49 girls, 69 boys; age 11 months to 14 years), with height less than third centile for age. Preliminary work up (absorption, hormonal and genetic studies, sweat test, X-ray for bone age, serum IgA AGA) was performed.	Prospective cohort study (level 2b)	Proportion of coeliac disease in the study group	18.6% (22/118) of children with short stature had biopsy proven coeliac disease.	Results were not presented. Numbers do not add up properly. Gold standard was not applied to all children. Diagnosis was not according to ESPGAN-criteria. Basic data were not adequately described.
Altuntas B, et al. (1998), Turkey[11]	47 patients (18 girls, 29 boys; age 4-16 years) of short stature (below third centile for height) without gastrointestinal tract symptoms or endocrinologic, cardiac, renal or chromosomal disorders. There were no symptoms associated with coeliac disease or signs of cow's milk allergy.	Cross-sectional study (level 1b/2b)	Proportion of coeliac disease in the study group	55.3% (26/ 47) of the short children had biopsy proven coeliac disease	All children were biopsied. Results are not presented clearly; the reader cannot make his own conclusions. Diagnosis of coeliac disease was not according to ESPGAN-criteria.
Tumer L. et al (2001), Turkey[12]	84 children (46 girls, 38 boys; age 16 months – 14 years) with height less than third centile for age; preliminary work-up to evaluate other causes of short stature was found to be negative.	Prospective cohort study (level 2b)	Proportion of coeliac disease in the study group	Proportion of coeliac disease was found to be 8.3% (7/84). There is an association between coeliac disease and idiopathic short stature.	The IgA EmA test was not verified by a gold standard test (biopsy) in all patients. Diagnosis of coeliac disease was not according to ESPGAN-criteria

Commentary

Growth retardation in childhood may be one of the earliest signs of an underlying disease, such as coeliac disease. In the Netherlands, the growth of nearly every child is monitored. When growth is retarded, the child is referred to secondary health care. After referral it has been advised to perform a diagnostic work-up containing routine laboratory tests to search for diagnostic clues for, among others, coeliac disease. The tests presently used for coeliac disease are IgA EmA and IgA antitissue transglutaminase antibodies. The total immunoglobulin A count is determined as well, because coeliac disease is associated with IgA deficiency. It was questioned if diagnostic investigations for coeliac disease should be performed in all children with short stature, even without gastro-intestinal complaints.

Studies 1-5 were based on study groups, in which no preliminary (endocrine) work-up to exclude other causes for short stature had been performed. The proportion of coeliac disease in children with short stature and no gastrointestinal symptoms in these studies ranged from 1.7% to 8.3%. When a group of children was studied, in which endocrine causes for short stature had been excluded[6-11], the proportion of coeliac disease increased to a range of 18.6% to 59.1%. The characteristics of the preliminary work-up used in study 12 were not described.

The wide range of these percentages is probably mainly caused by the different methods of selecting the patients. The true variation in prevalences of coeliac disease throughout the world appears to be limited[13].

Screening on coeliac disease in the general population shows a prevalence of 1:300 to 1:100. About 50% of these children are completely symptomless[13]. In two British population-based studies on short stature[14,15], where coeliac disease was not specifically investigated, the prevalence of coeliac disease was 2:180 (one patient was already known with coeliac disease) and 0:149 respectively. In children with short stature and no gastrointestinal symptoms investigated for coeliac disease, the prevalence increases to 2-8%. When other (endocrine) causes for short stature are excluded, the prevalence might rise to even 59%.

Clinical bottom line

- In 2% to 8% of the children with short stature and no gastrointestinal symptoms, coeliac disease may be the underlying cause.
- Excluding other causes for short stature increases the risk of having coeliac disease by 19% to 59%.
- Children with short stature should be evaluated for coeliac disease.

References

1. Knudtzon J, Fluge G, Aksnes L. Routine measurements of gluten antibodies in children of short stature. J Pediatr Gastroenterol Nutr 1991; 12(2):190-194.
2. Stenhammar L, Fallstrom SP, Jansson G, Jansson U, Lindberg T. Coeliac disease in children of short stature without gastrointestinal symptoms. Eur J Pediatr 1986; 145(3):185-186.
3. Cacciari E, Salardi S, Lazzari R, Cicognani A, Collina A, Pirazzoli P et al. Short stature and celiac disease: a relationship to consider even in patients with no gastrointestinal tract symptoms. J Pediatr 1983; 103(5):708-711.
4. Cacciari E, Salardi S, Volta U, Biasco G, Lazzari R, Corazza GR et al. Can antigliadin antibody detect symptomless coeliac disease in children with short stature? Lancet 1985; 1(8444):1469-1471.
5. Rossi TM, Albini CH, Kumar V. Incidence of celiac disease identified by the presence of serum endomysial antibodies in children with chronic diarrhea, short stature, or insulin-dependent diabetes mellitus. J Pediatr 1993; 123(2):262-264.
6. Radzikowski T, Zalewski TK, Kapuscinska A, Chorzelski TP, Sulej J, Beutner EH et al. Short stature due to unrecognized celiac disease. Eur J Pediatr 1988; 147(3):334-335.
7. Bonamico M, Scire G, Mariani P, Pasquino AM, Triglione P, Scaccia S et al. Short stature as the primary manifestation of monosymptomatic celiac disease. J Pediatr Gastroenterol Nutr 1992; 14(1):12-16.
8. Groll A, Candy DC, Preece MA, Tanner JM, Harries JT. Short stature as the primary manifestation of coeliac disease. Lancet 1980; 2(8204):1097-1099.
9. Rosenbach Y, Dinari G, Zahavi I, Nitzan M. Short stature as the major manifestation of celiac disease in older children. Clin Pediatr (Phila) 1986; 25(1):13-16.
10. de Lecea A, Ribes-Koninckx C, Polanco I, Calvete JF. Serological screening (antigliadin and antiendomysium antibodies) for non-overt coeliac disease in children of short stature. Acta Paediatr Suppl 1996; 412:54-55.
11. Altuntas B, Kansu A, Ensari A, Girgin N. Celiac disease in Turkish short-statured children and the value of antigliadin antibody in diagnosis. Acta Paediatr Jpn 1998; 40(5):457-460.
12. Tumer L, Hasanoglu A, Aybay C. Endomysium antibodies in the diagnosis of celiac disease in short-statured children with no gastrointestinal symptoms. Pediatr Int 2001; 43(1):71-73.
13. Csizmadia CGDS, Mearin ML, von Blomberg BM, Brand R, Verloove-Vanhorick SP. An iceberg of childhood coeliac disease in the Netherlands. The Lancet 1999; 353(9155):813-814.

Chapter 3

The probability of Cystic Fibrosis in infants and children with poor growth

Floor K. Grote[1], Wendelien A. Planten[1], Wilma Oostdijk[1], Friedo W. Dekker[2], Jan M. Wit[1].

[1] Department of Paediatrics, Leiden University Medical Center, Leiden, The Netherlands
[2] Dept. of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands

Clinical scenario

A boy of one and a half years old is referred to the paediatrician because of failure to thrive. At this clinic visit his length is –0.55 SDS (≈ 30% tile) and weight –2.3 SDS (≈1% tile). His target height is 194 cm (1.37 SDS ≈ 90% tile). He was born at a gestational age of 40 weeks with a length standard deviation score (SDS) of 0.33 SDS (≈ 60% tile) and a weight SDS of –0.12 SDS (≈ 45% tile). There were no problems during pregnancy or labor. After growing well during the first 3 months he started to fall behind in weight and length increase. There is no report of repeated pulmonary infections or severe gastro-intestinal problems. The family history is uninformative for hereditary diseases. The paediatrician considers to include a sweat test into the diagnostic workup. He knows that the sensitivity and specificity of this test are high, but for an accurate interpretation of the predictive value he would need the baseline risk of cystic fibrosis in children with failure to thrive.

Structured clinical question

What is the prior-probability of CF [outcome] in infants and children with short stature and/or poor weight (Failure to thrive FTT (SDS <-1.5; <-2.0; <-2.5)) [patients]?

Search strategy and outcome

Pubmed - "Cystic Fibrosis AND (body height OR failure to thrive OR short stature OR dwarfism)". Only articles were included if they contained data on either length or weight before treatment and more than just birth weight and length; 226 references of which 11 relevant and of sufficient quality.
Embase – Same search strategy; 211 references of which 1 new, relevant and of sufficient quality.
Cochrane database - Same search strategy; no additional relevant articles.

Table 1: Studies evaluating either length or weight at the diagnosis of CF patients

Citation	Patient group	Study type (level of evidence)	Outcome	Key results	Estimated percentages of low length or weight† in patient group (%)	Comments*
Screened CF population						
Giglio et al (1997), Italy[1]	n=103 between '82-'92, in North-East-Italy median age: 1.07 months (0.60 to 4.53)	Retrospective cohort study (2a-b)	Proportion of children poor weight-gain at diagnosis	68.9% of study population grew less than 15 g/day	21.7	
Waters et al (1999), Australia[2]	n=60 between July '81 and July '84 in New South Wales Newborn Screening Programme median age (range) screened: 1.80 months (0.10 to 81.0)	Retrospective cohort study (2b)	Average length at diagnosis:	-0.2 SDS	9.9	Method of diagnosis not reported
			Average weight at diagnosis:	-0.1 SDS	6.9	
Farrell et al (2001), USA[3]	n=56 between 15/4/85 and 30/6/94 median age (range): Screened: 1.63 months (0.93 to 65.57)	Randomized controlled trial (2a)	Average length at diagnosis:	Z-score -0.21	10.1	
			Average weight at diagnosis:	Z-score -0.5	12.1	
Bronstein et al (1992), USA[4]	n=29 between July '84 and June '89 in Colorado median age (range): 1.40 months	Prospective cohort study (2b)	Average length at diagnosis:	Z-score -0.69	17.5	Only children whose weight was appropriate for gestational age at birth
			Average weight at diagnosis:	Z-score -0.69	15.3	
Abman et al (1985), USA[5]	n=27 between 1982 and 1984, in Colorado mean age (range): 1.28 months (0.70 to 1.87)	Prospective cohort study (2b)	Proportion of children with poor weight	Average of study population on 32nd percentile	9.2	
Greer et al (1991), Australia[6]	n=20 between Nov '85 and July '89 in Queensland median age (range): 1.26 months	Prospective cohort study (2b)	Average length at diagnosis:	Z-score -0.52	14.5	
			Average weight at diagnosis:	Z-score -0.82	17.8	

Non-screened CF population						
Lai et al (1998), USA[7]	n=790 newly diagnosed CF patients in 1993 as reported to the 1993 National CF Patient Registry median age: 6 months	Retrospective cohort study (2a-b)	Proportion of children with short stature:	34.4 % of study population below 5th percentile	25.5	
			Proportion of children with poor weight	35.9 % of study population below 5th percentile	26.2	
Haeusler et al (1994), Austria[8]	n=103 between 1955-1989, 97% of CF-population in Paediatric Department of University of Vienna mean age (range): 17.5 months (0 to 144)	Retrospective cohort study (2a-b)	Average length at diagnosis:	Z-score -1.10	26.0	
			Average weight at diagnosis:	Z-score -1.52	35.4	
Reisman et al (1989), Canada[9]	n=81 between '75- and '86 at Hospital for Sick Children (Ontario) mean age (range): 1 month (0 to 7)	Prospective cohort study (2b)	Proportion of children with short stature:	56% of study population below 3rd percentile	52.7	
			Proportion of children with poor weight	48% of study population below 3rd percentile	44.3	
Kreamer et al (2000), Switzerland [10]	n=80 mean age (range): 4.6 months (0.1 to 12.7)	Prospective cohort study (2a-b)	Average length at diagnosis:	-1.49 SDS	35.8	Method of diagnosis not reported
			Average weight at diagnosis:	-1.55 SDS	36.3	
Waters et al (1999), Australia[2]	n=57 between '78-'81. median age (range) : 5.7 months (0.1-51.5)	Retrospective cohort study (2b)	Average length at diagnosis:	-1.2 SDS	28.4	Method of diagnosis not reported
			Average weight at diagnosis:	-1.2 SDS	26.6	
Farrell et al (2001), USA[3]	n=48 between 15/4/85 and 30/6/94 median age (range): 6.53 months (0.7 – 86.8)	Randomized controlled trail (2a)	Average length at diagnosis:	Z-score -1.0	23.8	
			Average weight at diagnosis:	Z-score -1.0	21.7	
Ranganathan et al (2004), UK[11]	n=37 between Jan '99 and May '01 median age (range): 6.63 months (3.9 to 10.0)	Prospective cohort study (2a-b)	Average length at diagnosis:	Z-score -0.73	18.2	
			Average weight at diagnosis:	Z-score -1.78	43.2	

† length for age < -2 SDS or weight for age < -2 SDS. For each study we estimated the percentage of infants or children with a length or weight below -2 SDS. This was done in several steps (see appendix II). First, the Standard deviations scores (SDS) for mean length and weight at diagnosis were either directly derived from the data or

by converting percentiles into SD-scores. Second, a weighted average SD for length and weight in newly diagnosed CF patients was calculated from data given in the articles[2, 3, 11]. This led to an SD for length of 1.41 and for weight of 1.28. Thus, the distribution is wider than in the general population. Third, for each study the mean SD-scores for length and weight were subtracted from the chosen cut-off point for low weight and short stature (in this case -2) and divided by the weighted average SD. This gave the SDS for length or weight in that patient sample that concurred with -2 SDS in the general population. Fourth, this sample-specific SDS value was converted into percentiles and the percentages of children with a low length or weight was calculated.

Table 2: Prior-probabilities of CF in infants and children with failure to thrive (with different cut-off points for weight and length).

	Weight			Length		
	< -1.5 SDS	< -2.0 SDS	< -2.5 SDS	< -1.5 SDS	< -2.0 SDS	< -2.5 SDS
Prior probability of CF (non-screened) (%)▲	0.21	0.42	0.91	0.20	0.40	0.90
Prior probability of CF (screened) (%)▲	0.12	0.20	0.38	0.10	0.17	0.32

▲ Prior-probabilities of CF in infants and children with failure to thrive were recalculated using a 'two-by-two table' (see appendix II) based on the assumption that the average incidence of CF is 1:3000 in the Caucasian population.[12] A weighted average from the estimated percentages of low length or weight in table 1 was used as percentage of children with FTT in a CF-population. The percentage of low length or weight in a normal population was directly calculated from the SDS used as cut-off. The recalculation was done for several cut-offs for FTT (we used –1.5, -2 and –2.5 SDS as cut-offs).

Commentary

The term failure to thrive is mostly used to describe growth impairment, but a clear definition is lacking; there is no consensus on the choice of anthropometric indicators or their criteria for abnormality.[13] The term implies that growth parameters (length and/or weight) decrease over time, i.e. cross the centiles of SD lines on a growth diagram. The best objective expression of failure to thrive would therefore be an index of change of length or weight over time. In our literature search we did not encounter studies which had analysed longitudinal growth in CF patients. We therefore had to use a proxy parameter for failure to thrive, i.e. a low length or weight for age.

Failure to thrive can be the first sign of malnutrition, but also the first symptom of a congenital disease like CF. This is the most common life shortening hereditary disease in the Caucasian population, with a prevalence of 1:3000.[12, 14, 15] In other ethnic groups the prevalence varies considerably. Patients with CF are known to have gastro-intestinal and pulmonary problems besides failure to thrive, but some patients with CF only present with failure to thrive.[1, 11, 16, 17, 18, 19]
Early diagnosis of CF improves the patient condition and probably increases survival, so that several countries have initiated a newborn screening (NBS) program for CF.[20, 21]

In countries where such screening program has not been implemented, CF is detected on clinical grounds. Besides respiratory and gastrointestinal symptoms and signs, failure to thrive is one of the key clinical cues, but there are no data available indicating at which cut-off point of which growth parameter the physician should consider a specific diagnostic test for CF.
The standard test for the diagnosis of CF is the sweat test. By collecting at least 50 mg of sweat with pilocarpine iontophoresis the chloride concentration can be chemically determinated.[22] We wondered what the prior-probablity is of CF in children with failure to thrive, so that a rational decision could be made as to perform a sweat test.

Only one study was found on the prior-probability of CF in infants and children with short stature. Oliveira et al. reported in this Brazilian article on a group of children with monosymptomatic short stature (height SDS below -1.9 or a growth rate less than 5 cm per year) a prior-probability of 7.8 % and concluded that CF besides celiac disease must be included in the differential diagnosis of short stature.[17] We then decided to search for scientific reports on length and weight in groups of patients with CF (see table 1). These studies were divided into two groups; screened and non-screened. The screened study-population was up to two months old when diagnosed, whereas the non-screened population were on average older than 6 months. Most children had respiratory and gastro-intestinal problems, but some presented themselves with failure to thrive as main complaint.

The prior-probability of CF in children with a low length or weight for age derived from the studies on children with CF is low (<1%) (see table 2). This contrasts with the observations of Oliviera et al, who showed a considerably higher proportion (7.8%). The difference may be explained by differences in auxological criteria (growth rate versus weight and length for age) and in populations (a group of children with monosymptomatic FTT, referred to a specialised clinic versus a group of children with FTT, disregarding other symptoms, taken from a general population).

Given the low prior probability of CF in infants with a low length or weight for age, the sweat-test will only provide a reliable result if the positive likelihood ratio (and therefore the sensitivity and specificity) of the test would be very high. This is apparently not the case, as there is a widely variable practice of, and standards in sweat testing resulting in inconsistent test accuracies.[23, 24] Even under the assumption that the test is performed under the best conditions with a sensitivity of 98% and a specificity of 98%, the probability of having CF for a child with a positive sweat test, who was not screened for CF and has a length or weight < -2.5 SDS, would still be less than 35%.

We therefore conclude that in an infant with a low length or weight for age the prior probability of CF is less than 1%, so that we can assume that in an asymptomatic infant the probability will be (much) lower. This would argue against performing a sweat test. Parameters of poor longitudinal growth may be more predictive, but this has not been studied so far. If clinical symptoms or signs suggestive for CF are found in combination

with growth faltering, the prior probability is expected to be higher, so that obviously further diagnostic steps are warranted.

Clinical bottom line

- The underlying cause of a low length or weight for age in an infant or a child with no other symptoms can be CF. (Grade A)
- The prior-probability of CF in infants or children with a low weight or length for age is 0.20-0.91 percent (depending on the cut-off point). (Grade B)

Acknowledgements

The study is part of a larger project to establish evidence-based guidelines on referral criteria for growth monitoring and diagnostic work-up for children with short stature.
This project was supported by an educational grant from Pfizer.
Competing interests: none declared.

References

1. Giglio L, Candusso M, D'Orazio C, Mastella G, Faraguna D. Failure to thrive: the earliest feature of cystic fibrosis in infants diagnosed by neonatal screening. Acta Paediatr 1997;86(11):1162-5.
2. Waters DL, Wilcken B, Irwing L, Van Asperen P, Mellis C, Simpson JM et al. Clinical outcomes of newborn screening for cystic fibrosis. Arch Dis Child Fetal Neonatal Ed 1999;80(1): F1-F7.
3. Farrell PM, Kosorok MR, Rock MJ, Laxova A, Zeng L, Lai HC et al. Early diagnosis of cystic fibrosis through neonatal screening prevents severe malnutrition and improves long-term growth. Wisconsin Cystic Fibrosis Neonatal Screening Study Group. Pediatrics 2001;107(1):1-13.
4. Bronstein MN, Sokol RJ, Abman SH, Chatfield BA, Hammond KB, Hambidge KM et al. Pancreatic insufficiency, growth, and nutrition in infants identified by newborn screening as having cystic fibrosis. J Pediatr 1992;120(4 Pt 1):533-40.
5. Abman SH, Reardon MC, Accurso FJ, Hammond KB, Sokol RJ. Hypoalbuminemia at diagnosis as a marker for severe respiratory course in infants with cystic fibrosis identified by newborn screening. J Pediatr 1985;107(6):933-5.
6. Greer R, Shepherd R, Cleghorn G, Bowling FG, Holt T. Evaluation of growth and changes in body composition following neonatal diagnosis of cystic fibrosis. J Pediatr Gastroenterol Nutr 1991;13(1):52-8.
7. Lai HC, Kosorok MR, Sondel SA, Chen ST, FitzSimmons SC, Green CG et al. Growth status in children with cystic fibrosis based on the National Cystic Fibrosis Patient Registry data: evaluation of various criteria used to identify malnutrition. J Pediatr 1998;132(3 Pt 1):478-85.
8. Haeusler G, Frisch H, Waldhor T, Gotz M. Perspectives of longitudinal growth in cystic fibrosis from birth to adult age. Eur J Pediatr 1994;153(3):158-63.
9. Reisman J, Petrou C, Corey M, Stringer D, Durie P, Levison H. Hypoalbuminemia at initial examination in patients with cystic fibrosis. J Pediatr 1989;115(5 Pt 1):755-8.
10. Kraemer R, Aebi C, Casaulta AC, Gallati S. Early detection of lung disease and its association with the nutritional status, genetic background and life events in patients with cystic fibrosis. Respiration 2000;67(5):477-90.
11. Ranganathan SC, Stocks J, Dezateux C, Bush A, Wade A, Carr S et al. The evolution of airway function in early childhood following clinical diagnosis of cystic fibrosis. Am J Respir Crit Care Med 2004;169(8):928-33.
12. Bobadilla JL, Macek M, Jr., Fine JP, Farrell PM. Cystic fibrosis: a worldwide analysis of CFTR mutations--correlation with incidence data and application to screening. Hum Mutat 2002;19(6):575-606.
13. Wilcox WD, Nieburg P, Miller DS. Failure to thrive. A continuing problem of definition. Clin Pediatr (Phila) 1989;28(9):391-4.
14. Sarles J, Barthellemy S, Ferec C, Iovanna J, Roussey M, Farriaux JP et al. Blood concentrations of pancreatitis associated protein in neonates: relevance to neonatal screening for cystic fibrosis. Arch Dis Child Fetal Neonatal Ed 1999;80(2):F118-F122.
15. Wilson DC, Pencharz PB. Nutrition and cystic fibrosis. Nutrition 1998;14(10):792-5.
16. Armstrong DS, Grimwood K, Carzino R, Carlin JB, Olinsky A, Phelan PD. Lower respiratory infection and inflammation in infants with newly diagnosed cystic fibrosis. BMJ 1995;310(6994):1571-2.
17. Oliveira MC, Reis FJ, Chagas AJ, Brasileiro FG, Bahia M, Silva LD et al. [Study of intestinal malabsorption diseases as cause of monosymptomatic short stature]. J Pediatr (Rio J) 1998;74(3):213-6.
18. Tepper RS, Hiatt P, Eigen H, Scott P, Grosfeld J, Cohen M. Infants with cystic fibrosis: pulmonary function at diagnosis. Pediatr Pulmonol 1988;5(1):15-8.

19. Wesley AW, Horne AM, Elliott RB. Problems in diagnosis of cystic fibrosis. N Z Med J 1984;97(767):773-5.
20. Dankert-Roelse JE, Merelle ME. Review of outcomes of neonatal screening for cystic fibrosis versus non-screening in Europe. J Pediatr 2005;147(3 Suppl):S15-S20.
21. Farrell PM, Lai HJ, Li Z, Kosorok MR, Laxova A, Green CG et al. Evidence on improved outcomes with early diagnosis of cystic fibrosis through neonatal screening: enough is enough! J Pediatr 2005;147(3 Suppl):S30-S36.
22. Denning CR, Huang NN, Cuasay LR, Shwachman H, Tocci P, Warwick WJ et al. Cooperative study comparing three methods of performing sweat tests to diagnose cystic fibrosis. Pediatrics 1980;66(5):752-7.
23. Baumer JH. Evidence based guidelines for the performance of the sweat test for the investigation of cystic fibrosis in the UK. Arch Dis Child 2003;88(12):1126-7.
24. Leigh MW. Diagnosis of CF despite normal or borderline sweat chloride. Paediatr Respir Rev 2004;5 Suppl A:S357-S359.

Part B

Current methods of growth monitoring and diagnostic work-up of short stature

Chapter 4

Growth monitoring and diagnostic work-up of short stature: an international inventorisation.

F.K. Grote[1], W. Oostdijk[1], S.M.P. F. de Muinck Keizer-Schrama[2], F.W. Dekker[3], P.H. Verkerk[4], J.M. Wit[1]

[1] Dept of Pediatrics, Leiden University Medical Center, Leiden, The Netherlands
[2] Dept of Pediatrics, Erasmus University Medical Centre / Sophia Children's Hospital, Rotterdam, The Netherlands
[3] Dept of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands
[4] TNO Prevention and Health, Leiden, The Netherlands

J Pediatr Endocrinol Metab 2005;18:1031-8.

Summary

Background/ Aims: Growth monitoring is almost universally performed, but little data is available on which referral criteria and diagnostic work-up are used worldwide for children with short stature.

Methods: A short questionnaire, containing questions on auxological screening and on diagnostic criteria for short stature was sent to all members of the European Society of Paediatric Endocrinology (ESPE) and to several pediatric endocrinologists outside Europe.

Results: A response was received from 36 countries. In 27 (75 %) a child health care program existed and in 14 (39%) there was a protocol for referral of growth-retarded children. Height for age was mostly used as a referral criterion. Sixteen countries (45%) reported having a guideline in secondary health care for the diagnostic work-up. Although all countries agreed on having biochemical, radiological and/or genetic tests in the diagnostic work-up, there was a wide variety in recommended tests.

Conclusions: There is little consensus on referral criteria and diagnostic work-up of children with short stature among industrialized countries. There is a need to establish evidence-based guidelines.

Introduction

Short stature or growth retardation is considered a relatively early sign of poor health in children. Growth monitoring is therefore widely accepted, although no reliable evidence was found to support this activity.[1]

Short stature has many causes and the purposes and objectives of growth monitoring programs are therefore different, depending on its setting. In developing countries the principle aim of growth monitoring is to detect malnutrition. Given this aim the WHO promotes growth monitoring and research to improve the monitoring itself.[2,3]

In industrialized countries, where there is less malnutrition, growth monitoring is aimed at detecting other causes of growth retardation, of which Turner syndrome and Growth Hormone deficiency are most prevalent. Because early diagnosis and treatment of children with growth disorders favorably influences outcome, there is a need for correct referral criteria and diagnostic work-up for children with short stature. However, only few guidelines have been published,[4,5] and these are based on consensus meetings rather than on experimental evidence. Only recently, we reported on the predictive value of various auxological criteria for detecting Turner syndrome.[6]

One of those guidelines[4] concentrates on the referral of children with short stature after a single height measurement at school entrance (at age 5) only and does not offer information on the diagnostic work-up afterwards. According to the Dutch consensus guideline[5] seven referral criteria should be used, but we recently reported that strictly adhering to this guideline would lead to too many referrals.[7] In this guideline also the diagnostic work-up is described, including biochemical and radiological tests.

In view of the possible discrepancy between the widespread practices of growth monitoring and the scarcity of experimental or observational data, we started a project to establish new, and more evidence-based guidelines on referral criteria for growth monitoring and diagnostic work-up for children with short stature. As part of this effort, we performed an inquiry among pediatric endocrinologists in Europe and most industrialized countries around the world about the referral criteria advised for growth monitoring in primary care, and about diagnostic procedures for short stature in secondary care.

Material and methods

In the Spring of 2002 a short questionnaire was sent to all members of the European Society of Paediatric Endocrinology (ESPE) and to several pediatric endocrinologists in the USA, Canada, Brazil, Japan, Australia and New Zealand. The total number of countries approached was 45. If a first reminder was unsuccessful, we tried to increase the response rate by directly asking individuals from the missing countries to be instrumental in collecting the information.

The questionnaire contained questions on auxological screening in child health programs and on diagnostic criteria for short stature in specialist centers, including biochemical and radiological tests. If any formal guidelines/protocols for auxological screening or diagnostic procedures in children with short stature were used the respondents were requested to send copies with their reply.

For the questions on the diagnostic procedures in specialist centers, we used the Dutch consensus guideline as baseline. According to this guideline, short children without any suspicion of a particular diagnosis after the auxological diagnostic work-up, should undergo the laboratory investigations shown in table 1. The guideline also includes that if in a short girl no explanation for her shortness is found, chromosomal analysis for excluding Turner syndrome should be performed.

After data collection, the answers were checked with the copies of the existing protocols/ guidelines. From each country only one returned survey was selected for further analysis. The selected survey either corresponded most with the existing protocols or with responses from other pediatric endocrinologists from the same country.

All data were entered into Access 2000 and analyzed both in Access and SPSS 11.

Table 1. Routine laboratory investigations for short stature according to the Dutch consensus

Laboratory investigations	In order to diagnose
Blood	
Hb, Ht, leukocytes, celindices, leukocyte differentiation, erythrocyte sedimentation rate (ESR), (ferritin)	Anemia, Infections, Celiac disease, Cystic fibrosis
ALAT, ASAT, γ GT	Liver diseases
albumin, creatinine, sodium, potassium, calcium, phosphate, alkaline phosphate, acid-base equilibrium	Renal diseases
IgA-anti endomysium, IgA- antigliadin, anti-tissue glutaminase*, total IgA	Celiac disease
TSH, FT4	Hypothyroidism
FSH**	Turner's syndrome
insulin-like-growth factor (IGF-I)	Growth hormone deficiency
Urine	
pH, glucose, protein, blood and sedimentation	Renal diseases

* At the moment the consensus meeting took place, anti tissue glutaminase was not yet nation wide introduced as a diagnostic tool for celiac disease.

** Only in girls <2 years of age and >9 years of age.

Table 2. References of growth charts used in the responding 36 countries

Reference of growth chart	n = 36 (100%)
National/ Local	18 (50)
NCHS	4 (11)
Other	2 (6)
Unknown	2 (6)
Tanner	1 (2.5)
Prader	1 (2.5)
No use of growth chart reported	8 (22)

Results

The availability of programs and protocols on growth monitoring and diagnostic work-up

Responses were received from 36 countries. Figure 1 shows the availability of programs on growth monitoring and protocols for referral and diagnostic work-up of children with short stature. In 5 (14%) countries no organized growth monitoring appeared to take place. In 27 countries (75%) a child health care program was present and 14 countries (39%) reported having a primary health care protocol for referral of children with short stature. From 16 countries (45%) guidelines for diagnostic procedures in children with short stature in secondary health care were reported. Not all of these programs or protocols were nationally implemented.

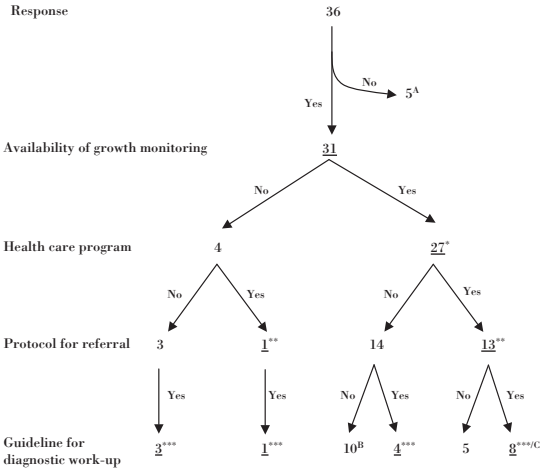


Fig. 1. The availability of programs and protocols on growth monitoring in the responding 36 countries.

* Countries with child health care program (total = 27 (75%))

** Countries with protocol for referral of children with short stature (total = 14 (39%))

*** Countries with guideline for diagnostic work up of children with short stature (total = 16 (45%))

A. Countries without any organized growth monitoring (total = 5 (14%))
B. Countries with only a child health care program (total = 10 (28%))
C. Countries with both a child health program and protocols for referral and guidelines for the diagnostic work up (total = 8 (22%))

Charts used throughout the world

On the question if growth charts are used for the growth monitoring/ screening, 28 countries (78 %) responded affirmative. Most of the other countries did not respond to this question because of a lack of a growth monitoring/ screening program. In 18 countries (50 %) national reference charts were used, in others British,[8] Swiss[9] or other international reference charts.[10-12]

Auxological referral criteria

Height for age, either expressed as centile position or as standard deviation score, was mostly used as a referral criterion by countries with referral-protocols for children with short stature, followed by the deviation of height either expressed as height velocity or delta height SDS. The distance to target height appeared to be used less frequently (table 3). Clinicians from countries without auxological screening criteria also considered the deviation of height more important than the distance to target height. A wide variety of cut-off points were described for the different criteria. For height for age cut-off limits were reported but varied from –3 SDS (~ P0.2) to –1.28 SDS (~ P10). For deviation of height however different methods were reported like changing canals or percentiles, cm per year, deviation of SDS (-2 to -0.25 SDS) or even percentages of deviation. The cut-off for the distance to target height was either expressed in cm (7-8) or in SDS (-2 SDS) and the target height itself or the lower limit of the target range was taken as reference point.

Table 3. The use and/or consideration of auxological criteria for the referral of a child with short stature.

Auxological criterion	Countries with protocol n=14 (100%)	Countries without protocol n=22 (100%)
Height for age	14 (100)	19 (86)
Deviation of height	7 (50)	10 (46)
Distance to target height	6 (43)	5 (23)
Weight	3 (21)	6 (27)
Delta weight	2 (14)	3 (14)

Laboratory investigations in the diagnostic work-up of short stature

Sixteen countries (46%) reported having guidelines in secondary health care for the diagnostic work-up of children with short stature. In all these countries biochemical tests were used in the diagnostic work-up. Out of the 27 proposed biochemical investigations, 6 were considered useful in 25-50% of all countries, 14 in 50-75% and 7 in 75-100% (fig 2). Clinicians of countries without existing guidelines reported a similar pattern in the laboratory investigations in the diagnostic work-up for short stature as given in figure 2.

The reported use of the various tests was about 10% less than in the countries with existing guidelines.

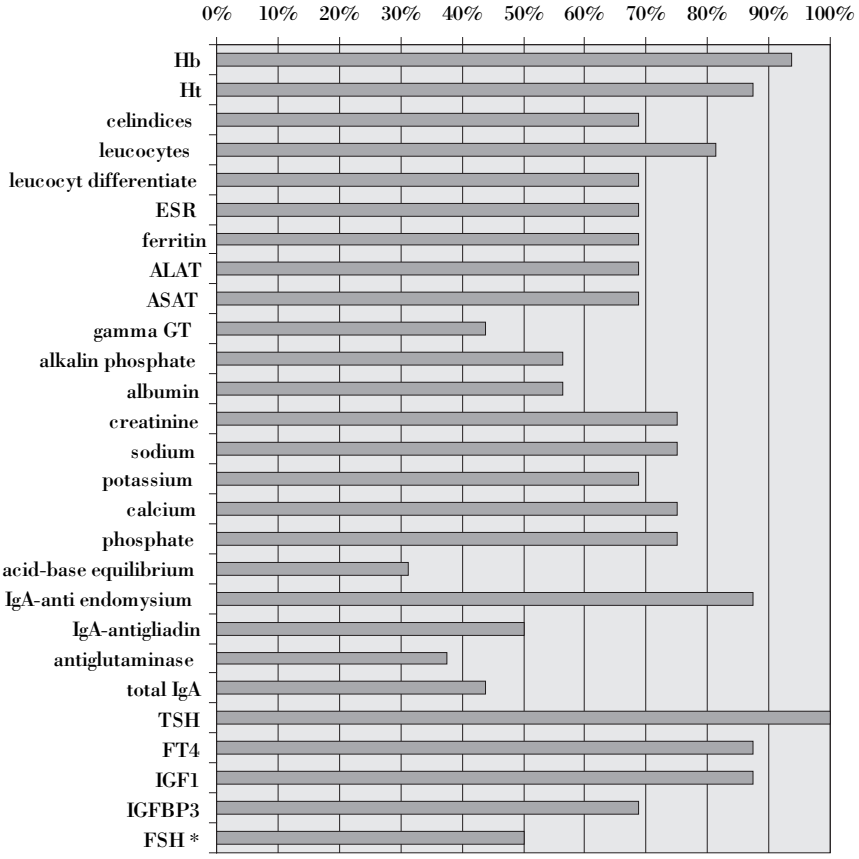


Fig 2. The routine use of various biochemical tests in the diagnostic work-up for short stature in countries with a guideline. (*Only in girls <2 years of age and >9 years of age).

Chromosomal analysis, genetic tests and bone age determination in the diagnostic work-up of a child with short stature.

Genetic and/or chromosomal investigations are widely (100%) proposed in the diagnostic work-up of short stature in countries with a guideline. From 50% of the countries it was reported that chromosomal analysis should always be part of the diagnostic work-up in girls. From 35% of the countries tests for the short stature homeobox-containing gene (SHOX) and/or uniparental disomy (UPD) were reported (table 4). It was also generally accepted (100%) that determining bone age should be part of the diagnostic work-up (table 4). The method of Greulich and Pyle was reported most, either alone (in 19 countries (53%)) or in combination with the method of Tanner and Whitehouse (in 11 countries (31%)). Clinicians of countries without existing guidelines reported a similar pattern in the diagnostic work-up for short stature (table 4).

Table 4. The use and/or consideration of chromosomal, genetic tests and determination of bone age in the diagnostic work up of a child with short stature in countries with a guideline for diagnostic work up.

	countries with guideline n=16 (100%)
Chromosomal and/or genetic tests	
General use	16 (100)
Chromosomal analyses in girls	8 (50)
SHOX/UPD	6 (38)
Determination of bonage	
General use	16 (100)
Greulich and Pyle (GP)	14 (88)
Tanner and Whitehouse (TW)	8 (50)
GP & TW	6 (38)

Discussion

We conducted an international survey to investigate referral criteria in primary care growth monitoring and the diagnostic procedures for short stature in secondary care used throughout the world. A child health care system was available in 75% of the responding countries. In 39% of the countries protocols for the referral of children with short stature existed and in 45% guidelines for a diagnostic work-up. In general height for age was considered as the most important referral criterion followed by height velocity and distance to target height. Although all countries reported on the inclusion of biochemical, radiological and/or genetic tests in the diagnostic work-up, there were substantial differences between countries with respect to the tests of choice.

In developing countries, growth monitoring is widely accepted as a screening tool for detecting malnutrition, and strongly supported by health professionals. There, weight for age is the usual parameter, and only in 41% of the countries length and height for age (H/A) is used for growth monitoring.[13] In industrialized countries growth monitoring may be conducted less frequently, the preferred parameter is H/A, the purpose is to detect other causes of growth failure than malnutrition alone, and the anticipated outcomes are less severe.[14] In fact, in 14% of the countries participating in our study no organized growth monitoring took place. In these countries growth monitoring may occur in specialized settings in a selected sample of the population.

With respect to the reference charts used, in our study 50 % of the countries based their charts on national/ local reference populations. This percentage is comparable to the data for Europe collected by Onis et al., [13] but considerably higher than the 17 % found in the same study for 202 countries all over the world. Outside of Europe the NCHS/WHO reference population is frequently used.

The choice of the principal referral criterion may differ in function of the principal aim of growth monitoring. In our survey, height for age was generally considered the most important referral criterion in our study. The deviation of height, either expressed as height velocity or delta HSDS was considered the second most important criterion, followed by the distance to target height. In the UK guidelines, target height is not taken into account at all, because it is felt that parental height is unreliable.[4] In contrast to this opinion, we have recently shown that the best decision rule to detect children with Turner syndrome, one of the major causes of short stature, is the distance between height SDS and target height.[6]

Although there is agreement on using biochemical, radiological and genetic tests in the diagnostic work-up for short children, our study shows that there is no full consensus on the tests to be used among specialists. Apart from the Dutch consensus guideline there is no literature on the general diagnostic work-up for short stature in secondary health care, although specific guidelines on the diagnosis of growth hormone deficiency in childhood and adolescence have been published.[15,16] However, these guidelines cover only part of the diagnostic work-up, since they start from the assumption that other causes of short stature have been excluded earlier.

With respect to radiological investigations, we only collected information about bone age determination, which are apparently universally used. We assume that in case of disproportionate shortness, clinicians usually perform additional radiological and genetic investigations as part of a multidisciplinary approach for the diagnosis of skeletal dysplasias,[17] but we have not investigated this. An increasing number of genetic causes of short stature are being found and several genetic tests are available in the diagnosis of short stature nowadays.[18] However, according to our survey, genetic analysis for UPD or SHOX is only considered in 30-39% of the cases. Meanwhile treatment with growth hormone in children with SHOX seems to be effective and therefore early diagnosis is of great importance.[19] In 50% of the countries routinely screening for Turner syndrome in short girls has been recommended.

Even though the results presented in this paper are derived from the responses of a relatively small group of pediatric endocrinologists to questionnaires, and thus potentially biased, we believe that they give a good impression of the diversity in the growth monitoring process and the diagnostic work-up of growth disorders in industrialized countries. This is not astonishing, because little experimental data has been published on these topics. We believe that more studies are needed on the diagnostic value and cost-effectiveness of auxological screening for the diagnosis of various diseases, similarly to the recent report on Turner syndrome.[6] Secondly, we believe that the prevalence of the disorders known to cause short stature has to be established in short children without any abnormal symptoms or signs. This prevalence, in combination with the severity of the disorder and possibilities for treatment, should be taken into account for the decision to use certain diagnostic tests in the work-up. For example, in a recent study we showed that the prevalence of celiac disease is considerable in asymptomatic short children, so that all children with short stature should be evaluated for celiac disease.[20] Thirdly, data should

be collected about the diagnostic performance of the various biochemical, radiological and genetic tests, so that evidence-based guidelines can be constructed with an acceptable cost-benefit ratio.

We conclude that there is little consensus on referral criteria and diagnostic work-up of children with short stature among industrialized countries and that there is a need for more research to establish evidence-based guidelines on the screening and diagnosis of growth disorders.

Acknowledgements

The financial support of Pfizer is greatly acknowledged. We further are grateful to all pediatric endocrinologists who responded to the questionnaire and to Dr. Martin Savage, secretary of ESPE (European Society for Paediatric Endocrinology), for his assistance in distributing the questionnaire to ESPE members.

References

1. Garner P, Panpanich R, Logan S: Is routine growth monitoring effective? A systematic review of trials. Arch Dis Child 2000;82:197-201.
2. Use and interpretation of anthropometric indicators of nutritional status. WHO Working Group. Bull World Health Organ 1986;64:929-941.
3. An evaluation of infant growth: the use and interpretation of anthropometry in infants. WHO Working Group on Infant Growth. Bull World Health Organ 1995;73:165-174.
4. Hall DM: Growth monitoring. Arch Dis Child 2000;82:10-15.
5. de Muinck Keizer-Schrama SM: [Consensus 'diagnosis of short stature in children.' National Organization for Quality Assurance in Hospitals]. Ned Tijdschr Geneeskd 1998;142:2519-2525.
6. Buuren van S, Dommelen van P, Zandwijken GR, Grote FK, Wit JM, Verkerk PH: Towards evidence based referral criteria for growth monitoring. Arch Dis Child 2004;89:336-341.
7. Buuren van S, Bonnemaijer-Kerckhoffs DJ, Grote FK, Wit JM, Verkerk PH: Many referrals under Dutch short stature guidelines. Arch Dis Child 2004;89:351-352.
8. Tanner JM, Whitehouse RH: Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. Arch Dis Child 1976;51:170-179.
9. Prader A, Largo RH, Molinari L, Issler C: Physical growth of Swiss children from birth to 20 years of age. First Zurich longitudinal study of growth and development. Helv Paediatr Acta Suppl 1989;52:1-125.
10. Freeman JV, Cole TJ, Chinn S, Jones PR, White EM, Preece MA: Cross sectional stature and weight reference curves for the UK, 1990. Arch Dis Child 1995;73:17-24.
11. Hamill PV, Drizd TA, Johnson CL, Reed RB, Roche AF: NCHS growth curves for children birth-18 years. United States. Vital Health Stat 11 1977;i-74.
12. Sempe M: [Study of growth from birth to 18 months]. Arch Fr Pediatr 1977;34:687-688.
13. Onis de M, Wijnhoven TM, Onyango AW: Worldwide practices in child growth monitoring. J Pediatr 2004;144:461-465.
14. Panpanich R, Garner P: Growth monitoring in children. Cochrane Database Syst Rev 2000;CD001443.
15. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. GH Research Society. J Clin Endocrinol Metab 2000;85:3990-3993.
16. Butler J: Biochemical tests of growth hormone status in short children. Ann Clin Biochem 2001;38:1-2.
17. Mortier GR: The diagnosis of skeletal dysplasias: a multidisciplinary approach. Eur J Radiol 2001;40:161-167.
18. Kant SG, Wit JM, Breuning MH: Genetic analysis of short stature. Horm Res 2003;60:157-165.
19. Munns CF, Berry M, Vickers D, Rappold GA, Hyland VJ, Glass IA, Batch JA: Effect of 24 months of recombinant growth hormone on height and body proportions in SHOX haploinsufficiency. J Pediatr Endocrinol Metab 2003;16:997-1004.
20. Rijn van JC, Grote FK, Oostdijk W, Wit JM: Short stature and the probability of coeliac disease, in the absence of gastrointestinal symptoms. Arch Dis Child 2004;89:882-883.

Chapter 5

Signalering van groeistoornissen binnen de Huisartsgeneeskunde en Jeugdgezondheidszorg

F.K. Grote, N.I. Bootsma, W. Oostdijk, S.M.P.F. de Muinck Keizer-Schrama, A.P. Timmers, P.H. Verkerk, F.W. Dekker, J.M. Wit

Leids Universitair Medisch Centrum, Willem Alexander Kinder- en Jeugdcentrum, Postbus 6900 2300 RC Leiden:
Drs. F.K. Grote, arts-onderzoeker; N.I. Bootsma, student geneeskunde; Dr. W. Oostdijk, kinderendocrinoloog; Prof. dr. J. M. Wit, kinderendocrinoloog.
ErasmusMC - Sophia, Rotterdam: Dr. S.*M.P.F. de Muinck Keizer-Schrama, kinderendocrinoloog.*
Huisartsenpraktijk Wantveld, Noordwijk: Drs. A. Timmers, huisarts
TNO Kwaliteit van Leven, Jeugd preventie en bewegen, sector 0-19, Leiden: Dr. P.H. Verkerk, arts- epidemioloog JGZ
Leids Universitair Medisch Centrum, afdeling Klinische Epidemiologie, Leiden: Dr. F.W. Dekker, epidemioloog

Samenvatting

Inleiding: In 1996 werd de CBO-richtlijn "Diagnostiek kleine lichaamslengte bij kinderen" opgesteld, maar het is onbekend in hoeverre deze richtlijn bekend is en wordt toegepast binnen de huisartsenpraktijk en Jeugdgezondheidszorg (JGZ). Het doel van deze studie was om middels enquetes hierover informatie verzamelen en tevens over de meningen over de waarde van de verschillende verwijscriteria en over de definitie "failure to thrive".

Methode: In 2002 werden enquêtes verstuurd aan 365 huisartsen uit de regio Zuid-Holland Noord en 460 artsen JGZ uit geheel Nederland.

Resultaten: Door 207 huisartsen (57%) en 152 artsen JGZ (33%) werden bruikbare enquêtes geretourneerd. In de huisartsenpraktijk was de CBO-richtlijn (CBO-R) weinig bekend (16%) en werd zelden gebruikt. De meeste artsen JGZ (82%) kenden de CBO-R en 46% gaven aan deze te gebruiken. 49% van de artsen JGZ meende dat de verwijscriteria, met name afbuigende groei, tot teveel verwijzingen leiden. Zij vonden klinische symptomen (disproportie en dysmorfie) en extreem kleine lengte de belangrijkste verwijscriteria. "Failure to thrive" werd meestal gedefinieerd als afbuigend gewicht-naar-lengte.

Conclusie: De CBO-R is vrijwel onbekend bij huisartsen, maar wordt door circa 50% van de artsen JGZ gebruikt, ondanks dat velen menen dat strikte toepassing van de richtlijn zou leiden tot teveel verwijzingen. Inmiddels is een nieuwe evidence-based richtlijn opgesteld, waarmee een hoog percentage pathologie kan worden opgespoord bij een percentage verwijzingen van ongeveer 1%.

Inleiding

Het periodiek meten van lengte en gewicht van kinderen , in de Engelstalige literatuur aangeduid met de term "growth monitoring", wordt sinds lange tijd wereldwijd uitgevoerd. Desondanks zijn er maar weinig gegevens beschikbaar over de effectiviteit[1] In tegenstelling tot ontwikkelingslanden, waar signalering van ondervoeding het primaire doel is van groei-monitoring, is in de westerse wereld het opsporen van onderliggende pathologie, zoals het syndroom van Turner, groeihormoondeficiëntie en coeliakie, een belangrijk doel. Voor optimale behandeling van deze en andere groeigerelateerde aandoeningen is het van belang dat de diagnose zo vroeg mogelijk wordt gesteld.[2,3]

Voor vroege opsporing van groeistoornissen zijn er naast een goed groei-monitoring systeem duidelijke verwijscriteria voor afwijkende groei en goede protocollen voor verdere diagnostiek nodig. In de literatuur worden slechts enkele richtlijnen vermeld. [3,4] Deze zijn gebaseerd op consensus en maken gebruik van verschillende criteria voor verwijzing met verschillende afkappunten voor afwijkende lengtegroei. [5-7] Bij jonge kinderen wordt vaak de term "failure to thrive" gebruikt om een afwijkende groei bij jonge kinderen aan te geven, maar hiervan bestaat geen eenduidige definitie: zowel gewicht naar leeftijd, gewicht naar lengte en lengte naar leeftijd worden gebruikt om "failure to thrive" te objectiveren.[8,9]

Om vroegtijdige opsporing van een afwijkende lengtegroei te bevorderen en onnodige verwijzingen te voorkómen vond in 1996 in Nederland de consensusbijeenkomst 'Diagnostiek kleine lichaamslengte bij kinderen' plaats, waarin een multidisciplinaire richtlijn werd vastgesteld. Consensus werd bereikt over de diagnostiek en verwijzing van met name kinderen ouder dan 3 jaar met kleine lichaamslengte. Aangezien er, behoudens het verschijnen van deze CBO-richtlijn (CBO-R) in boekvorm, een publicatie in het Nederlands Tijdschrift voor Geneeskunde (NTVG) en meerdere nascholingscursussen, weinig publiciteit is gegeven aan de resultaten van de consensus-bijeenkomst, is het onbekend in hoeverre de CBO-R gebruikt wordt en hoe de huidige praktijk van groei-monitoring is.[4,10] Daarnaast concludeerden Van Buuren et al. spoedig na het verschijnen van de CBO-richtlijn dat de verwijscriteria , indien strikt toegepast, in de praktijk teveel verwijzingen geven, met name door het verwijscriterium afbuigende groei.[11]

Om deze redenen werd er een project gestart om de CBO-R te evalueren en uiteindelijk met een nieuwe evidence-based richtlijn te komen. In dit artikel beschrijven wij de resultaten van een inventarisatie onder huisartsen en artsen Jeugdgezondheidszorg (JGZ 0-19 jaar) over de huidige praktijk met betrekking tot groei-monitoring, in het bijzonder de mening over de huidige CBO-R en diverse verwijscriteria. Tevens werd geinventariseerd welke definitie van "failure to thrive" werd gehanteerd. Op basis van deze inventarisatie en aanvullend onderzoek naar de effectiviteit van verschillende verwijscriteria, is inmiddels een nieuwe richtlijn opgesteld die kort wordt besproken.

Materiaal en methode

Begin December 2002 werden vragenlijsten gestuurd aan 365 huisartsen in de regio Zuid-Holland Noord, een regio met zowel plattelands als stedelijke gemeenten, waarin artsen qua geslacht en leeftijdsverdeling overeen komen met alle ingeschreven huisartsen uit geheel Nederland.[12] Aansluitend werd voorafgaande aan het symposium "te klein, te lang, te dun, te dik" op 12 december 2002 bij TNO Preventie en Gezondheid in Leiden enquêtes verstuurd aan de verschillende Thuiszorgorganisaties (kinderen 0-4 jaar) en GGD'en (kinderen 4-19 jaar), bestemd voor in totaal 460 artsen JGZ verspreid over geheel Nederland.

De enquête bestond uit 4 onderdelen. In het eerste onderdeel werden algemene gegevens van de artsen verzameld met betrekking tot het aantal jaren werkervaring, de functie, het geslacht en de leeftijd. In het tweede onderdeel werd gevraagd naar presentatie, diagnostiek en verwijzing van kinderen met kleine lengte in de praktijk. In het derde onderdeel werd gevraagd naar richtlijnen voor kleine lichaamslengte (m.n. CBO-consensus 'Diagnostiek kleine lichaamslengte bij kinderen'). De artsen JGZ werden daarbij extra naar hun mening gevraagd over de 8 verschillende verwijscriteria van de CBO-consensus (tabel 1) [4,10]

Tabel 1 Verwijscriteria volgens de CBO-richtlijn "Diagnostiek kleine lichaamslengte bij kinderen" uit 1996. [10]

Omschrijving regel		Criteria	*Regel nr.*
Extreem kleine lengte		lengte SDS* < -2,5	1.
Klinische symptomen		lengte SDS < -1,3 en (dysmorfie of disproportie)	2.
Intra-uteriene groeivertraging zonder inhaalgroei		IUGR en lengte SDS < -1,88 na de leeftijd van 2 jaar	3.
Lengte beneden de target range†	♂: < 10 jr en > 13,4 jr; ♀: < 9 jr en > 12,3 jr	Lengte SDS < -1,3 en Lengte SDS-THSDS‡ < -1,3	4.
	♂: 10 – 13,4 jr; ♀: 9 – 12,3 jr	Lengte SDS < -1,3 en Lengte SDS-THSDS < -1,3 en puberteitskenmerken ■	5.
Afbuiging	♂: < 10 jr en > 13,4 jr; ♀: < 9 jr en > 12,3 jr	Delta lengte SDS<-0,25 per jaar of delta lengte SDS <-1SDS over een langere periode	6.
	♂: 10 – 13,4 jr; ♀: 9 – 12,3 jr	Delta lengte SDS<-0,25 per jaar of delta lengte SDS <-1 over een langere periode en puberteitskenmerken ■	7.
Psychogene kleine gestalte		Emotionele deprivatie	8.

* Lengte SDS (lengte standaarddeviatiescore) = [lengte (in cm) – gemiddelde lengte voor leeftijd en geslacht]/ SD voor leeftijd en geslacht

‡ TH-SDS: TH (Target height) zoon/dochter (in cm) = [(vaderlengte + moederlengte +/- 13)/2] + 4,5) TH-SDS zoon/dochter = (TH – P50 volwassen man/vrouw)/SD volwassen man/vrouw)

† Target range = TH ±1,3 SD (ofwel ongeveer 9 cm boven of onder de TH)

IUGR= Intrauteriene Groei Retardatie

■ Puberteitskenmerken: ♂: Pubesbeharing >= Tannerstadium 2 of Testisvolume >= 4 ml; ♀: borstontwikkeling >= Tannerstadium 2.

In het vierde onderdeel van de enquête werd ingegaan op de definitie van failure to thrive bij kinderen jonger dan 3 jaar. Voor de definitie van failure to thrive kon uit de volgende 4 criteria worden gekozen (combinaties waren ook mogelijk): afbuigende lengte naar leeftijd, afbuigend gewicht naar lengte, afbuigend gewicht naar leeftijd en vertraagde psychomotore ontwikkeling. Eveneens werd gevraagd naar het beleid bij "failure to thrive" in de praktijk.

De enquêtes werden geanalyseerd met behulp van SPSS (11.0). De frequenties van vergelijkbare vragen in de enquêtes van de artsen JGZ en huisartsen werden getoetst op statistische significantie $p < 0,05$ (chi kwadraat toets).

Resultaten

Respons

In totaal hebben 216 van de 365 aangeschreven huisartsen de vragenlijst geretourneerd. Door 9 niet-praktiserende huisartsen werd de vragenlijst leeg teruggestuurd (2%). Er bleven 207 bruikbare vragenlijsten over voor analyse (57%). Daarnaast werd de enquête door 152 van de 460 artsen JGZ ingevuld en teruggestuurd (33%). Algemene gegevens van de respondenten zijn weergegeven in tabel 2.

Tabel 2 Algemene gegevens van de huisartsen (n=207) en artsen JGZ (n=152)

		Huisartsen n (%)	Artsen JGZ n (%)
geslacht	man	150 (72)	17 (11)
leeftijd	<30 jaar	0 (0)	5 (3)
	30-39 jaar	31 (15)	28 (18)
	40-50 jaar	86 (42)	74 (49)
	>50 jaar	89 (43)	45 (30)
aantal jaren werkzaam	<5 jaar	22 (11)	21 (14)
	5-9 jaar	24 (12)	17 (11)
	10-20 jaar	72 (35)	64 (42)
	>20 jaar	89 (43)	49 (32)
vakgebied	JGZ(0-4jr)		79 (52)
	JGZ(4-19jr)		73 (48)
ander specialisme	JGZ(0-19jr)	7 (3)	
	Anders*	11 (5)	

* huisartsen werkzaam binnen ander specialisme: arts JGZ, arts voor verstandelijk gehandicapten, militair-, offshore-, palliatief-, tropen- of manueel arts, onderzoeker of medisch adviseur

Diagnostiek en/of verwijzing van kleine lengte bij kinderen in de praktijk

Vrijwel alle artsen, zowel huisartsen (92%) als artsen JGZ (91%) vermeldden dat afbuigende groei een belangrijke reden was om een kind met kleine lengte daadwerkelijk door te sturen (tabel 3). Door de meeste huisartsen werd vervolgens extreem kleine

lengte (82%) als belangrijke verwijsreden ervaren, gevolgd door lengte beneden de target range (64%). Onder de artsen JGZ daarentegen werd lengte beneden de target range (81%) belangrijker ervaren dan extreem kleine lengte (76%). Onrust bij ouders werd door huisartsen significant vaker als belangrijke reden voor verwijzing vermeld dan bij artsen JGZ (p< 0,01). De artsen JGZ spraken vaker dan huisartsen een extra controle af na een periode variërend van 2 weken tot 1 jaar, afhankelijk van de leeftijd van het kind en de ernst van de situatie. In vergelijking met de huisartsen gaven artsen JGZ vaker andere redenen, zoals disproportie, dysmorfe kenmerken, uitblijvende inhaalgroei na de leeftijd van 2 jaar of een afwijkend puberteitsstadium, aan als reden voor verwijzing (p=0,01). Bijna een kwart van de huisartsen verwees automatisch door naar de specialist als een kind met een groeistoornis verwezen werd door een arts JGZ. De overige huisartsen (76%) gaf aan dat zij eerst zelf nader onderzoek wilden doen, door bijvoorbeeld de groeicurve op te vragen, de familieanamnese uit te vragen, lichamelijk onderzoek te verrichten, laboratoriumonderzoek te doen of een handfoto aan te vragen.

Tabel 3 Belangrijke redenen voor verwijzing volgens huisarten (n=207) en artsen JGZ (n=152)*

	Huisartsen n (%)	Artsen JGZ n (%)
Onrust bij de ouders	106 (51)	36 (24)
Extreem kleine lengte	170 (82)	116 (76)
<P3 (= -1,88 SDS)	51 (25)	26 (17)
<-2,5 SDS (nieuwe curve)	29 (14)	85 (56)
Anders†	3 (1)	16 (11)
Afbuigende groei	190 (92)	139 (91)
Lengte beneden target range	133 (64)	124 (82)
Anders†	16 (8)	25 (16)

* meerdere redenen voor verwijzing mogelijk
† andere redenen voor verwijzing

CBO-richtlijn

De CBO-R was bekend bij 16% van de huisartsen. Zij waren op de hoogte gesteld via de publicatie in het NTvG (8%) en/of via een nascholingscursus (6%) en/of via een collega (3%) en/of via de CBO-website (3%). Slechts 5% van de huisartsen had de consensus in zijn bezit en 4% gebruikte deze in de praktijk. Het merendeel van de huisartsen maakte geen gebruik van de consensus, omdat zij er nog nooit van gehoord hadden (71%). Andere redenen waren dat men de consensus niet ter beschikking had of de incidentie van kleine lichaamslengte te laag was binnen hun patiëntenpopulatie. Het bestaan van goede richtlijnen voor verwijzing van kleine lichaamslengte binnen de huisartsenpraktijk werd wel belangrijk gevonden door 83% van de huisartsen. Door 4% werd aangegeven dat de verwijzing rechtstreeks vanuit de JGZ naar de specialist moest plaatsvinden en dat richtlijnen voor huisartsen niet nodig waren. Ook de grote meerderheid van de artsen JGZ vonden duidelijke richtlijnen van groot belang.

Bij het overgrote deel van de artsen JGZ (82%) was de CBO-consensus wel bekend. Zij waren veelal op de hoogte gesteld via een collega (36%) en/of via de publicatie in het NTvG (32%) en/of via een nascholingscursus (24%). 49% van de artsen JGZ rapporteerden dat zij de CBO-R in hun bezit hadden en 46% dat deze in de praktijk werd gebruikt. Bij 27% van de artsen JGZ bestond binnen de organisatie een protocol gebaseerd op de consensus en bij 7% een protocol los van de consensus. De meeste artsen JGZ, die geen gebruik van de consensus maakten, werkten volgens een eigen protocol of hadden geen beschikking over de consensus. Andere redenen voor geen gebruik van de consensus waren, dat men nog nooit van de consensus gehoord had, men het oneens was met de inhoud, of dat de consensus veel te uitgebreid of te ingewikkeld was.

Mening van artsen JGZ over verwijscriteria CBO-consensus

De artsen JGZ gaven hun mening over het belang van de 8 verwijscriteria van de CBO-R in de besluitvorming (tabel 4). Zij waren van mening dat klinische symptomen (disproportie/dysmorfie) (24%), extreem kleine lengte (21%) en prepubertair afbuigende groeicurve (19%) de belangrijkste drie verwijscriteria waren. De toepasbaarheid van de verwijscriteria werd als redelijk ervaren door 49% van de artsen JGZ, als moeizaam door 29% en gemakkelijk door 9%. Ongeveer de helft van de artsen JGZ (49%) gaf aan dat strikte toepassing van de verwijscriteria tot teveel verwijzingen zou leiden, 28% dat tot het juiste aantal verwijzingen zou leiden en 4% tot te weinig verwijzingen.

Tabel 4 Belang dat artsen JGZ (n=152) aan de verwijscriteria CBO-consensus hechten

	Belangrijkste verwijscriterium (%)
Extreem kleine lengte	21
Dysmorfe kenmerken en/of disproportie	24
IUGR zonder inhaalgroei	7
Lengte beneden target range prepubertair	9
Lengte beneden target range postpubertair	1
Afbuigende groeicurve prepubertair	19
Afbuigende groeicurve postpubertair	3
Psychogene kleine gestalte	1

"Failure to thrive"

De criteria afbuigend gewicht naar lengte en afbuigende lengte naar leeftijd werden het meest gebruikt door de huisartsen en de artsen JGZ voor de definitie van "failure to thrive" (tabel 5). Door 71% van de huisartsen en door 43% van de artsen JGZ werd aangegeven dat er behoefte was aan specifieke richtlijnen voor de verwijzing van kinderen met "failure to thrive".

Tabel 5 Definitie van "failure to thrive" volgens huisartsen (n=207) en artsen JGZ (n=152)*

	Huisartsen n (%)	Artsen JGZ n (%)
Afbuigende lengte naar leeftijd	88 (43)	72 (47)
Afbuigend gewicht naar lengte	95 (46)	72 (47)
Afbuigend gewicht naar leeftijd	67 (32)	30 (20)
Vertraagde psychomotorische ontwikkeling	53 (26)	30 (20)

* meerdere criteria konden worden aangegeven

Beschouwing

Voor een vroege opsporing van groeistoornissen is het van belang dat er naast een goed groei-monitoring systeem duidelijke verwijscriteria voor afwijkende groei en goede protocollen voor verdere diagnostiek bestaan. Uit enquêtes aan huisartsen en artsen JGZ naar het huidige beleid van groeimonitoring blijkt dat de CBO-richtlijn "Diagnostiek kleine lichaamslengte bij kinderen" bij weinig huisartsen bekend is en nog minder wordt toegepast. Binnen de jeugdgezondheidszorg is de CBO-R in het algemeen wel bekend (bij 82%) en wordt door circa 50% van de artsen JGZ gebruikt. Met name afbuigende groei leidt in de praktijk tot daadwerkelijke verwijzing, gevolgd door extreem kleine lengte en lengte beneden de target range. De meeste artsen JGZ zijn van mening dat de belangrijkste criteria van de CBO-R klinische symptomen, extreem kleine lengte en prepubertair afbuigende groeicurve zijn. Als definitie van "failure to thrive" worden door zowel huisartsen als JGZ artsen voornamelijk de criteria afbuigende lengte naar leeftijd en afbuigend gewicht naar lengte gehanteerd. Beide groepen artsen vinden het bestaan van goede evidence-based richtlijnen van belang voor zowel kleine lichaamslengte als "failure to thrive".

De helft van de artsen JGZ was van mening dat de verwijscriteria van de CBO-R, indien strikt toegepast, in de praktijk tot teveel verwijzingen leiden. Dit is in overeenstemming met bevindingen van Van Buuren et al.[11] Met name onder de leeftijd van 3 jaar zouden er veel te veel kinderen verwezen moeten worden (Hoofdstuk 6). Dit is waarschijnlijk te wijten aan het feit dat de ***lengte*** van kinderen tot de leeftijd van 2-3 jaar migreert in de richting van het genetisch bepaalde groeikanaal, waarin het kind uiteindelijk gewoonlijk zal blijven groeien (kanalisatie). Dit groeikanaal wordt beïnvloed door de geslachts-gecorrigeerde gemiddelde lengte van de ouders, die kan worden uitgedrukt als "target height".[13] Zowel huisartsen als artsen JGZ noemen een vertraagde groei van lengte of gewicht bij jonge kinderen vaak "failure to thrive".

Het aantal verschillende definities voor "failure to thrive" (gewicht-naar-leeftijd, gewicht-naar-lengte en lengte-naar-leeftijd) die in de enquete werden ingevuld reflecteert het gebrek aan overeenstemming welke groeiparameter het best gebruikt kan worden.[14] Naar onze mening dient de term "failure to thrive" te worden beperkt tot een groeipatroon waarbij door ondervoeding of ernstige aangeboren of verworven ziekten in eerste instantie de gewichtstoename stagneert, gewoonlijk pas later gevolgd door een afbuigende

lengtegroei (zoals bijvoorbeeld bij cystic fibrosis en coeliakie). Voor een vroege signalering van "failure to thrive" is dus de gewicht-naar-leeftijd curve het meest belangrijk. Uiteraard komt dat ook in het verloop van gewicht-naar-lengte tot uitdrukking, maar het ontbreken van referentiediagrammen daarvan voor de leeftijd van 0-15 maanden maakt deze parameter minder geschikt.

In een recente studie hebben wij laten zien dat de enige bruikbare verwijscriteria met betrekking tot de lengtegroei van kinderen onder de 3 jaar een extreem kleine lengte (< -3 SDS) of een herhaalde kleine lengte (<-2,5 SDS)zijn, alhoewel hiermee slechts weinig pathologie wordt opspoort (Hoofdstuk 12). Dit kan worden afgelezen in het bijgaande flowdiagram, waarin ook alle andere verwijscriteria zijn opgenomen (figuur 1). In onze studies over opsporing van coeliakie en cystic fibrosis vonden wij dat gewicht op jonge leeftijd een betere parameter is dan lengte (Hoofdstuk 9 en 10). Bij een afbuigend gewicht op jonge leeftijd, moet men dus op deze ziekten bedacht zijn. Het verdient aanbeveling dat in de toekomst verwijsregels worden opgesteld voor het beloop van het gewicht naar leeftijd bij zuigelingen en peuters, analoog aan de "thrive lines" die zijn gerapporteerd vanuit het Verenigd Koninkrijk.[15,16]

Zowel huisartsen als JGZ artsen geven aan dat afbuigende groei de belangrijkste reden is voor verwijzing en een groot percentage van de artsen JGZ beoordeelt dit als het belangrijkste criterium uit de CBO-R. Toch is het vooral dit verwijscriterium, dat tot een groot aantal onterechte verwijzingen leidt.[11] Bovendien hebben meerdere studies uitgewezen dat groeiafbuiging als zodanig een lage sensitiviteit heeft voor het opsporen van pathologische groeiafwijkingen.[7,17] Aangezien er toch meerdere voorbeelden te noemen zijn van kinderen met een groei-gerelateerde aandoening, zoals groeihormoondeficientie t.g.v. hersentumoren, juveniele hypothyroidie en Cushing syndroom, die initieel alleen ontdekt worden als men afbuiging in ogenschouw wordt genomen, blijft afbuiging een criterium voor de verwijzing van kinderen met vertraagde groei. Een afbuiging van meer dan 1 SD over een onbepaalde tijd in combinatie met een lengte SDS < -2 is daarbij het meest praktisch en geeft een redelijke sensitiviteit bij een acceptabel aantal onterecht verwijzingen. (Hoofdstuk 12)

Uit de enquête komt naar voren dat lengte beneden de target height een belangrijke reden is om een kind met kleine lengte daadwerkelijk door te verwijzen. Toch vindt men dit niet het belangrijkste criterium in de opsporing van pathologie. Dit is in tegenstelling met recent onderzoek waaruit blijkt dat criteria gebaseerd op target height juist effectief zijn om pathologie op te sporen,[17] (Hoofdstuk 7) ook al zijn ouderlengtes niet altijd betrouwbaar.[3] Een afstand tot target height van meer dan 2 SD in combinatie met een lengte SDS <-2 levert de meeste pathologie op en zorgt bovendien voor een acceptabel aantal onterecht verwezen kinderen. (Hoofdstuk 12).

Naast auxologische regels zijn uiteraard klinische symptomen en informatie uit de anamnese, zoals vermeld in de CBO-R, belangrijk voor de opsporing van pathologie bij kinderen met een kleine lengte. Zo kan bij een kind met kleine lengte na een te kleine geboortelengte voor de zwangerschapsduur (Small for Gestational Age (SGA), vaak ook

aangeduid als Intrauterine Growth Retardation (IUGR)) de diagnose “aanhoudende kleine lengte na SGA (of IUGR)“ worden gesteld In tegenstelling tot de CBO-R wordt in de nieuwe richtlijn gekozen voor een leeftijd van 3 jaar, waarna de aanhoudende kleine lengte nog aanwezig moet zijn, aangezien er tot deze leeftijd inhaalgroei kan optreden. (Hoofdstuk 12) Aan emotionele deprivatie moet gedacht worden als er aanwijzingen voor zijn in de anamnese.[18-20] Aangezien meerdere primaire groeistoornissen (syndromen) gepaard gaan met afwijkende lichaamsproporties, is het belangrijk om hierop te letten bij lichamelijk onderzoek. Om praktische redenen is gekozen om een lengte SDS<-2 als afkappunt te combineren met de klinische symptomen en informatie uit anamnese bij kinderen met kleine lengte.

Nieuwe richtlijnen vinden vaak moeizaam hun weg naar de praktijk.[21] Of en in welke mate een richtlijn wordt toegepast in de praktijk, is afhankelijk van de bekendheid, het gepresenteerde bewijs achter het aanbevolen handelen, de complexiteit van het gevraagde handelen, de vaardigheden of de veranderingen in de organisatie die ervoor nodig zijn en van vormgeving (helderheid, overzichtelijkheid).[22] Hierbij kunnen grote verschillen optreden tussen beroepsgroepen, zoals bleek in ons onderzoek: de CBO-R,was slechts bij een klein deel van de huisartsen bekend, terwijl de artsen JGZ er veel beter mee bekend waren. Mogelijke knelpunten bij de implementatie waren, dat de richtlijn slechts in geringe mate op wetenschappelijke gegevens (“evidence”) gebaseerd was en dat artsen moeite hadden met het toepassen van de verwijscriteria, zoals uit de enquêtes naar voren kwam. De richtlijn werd bovendien niet uitgegeven door een eigen wetenschappelijke vereniging, zoals het Nederlands Huisartsen Genootschap (NHG). De middelen die werden gebruikt om de consensus bekend te maken waren mogelijk niet voldoende om het implementeren van een richtlijn tot een succes te maken. Met de nieuwe richtlijn die gebaseerd is op evidence en is verwerkt in een handzaam flowdiagram (figuur 1), hopen wij een groter publiek te bereiken en streven wij naar een gerichte, intensieve systematische aanpak voor implementatie.

Conclusie

Uit enquêtes aan huisartsen en artsen JGZ naar het huidige beleid van groeimonitoring blijkt dat de CBO-richtlijn “diagnostiek kleine lichaamslengte bij kinderen” bij weinig huisartsen bekend is. Bovendien hebben ervaringen uit de praktijk en onderzoek uitgewezen dat de huidige criteria toe zijn aan vernieuwing. In de vernieuwde evidence-based richtlijn krijgt de afstand tot target height een prominentere rol, zijn er aangepaste afkappunten en worden er andere criteria gehanteerd voor kinderen onder de 3 jaar. De richtlijn is samengevat in een handzaam flowdiagram.

Dankbetuiging

Deze studie is ondersteund door een studie-beurs van Pfizer. Verder danken wij de afdeling Public health en Eerstelijnsgeneeskunde van het LUMC voor hun medewerking met het aanschrijven van de huisartsen en TNO Kwaliteit van Leven, sector 0-19, voor het aanschrijven van de Thuiszorgorganisaties en GGD’en.

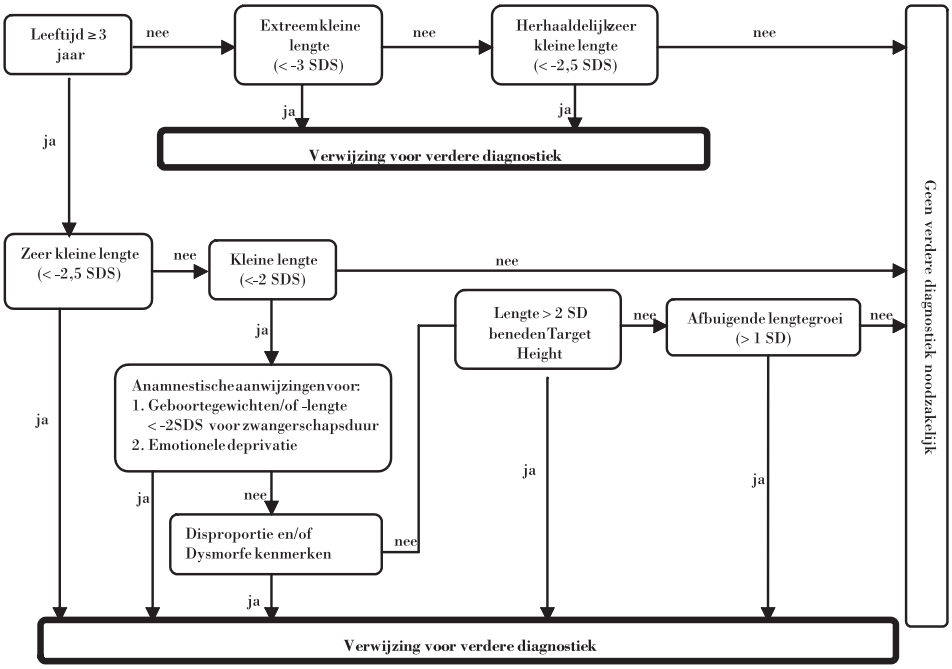


Fig 1. Flowdiagram van de nieuwe evidence based richtlijn voor verwijzing van kinderen met kleine lengte. (zie hoofdstuk 12)
SDS = standaard deviatie score
TSDS = Target Height standaard deviatie score

Literatuurlijst

1. Garner P, Panpanich R, Logan S. Is routine growth monitoring effective? A systematic review of trials. Arch Dis Child 2000;82:197-201.
2. Goldberg MJ, Yassir W, Sadeghi-Nejad A, Stanitski CL. Clinical analysis of short stature. J Pediatr Orthop 2002;22:690-6.
3. Hall DM. Growth monitoring. Arch Dis Child 2000;82:10-5.
4. de Muinck Keizer-Schrama SM. [Consensus 'diagnosis of short stature in children.' National Organization for Quality Assurance in Hospitals]. Ned Tijdschr Geneeskd 1998;142:2519-25.
5. Ahmed ML, Allen AD, Sharma A, Macfarlane JA, Dunger DB. Evaluation of a district growth screening programme: the Oxford Growth Study. Arch Dis Child 1993;69:361-5.
6. Frindik JP, Kemp SF, Kearns FS, Hale B. Growth screening. A positive medical experience. Clin Pediatr (Phila) 1992;31:497-500.
7. Voss LD, Mulligan J, Betts PR, Wilkin TJ. Poor growth in school entrants as an index of organic disease: the Wessex growth study. BMJ 1992;305:1400-2.
8. Jolley CD. Failure to thrive. Curr Probl Pediatr Adolesc Health Care 2003;33:183-206.
9. Wright CM. Identification and management of failure to thrive: a community perspective. Arch Dis Child 2000;82:5-9.
10. Consensus Diagnostiek kleine lichaamslengte bij kinderen. Centraal Begeleidingsorgaan voor de Intercollegiale Toetsing (CBO), 1996.
11. Van Buuren, S, Bonnemaijer-Kerckhoffs DJ, Grote FK, Wit JM, Verkerk PH. Many referrals under Dutch short stature guidelines. Arch Dis Child 2004;89:351-2.
12. Aantal huisartsen naar leeftijd en geslacht op 1 januari 2003 beroepenregistratie. 2003. NIVEL.
13. Gibson AT, Carney S, Cavazzoni E, Wales JK. Neonatal and post-natal growth. Horm Res 2000;53 Suppl 1:42-9.
14. Olsen EM, Petersen J, Skovgaard AM, Weile B, Jorgensen T, Wright CM. Failure to thrive: the prevalence and concurrence of anthropometric criteria in a general population. Arch Dis Child 2006.
15. Cole TJ. Conditional reference charts to assess weight gain in British infants. Arch Dis Child 1995;73:8-16.
16. Wright CM, Matthews JN, Waterston A, Aynsley-Green A. What is a normal rate of weight gain in infancy? Acta Paediatr 1994;83:351-6.
17. van Buuren S, van Dommelen P, Zandwijken GR, Grote FK, Wit JM, Verkerk PH. Towards evidence based referral criteria for growth monitoring. Arch Dis Child 2004;89:336-41.
18. Doeker B, Simic S, Hauffa BP, Andler W. [Psychosocially stunted growth masked as growth hormone deficiency]. Klin Padiatr 1999;211:394-8.
19. Gohlke BC, Khadilkar VV, Skuse D, Stanhope R. Recognition of children with psychosocial short stature: a spectrum of presentation. J Pediatr Endocrinol Metab 1998;11:509-17.
20. Gohlke BC, Frazer FL, Stanhope R. Growth hormone secretion and long-term growth data in children with psychosocial short stature treated by different changes in environment. J Pediatr Endocrinol Metab 2004;17:637-43.
21. Van Everdingen JJ. 'Een hoop gedoe, maar wel de moeite waard': oordelen van artsen over richtlijnen. Med Contact 2003; 58: 473-476.
22. Burgers JS, Grol RP, Zaat JO, Spies TH, van der Bij AK, Mokkink HG. Characteristics of effective clinical guidelines for general practice. Br J Gen Pract 2003;53:15-9.

Abstract

Introduction: For early identification of children with abnormal growth good growth monitoring systems as part of preventive child health programs are needed as well as well-defined and accurate referral criteria. In the Netherlands, a consensus meeting was held in 1996 to establish such referral criteria. This resulted in the Dutch Consensus Guideline (DCG). It is unknown to what extent this guideline is known and practiced in preventive health care (well-baby-clinic doctors and school doctors) and family practice. The aim of this study was to collect information on these elements, as well as on opinions about the value of the various referral criteria and about the definition of failure to thrive.

Method: In 2002 questionnaires were sent to 365 general practioners from the region South-Holland North and 460 Primary Health Care physicians from the whole country.

Results: Analysable questionnaires were returned by 207 general practioners (57%) and 152 Primary Health Care physicians (33%). Few general practioners (16%) knew the DCG and even less used it in their practice. In contrast, most Primary Health Care physicians knew the DCG and 46% indicated that they used it. 49% of Primary Health Care physicians thought that the referral-criteria, especially height deflection, would lead to too many referrals. They thoughtthat clinical signs and symptoms (e.g. disproportion or dysmorphic features) and extreme short stature were the most important referral criteria. Failure to thrive was mostly defined as deflection of weight to length.

Conclusion: The DCG is unknown to most general practitioners, but is used by approximately 50% of the primary health care physicians, although many of them think that strict application of the referral criteria would lead to too many referrals. In the meantime a new evidence-based guideline has been prepared, by which a high percentage of pathology can be detected at a referral percentage of about 1%.

Part C

Evaluation of existing guidelines

Chapter 6

Referral patterns of children with poor growth in primary health care.

F.K. Grote[1], W. Oostdijk[1], S.M.P.F. de Muinck Keizer-Schrama[2], F.W. Dekker[3], P. van Dommelen[4], S.van Buuren[4,5],A.M.Lodder-van der Kooij[6], P.H. Verkerk[7], J.M. Wit[1]

[1] Dept. of Paediatrics, Leiden University Medical Center, Leiden
[2] Dept. of Paediatrics, ErasmusMC - Sophia Children's Hospital, Rotterdam
[3] Dept of Clinical Epidemiology, Leiden University Medical Center, Leiden.
[4] Dept. of Statistics, TNO Quality of life, Leiden, The Netherlands
[5] Dept. of Methodology & Statistics, University of Utrecht, The Netherlands
[6] Dept. Child Health Care, Regional Public Health Service Hollands Midden, Leiden, The Netherlands
[7] Dept. of Child Health, TNO Quality of life, Leiden, The Netherlands

Submitted

Abstract

Background: To promote early diagnosis and treatment of short stature, consensus meetings were held in the mid nineteen nineties in the Netherlands and the UK. This resulted in guidelines for referral. In this study we evaluate the referral pattern of short stature in primary health care using these guidelines, comparing it with cut-off values mentioned by the WHO.

Methods: Three sets of referral rules were tested on the growth data of a random sample (n=400) of all children born between 01-01-1985 and 31-12-1988, attending school doctors between 1998 and 2000 in Leiden and Alphen aan den Rijn (the Netherlands): the screening criteria mentioned in the Dutch Consensus Guideline (DCG), those of the UK Consensus Guideline (UKCG) and the cut-off values mentioned in the WHO Global Database on Child growth and Malnutrition.

Results: Application of the DCG would lead to the referral of too many children (almost 80%). The largest part of the referrals is due to the deflection of height, followed by distance to target height and takes primarily place during the first 3 years. The deflection away from the parental height also leads to too many referrals. In contrast, the UKCG only leads to 0.3% referrals and the WHO-criteria to approximate 10%.

Conclusions: The current Dutch consensus guideline leads to too many referrals, mainly due to the deflection of length during the first 3 years of life. The UKCG leads to far less referrals, but may be relatively insensitive to detect clinically relevant growth disorders like Turner syndrome. New guidelines for growth monitoring are needed, which combine a low percentage of false positive results with a good sensitivity.

Introduction

Monitoring children's growth and development is fully integrated in preventive health care programmes throughout the world. In developing countries growth monitoring, implying regular height and weight measurements, is primarily aimed at identifying malnutrition to reduce mortality, whereas in industrialised countries it is mainly used to detect disorders associated with growth failure. The effect of routine growth monitoring in developing countries has recently been questioned.[1] Its efficacy and efficiency in developed countries has hardly been studied, and a recent international inquiry showed that there is considerable variability in growth monitoring practices worldwide.[2]

The primary aim of growth monitoring in industrialised countries is to detect growth disorders at an early age, thus the sensitivity (a statistical measure of how well the test correctly identifies a condition) of the screening procedure should be high at a young age. Poor growth can be caused by a great diversity of congenital or acquired conditions, some of which present with additional symptoms and signs. In other conditions, such as Turner syndrome, Growth Hormone Deficiency (GHD) and celiac disease, additional clinical features may be absent. Still, in such disorders early diagnosis and treatment is important, because early treatment has an optimal effect on growth in childhood, as well as on final height, expectedly resulting in a better quality of life. The second aim of growth monitoring is to keep the number of healthy children referred for further investigation at a minimum, meaning that the specificity should be very high.

In order to diminish the uncertainty among health workers in preventive child health care about the auxological criteria (auxology is the scientific study of growth) on which the decision to refer a child for further diagnosis should be based, and the resulting wide variation in the way growth monitoring is carried out, in 1996 a consensus meeting was held in the Netherlands on "Diagnosis of short stature in childhood". At this meeting representatives of general practitioners, well-baby clinic doctors, school doctors, paediatricians and paediatric endocrinologists came to a consensus guideline on referral criteria for aberrant growth.[3] Although the authors had aimed at promoting early diagnosis of aberrant growth as well as at preventing unnecessary referral and interventions, it was shown later that if this guideline would be followed, an unacceptable percentage of healthy children would be referred.[4] In the United Kingdom a similar consensus meeting on diagnosis of short stature was held, resulting in a guideline restricted to aberrant height at the age of 5 years, with assumingly a better specificity, but an unknown sensitivity to detect disorders timely.[5,6]

In the present study we wished to 1) study the performance of the Dutch Consensus Guideline (DCG) in a second sample with a wider age range; 2) count the actual referrals for short stature in that region; and 3) investigate the test characteristics of the UK Consensus Guideline (UKCG), WHO guideline and several other referral rules. This study was part of a larger program aimed at producing an evidence-based guideline on growth monitoring, in which we earlier investigated the best auxological criteria to detect Turner syndrome [7] Celiac Disease (van Dommelen et al, submitted), and Cystic Fibrosis (Grote et al, submitted).

Material and methods

We performed a retrospective observational study in primary health care. A random sample (n=400) of all children born between 01-01-1985 and 31-12-1988, attending school doctors between 1998 and 2000 in Leiden and Alphen aan den Rijn (located in the northern part of the province Zuid-Holland, at the western side of the Netherlands) was drawn from files of the regional public health organization (every 15th file) . The DCG was believed to be well known to the health personnel during the study period. There were no exclusion criteria.

The following baseline data and other observations, collected by the well-baby clinics and the school health services, were obtained from the medical records: date of birth; sex; height of parents; date and outcome of the different measurements of height and weight of the child since birth; presence of dysmorphic features or disproportion; birth weight and length, gestational age; and information about referral(s) to a specialist (date and reason). If ethnicity was not recorded, it was estimated based on the patient's first and family name according to an algorithm reported earlier.[8] If health records were incomplete, a short questionnaire was sent to all children in 2004 to obtain additional data on medical history, parental height and current height.

Three sets of referral rules were tested on the growth data: the auxological criteria mentioned in the DCG,[3] those of the UKCG[5] and the cut-off values mentioned in the WHO Global Database on Child growth and Malnutrition.[9] While the UKCG concentrates only on one auxological referral criterion (Height < -2.67 SDS (= 0.4th centile) at the age of 5 years[5]), the DCG[3] focuses on several referral criteria : Height in standard deviation score (SDS), clinical symptoms (indications of psycho-social growth retardation, dysmorfic or disproportionate features), Persistent short stature after born SGA (small for gestational age), HSDScor (the distance between height SDS and the target height SDS (the estimated final height SDS of a boy or a girl on the basis of their genetic potential)) and growth , deflection (a downward movement of height SDS) (table 1) Target height (TH) for a boy is [father's height + (mother' s height +13)]/ 2+4.5 cm and for a girl: [mother' s height + (father's height - 13)]/ 2+4.5 cm wherein 13 cm is the mean difference between final height of males and females, and 4.5 cm is the mean secular trend in one generation of 30 years. Target height can also be expressed as SDS (z-score), by taking the difference between TH and the mean final height of a young adult of the same sex, and then devide by the SD at that age. By correcting for secular trend the actual population reference diagrams can be used for calculating THSDS.

The WHO Global Database on Child growth and Malnutrition uses a cut-off point of -2 SD (≈ 2.3rd centle) to classify stunting (low height for age) and underweight at all ages.[9]

Because of the instability in growth pattern under the age of three years and the varying growth patterns in puberty caused by differences in pubertal timing, we decided to evaluate the guidelines in different age groups (0-3, 3-10 and 10-18 years), as well as over the whole age range. As it was hypothesized that in the age group 0-3 years a height

deflection in standard deviations scores (SDS) away from the target height SDS might be a good reason to refer, we decided to test this rule ($|\ HSDS_{x2} - TH\ SDS\ | > |\ HSDS_{x1} - TH\ SDS\ |$) for both a delta HSDS ($HSDSx_2$-$HSDSx_1$) of -0.5 or -1 with $x_2 > x_1$(see table 4).

Table 1. Seven auxological referral criteria taken from the Dutch Consensus Guideline.[3]

Description rule		Criteria	Rule nr.
Absolute height		HSDS* < -2.5	1
Clinical symptoms		HSDS* < -1.3 AND (dysmorphic features OR disproportions)	2
Persistent short stature after born SGA**		SGA** AND HSDS* < -1.88 after the age of 2 years	3
$HSDS_{cor}$†	♂: < 10 jr en > 13,4 jr; ♀: < 9 jr en > 12,3 jr	HSDS* < -1.3 AND HSDS-THSDS < -1.3	4
	Pubertal age ■: ♂: 10 – 13.4 yr; ♀: 9 – 12.3 yr	HSDS* < -1.3 AND HSDS-THSDS§ < -1.3 AND pubertal signs (♂: genit >= Tanner stage 2 OR testis volume >= 4 ml; ♀: breast>= Tanner stage 2)	5
	♂: < 10 yr and > 13.4 yr; ♀: < 9 yr and > 12.3 yr	T2 – T1 > 1(1) (SDS1 – SDS2)/(T2-T1) < -0.25	6a
		T2 – T1 > 1 (SDS1 – SDS2)< -1	6b
Deflection‡	Pubertal age ■: ♂: 10 – 13.4 yr; ♀: 9 – 12.3 yr	T2 – T1 > 1(1) (SDS1 – SDS2)/(T2-T1) < -0.25 With pubertal signs	7a
		T2 – T1 > 1 (SDS1 – SDS2)< -1 With pubertal signs	7b

* HSDS= Height Standard Deviation Score

** SGA = Small for Gestational Age

§ THSDS= Target Height Standard Deviation Score

† $HSDS_{cor}$= HSDS corrected for parental height

‡ Deflection: Deflection is divided into a slow deflection (7a) and a quick deflection (7b) The slow deflection represents a downward movement of HSDS (HSDS2-HSDS1) over time (T2-T1), while the quick deflection is more a downward movement of HSDS over a longer period (not specified). In the categories 3-10 and 10-18, T1 >= 3 years, in the other categories T1> 0.

■ Pubertal age: When a child does not show any pubertal signs (♂: genit >= Tanner stage 2 OR testis volume >= 4 ml; ♀: breast>= Tanner stage 2) at this age referral is not necessary.

All data were analysed in SPSS version 11 and S-plus version 7.0. Length (up to 2 years), height (from 2 years), weight and target height were expressed as standard deviation score (SDS), using the Dutch reference growth data for children of Dutch origin, children of Turkish origin, and children originating from Morocco, respectively.[10-12] HSDS (Height SDS) is the distance between the individual's height and the population's mean height for

age and sex, devided by the standard deviation in the population for the same age and sex: [individual's height - mean population height for the same age and sex]/ population's SD for the same age and sex.

A SDS can easily be converted to a percentile, using standard statistical tables. For growth SD lines are more suitable then percentiles a. o. because of the equidistance between the SDS lines. In the Dutch growth charts[10] 2.5, -2, -1, 0, +1, +2 and + 2.5 lines are drawn, corresponding withP 0.6, P 2.3, P 16, P 50, P 84, P 97.7, P 99.4.

In preterm infants (gestational age < 37 weeks) length and weight SDS were corrected for gestational age. The intrauterine growth curve of the Swedish reference population[13] was used to express SDS till the age corresponding with 40 weeks of gestation. Between 40 and 42 weeks an interpolation between the growth curve of the Swedish reference population and that of the Dutch reference population was used. From 42 weeks of gestation till the age of 2 years, SDS was calculated for age corrected for gestation, using the Dutch reference growth data.

Parental height was missing in 53% of the children. We imputed these data under the assumption that the data were missing at random using Multivariate Imputation by Chained Equations (MICE).[14] The method created multivariate imputations by applying sequential linear regressions, where each incomplete variable was imputed conditionally on all variables in an iterative fashion. The imputation model consisted of the height SDS, weight SDS, Body-mass-index SDS, age, gender, the height of the other parent, ethnicity, yes or no use of medication influencing growth and place of attendance of the school doctors. The number of iterations was set to 15. Predictive mean matching was used to create parental height imputations. The imputation method includes parameter uncertainty, preserves the multivariate structure in the data and has good coverage properties.[15]

Small for gestational age (SGA) was defined as a birth weight and/ or length SDS< -2, comparing the present birth weights and lengths with gestational age-matched reference values from Niklasson et al.[13]

The study was approved by the Medical Ethical Committee of the Leiden University Medical Center and the Regional Public Health Service Hollands Midden.

Results

From the initial 400 children, 8 were excluded from the analyses because of incomplete growth data (for example no date of measurement). The general characteristics of the remaining 392 children are illustrated in table 2.

Tabel 3 shows the percentage of referrals in different age groups, which would have taken place if the Dutch consensus guideline (DCG) had been followed. Almost 80% of the sample would have been referred at some age between 0-18 years. Most referrals would take place

in the first 3 years (73.9%); The first height deflection referral rule (refer if length or height SDS changes more than 0.25 SD per year) would lead to most referrals (69%), followed by the second referral rule (refer if height SDS decreases by more than 1 SD) leading to another unacceptably high number of referrals (34%). Also the referral rule based on distance to target height SDS (refer if the child's height SDS shows a distance of more than 1.3 SD to target height SDS) would lead to a high percentage of referrals (15%). In the other age groups, the deflection rules would also be responsible for the majority of referrals.

Table 2. General characteristics of the study population

		Total population n = 392
Gender Male: n (%)		199 (50.8)
Ethnicity: n (%)	Dutch/European	334 (85.2)
	Turkish	7 (1.8)
	Moroccan	7 (1.8)
	Others:	44 (11.3)
Dysmorphic features: n (%)		16 (4.1)
Disproportion: n (%)		18 (4.6)
Target height SDS: Mean (SD)		0.18 (0.86)
Number of measurements (median)		10

Table 3. Estimated percentage of referrals according to the DCG

Description rule		*Rule nr.*	*% referrals 0-3 years N=330*	*% referrals 3-10 year N=361*	*% referrals 10-18 year N=345*	*% referrals 0-18years N=392*
Absolute height		1	1.8	0.8	1.4	3.3
Clinical symptoms		2	2.4	1.1	0.9	2.3
Persistent short stature after born SGA		3	0.0	0.0	0.0	0.0
$HSDS_{cor}$	♂: < 10 yr and > 13.4 yr; ♀: < 9 yr and > 12.3 yr	4	15.2	5.0	4.9	16.8
	♂: 10 – 13.4 yr; ♀: 9 – 12.3 yr	5	na	na	2.0 (2.0)*	2.0 (2.0)*
Deflection*	♂: < 10 yr and > 13.4 yr;	6a	69.4	21.6	9.3	73.5
	♀: < 9 yr and > 12.3 yr	6b	34.2	6.4	15.4	50.5
	♂: 10 – 13.4 yr;	7a	n.a.	n.a.	3.8 (1.4)*	4.6 (1.3)*
	♀: 9 – 12.3 yr	7b	n.a.	n.a.	22.6 (5.5)*	23.0 (4.8)*
Total percentage of referrals			73.9	26.0	39.1	79.6

* Data on stage of puberty were frequently missing. Therefore we assumed children with missing data were in puberty at the reference pubertal age-period. The number between brackets however represents the exact percentage of referrals in the pubertal age-period, without the assumption.

† n.a means not applicable

Table 4 shows the percentage of referrals that had occurred if the UKCG or the WHO criteria would have been used. According to the UKCG only one child (0.3%) would have been referred, while 9-10% would have been referred according to the WHO. Like the DCG the criteria of the WHO are mainly met under the age of three years.

Tabel 4. Estimated percentage of referrals according to the UKCG, the WHO guideline, and a parental height deflection rule

Description rule	Criteria	% referrals 0-3 years	% referrals 3-10 years	% referrals 10-18 years	% referrals 0-18years
UKCG	HSDS§ < -2.67 at age 5	n.a.	0.3	n.a	0.3
Low height for age (HSDS) ‡	HSDS§ < - 2	7.3	3.6	3.2	9.2
Low weight for age (WSDS) ‡	WSDS** < -2	10.0	2.5	3.2	10.5
Parental height deflection rule (0.5 SDS)	(HSDS2§ – HSDS1§) < -0.5, AND | HSDS2§ – TH SDS† | > | HSDS1§ – TH SDS† |	58.8	18.3	28.7	62.0
Parental height deflection rule (1 SDS)	(HSDS2§ – HSDS1§) < -1, AND | HSDS2§ – TH SDS† | > | HSDS1 – TH SDS† |	30.0	3.9	11.6	41.1

* UKCG = UK consensus guideline
§ HSDS= Height Standard Deviation Score
** WSDS= Weight Standard deviation score
† THSDS= Target Height Standard Deviation Score
‡ Rules described by WHO Global database on Child growth and malnutrition.

Theoretically one could imagine that a deflection away from the target height SDS in the first 2-3 years of life could be a suitable referral rule. In this sample, however, these adapted deflection rules would lead to high percentages of referrals (table 4).

With respect to the actual number of referrals, 34 children were subject to extra visits to the well-baby clinic because of growth-retardation. Only one child was actually referred to a specialised centre for further diagnosis. This child had a deflection of length before the age of 1 year and was diagnosed with transient growth retardation due to dyspepsia.

Discussion

We have confirmed the results of an earlier report in showing that implementing the Dutch consensus guideline for growth monitoring would lead to a high number of referrals, particularly before the age of 3 years. The actual number of referrals that was found in practice was just 1 out of 392 cases, so evidently the proposed guidelines were (fortunately) not properly followed. The specificity of the UK Consensus guideline (limited to one cut-off criterion, i.e. a height<-2.66 SDS ($\approx 0.4^{th}$ centile) at 5 years of age) would be better. On the other hand in an earlier paper we showed that the sensitivity of a height SDS cut-off to detect Turner syndrome is lower than that of a cut-off of the distance to

target height.[7] The WHO guideline, as well as two additional criteria with respect to height deflection away from the target height, would lead to too many referrals.

To estimate the percentage of pathological conditions presenting with short stature and/or growth failure without further clinical symptoms or signs, one can refer to several studies. In the Wessex growth study 180 children (1.25 %) in whom height on screening at school entry was on or below the 3rd percentile, were further examined.[16] Among this group 8 children (4.4%) were newly identified as having an organic disease. Ahmed et al reported in the Oxford study 7 newly recognized children (3.0%) with organic disease among the 260 children (1.3% of all screened children) whose height was below 2 SDS, measured at the ages of 3 and 4.5 years.[17] From the 555 children (0.5% of the screened population) who were examined for their poor growth (height below the 3rd percentile and/or growth rate below 5 cm/yr) in the Utah growth study 25 children (4.5%) were newly discovered as having GHD, hypothyroidism or Turner syndrome, and another 53 children (9.5%) had other medical reasons.[18] So, one can conclude that out of the (by definition) 2.3% short children (height <-2 SDS) in the population, 3-14% have a condition that warrants additional diagnostic tests, corresponding with 0.07 to 0.32% of the population. This low prevalence of pathology in children presenting with short stature implies that the specificity of the referral rules should be high, in the order of 98-99%, in order to keep the number of unnecessary referrals acceptable.

This study confirmed and expanded the earlier analysis by Van Buuren et al of the consequences of following the DCG.[4] In the earlier study the overall referral percentage until the age of 10 years was 38% (without deflection 0-3 years) or over 84% (including deflection 0-3 years). Even in de 38% most referrals would have occurred due to deflection. The present study found that almost 80% would have been referred in the age range 0-18 years.

Short stature has many causes, and the relative prevalence of these causes varies considerably in the world. This implies that the objectives of growth monitoring programs heavily depend on the setting. In developing countries the principal aim of growth monitoring is to detect malnutrition. Given this aim the WHO promotes growth monitoring and research to improve the monitoring procedures.[9,19] In industrialized countries, however, where there is less malnutrition, growth monitoring is aimed at detecting disorders associated with growth retardation without other clinical symptoms or signs, of which Turner syndrome, Growth Hormone deficiency and Celiac Disease are most prevalent. We have now shown that, given the low prevalence of such pathology (0.07 to 0.32% of the population), also the WHO-criteria would lead to too many referrals.

Most experienced clinicians use three archetypal criteria in the analysis of growth: the distance of the child's height to the mean of the population (either expressed as centiles or as SD scores), the distance between height SDS and the target height (the gender-corrected mid-parental height) and growth retardation (i.e. deflection of the growth curve across the SD-lines or centiles). Our study confirmed that Height SDS deflection over time ("slow deflection") leads to far too many referrals in our study. In earlier studies we have

shown that the height SDS deflection is a poor predictor of congenital growth hormone deficiency[20] and Turner syndrome.[7] On the other hand clinical experience teaches that crossing the SD-lines (or centiles) can be the first sign of an acquired GH deficiency (e.g. caused by a brain tumor), Cushing syndrome or hypothyroidism. The distance to target height is the best decision rule to detect children with Turner syndrome, one of the main causes of short stature,[7] but it was left out of the UKCG because of practical and theoretical problems. For an optimally efficacious and efficient growth monitoring algorithm, a combination of the three main criteria should be sought.

In conclusion, we have confirmed that the current Dutch consensus guideline would lead to too many referrals, mainly due to the deflection of length during the first 3 years of life. The UKCG leads to far less referrals, but may be relatively insensitive to detect Turner syndrome, and probably other clinically relevant growth disorders. New guidelines for growth monitoring are needed, which combine a low percentage of false positive results with a good sensitivity. To achieve these goals more studies are needed on the diagnostic value and cost-effectiveness of auxological screening for the diagnosis of various diseases.

Competing interests

There are no economical or other competing interest among the authors.

Authors' contributions

All authors contributed to the planning, the design of the study and read and approved the final manuscript. FKG and AL were responsible for the collection of the data. All the other authors participated together with FKG in the analytical part. FKG wrote the manuscript.

Acknowledgements

We acknowledge Helene Trip, Tatiana Zwaan, two medical students and Bernadette Verbeek, social nurse at the GGD Leiden/Alphen for their great contribution to the study. The study was supported by an educational grant from Pfizer.

References

1. Garner P, Panpanich R, Logan S: Is routine growth monitoring effective? A systematic review of trials. Arch Dis Child 2000, 82:197-201.
2. Grote F.K., Oostdijk W, de Muinck Keizer-Schrama SMPF, Dekker FW, Verkerk PH, Wit JM: Growth monitoring and diagnostic work-up of short stature: an international inventorisation. J Pediatr Endocrinol Metab 2005, 18:1031-1038.
3. de Muinck Keizer-Schrama SM: [Consensus 'diagnosis of short stature in children.' National Organization for Quality Assurance in Hospitals]. Ned Tijdschr Geneeskd 1998, 142:2519-2525.
4. Van Buuren, S, Bonnemaijer-Kerckhoffs DJ, Grote FK, Wit JM, Verkerk PH: Many referrals under Dutch short stature guidelines. Arch Dis Child 2004, 89:351-352.
5. Hall DM: Growth monitoring. Arch Dis Child 2000, 82:10-15.
6. Hindmarsh PC: Monitoring children's growth. Abnormal growth should also be defined by the crossing of height centiles. BMJ 1996, 312:122.
7. van Buuren S, van Dommelen P, Zandwijken GR, Grote FK, Wit JM, Verkerk PH: Towards evidence based referral criteria for growth monitoring. Arch Dis Child 2004, 89:336-341.
8. Bouwmeester-Landweer MBR: Early home visitation in families at risk for maltreatment. PhD Thesis. Leiden University Medical Center; 2006.
9. An evaluation of infant growth: the use and interpretation of anthropometry in infants. WHO Working Group on Infant Growth. Bull World Health Organ 1995, 73:165-174.
10. Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E, Roede MJ, Verloove-Vanhorick SP, Wit JM: Continuing positive secular growth change in The Netherlands 1955-1997. Pediatr Res 2000, 47:316-323.
11. Fredriks AM, van Buuren S, Jeurissen SE, Dekker FW, Verloove-Vanhorick SP, Wit JM: Height, weight, body mass index and pubertal development reference values for children of Turkish origin in the Netherlands. Eur J Pediatr 2003, 162:788-793.
12. Fredriks AM, van Buuren S, Jeurissen SE, Dekker FW, Verloove-Vanhorick SP, Wit JM: Height, weight, body mass index and pubertal development references for children of Moroccan origin in The Netherlands. Acta Paediatr 2004, 93:817-824.
13. Niklasson A, Ericson A, Fryer JG, Karlberg J, Lawrence C, Karlberg P: An update of the Swedish reference standards for weight, length and head circumference at birth for given gestational age (1977-1981). Acta Paediatr Scand 1991, 80:756-762.
14. Van Buuren S, Boshuizen HC, Knook DL: Multiple imputation of missing blood pressure covariates in survival analysis. Stat Med 1999, 18:681-694.
15. Van Buuren S, Brand JPL, Groothuis-Oudshoorn CGM, Rubin DB: Fully conditional specification in multivariate imputation. Journal of Statistical Computation and Simulation 2006, 76:1049-1064.
16. Voss LD, Mulligan J, Betts PR, Wilkin TJ: Poor growth in school entrants as an index of organic disease: the Wessex growth study. BMJ 1992, 305:1400-1402.
17. Ahmed ML, Allen AD, Sharma A, Macfarlane JA, Dunger DB: Evaluation of a district growth screening programme: the Oxford Growth Study. Arch Dis Child 1993, 69:361-365.
18. Lindsay R, Feldkamp M, Harris D, Robertson J, Rallison M: Utah Growth Study: growth standards and the prevalence of growth hormone deficiency. J Pediatr 1994, 125:29-35.
19. Use and interpretation of anthropometric indicators of nutritional status. WHO Working Group. Bull World Health Organ 1986, 64:929-941.
20. Van den Broeck J, Hokken-Koelega A, Wit J: Validity of height velocity as a diagnostic criterion for idiopathic growth hormone deficiency and Turner syndrome. Horm Res 1999, 51:68-73.

Chapter 7

The diagnostic work up of growth failure in secondary health care; An evaluation of consensus guidelines.

F.K. Grote[1], W. Oostdijk[1], S.M.P.F. de Muinck Keizer-Schrama[2], P. van Dommelen[3], S.van Buuren[3,4], F.W. Dekker[5] A.G. Ketel[6], H.A. Moll[2], J.M. Wit[1]

[1] Dept. of Paediatrics, Leiden University Medical Center, Leiden, The Netherlands
[2] Dept. of Paediatrics, ErasmusMC - Sophia Children's Hospital, Rotterdam, The Netherlands
[3] Dept. of Statistics, TNO Quality of life, Leiden, The Netherlands
[4] Dept. of Methodology & Statistics, University of Utrecht, The Netherlands
[5] Dept of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands
[6] Dept. of Paediatrics, Spaarne Hospital, Haarlem, The Netherlands

Submitted

Abstract

Background

As abnormal growth might be the first manifestation of undetected diseases, it is important to have accurate referral criteria and a proper diagnostic work-up. In the present paper we assess how many children are correctly referred to secondary health care according to existing consensus guidelines, evaluate the diagnostic work-up in secondary health care and study the frequency of underlying medical disorders.

Methods:

Data on growth and additional diagnostic procedures were collected from medical records of new patients referred for short stature to the outpatient clinics of the general paediatric departments of two hospitals (Erasmus MC - Sophia Children's Hospital, Rotterdam and Spaarne Hospital, Haarlem) between January 1998 and December 2002. As the Dutch Consensus Guideline (DCG) is the only guideline addressing referral criteria as well as diagnostic work-up, the analyses were based on its seven auxological referral criteria to determine whether children were correctly referred or not and on all elements of the diagnostic work up.

Results

Of children older than 3 years 76% was correctly referred (CR). 74-88% of these children were short corrected for parental height, 40-61% had a height SDS <-2.5 and 21% showed height deflection (Δ HSDS < -0.25/ yr or Δ HSDS < -1). In none of the children a complete detailed routine diagnostic work up was performed and in more than 30% no routine laboratory examination was done at all. Pathologic causes of short stature were found in 27 children (5%).

Conclusions

Although the DCG was poorly put into practice, it detects at least 5 % pathologic causes of growth failure in children referred for short stature. New guidelines for referral are required with a better sensitivity and specificity, wherein distance to target height should get more attention. The general diagnostic work up for short stature should include testing for celiac disease in all children and for Turner syndrome in girls.

Introduction

Short stature or a poor growth rate can be the first manifestation of undetected diseases in children. Poor growth can be caused by a great diversity of congenital or acquired conditions, such as Turner syndrome, growth hormone deficiency (GHD) or celiac disease, for all of which early diagnosis and treatment are important. When treated at an early stage the effect on adult height is optimal and the quality of life will presumably improve. The possibility for proper treatment depends both on the early identification of these children in the community and on the accurate diagnostic work-up in the hospital afterwards.

For an early identification of children with abnormal growth it is important to have accurate and well-defined referral criteria, in combination with a good growth monitoring system. In a previous study we performed an inquiry about advised referral criteria among pediatric endocrinologists in Europe as well as in most industrialized countries around the world.[1] We concluded that there was little consensus. Moreover the literature provides only few guidelines for the analysis of short stature and these are based on consensus meetings rather than on experimental evidence.[2, 3] In experimental studies on growth monitoring various arbitrary referral criteria were used.[4-6]

There is not only scarce evidence on referral criteria, but also on the diagnostic work-up in secondary health care for children with poor growth. Although there are a number of consensus guidelines on the diagnosis of GHD[7-11] and some articles on the analysis of short stature in general,[12-19] the articles are primarily expert-based reviews on how to deal with short stature rather than experimental studies on the outcome of laboratory investigations. Only one study evaluated the outcome of the analysis of short stature in a growth clinic, but in this study no standard protocol for the diagnostic work-up was used [20]. The only guideline reported so far that addresses the diagnostic work-up for short stature is the Dutch Consensus Guideline (DCG).[3]

The DCG was prepared in 1996, containing a section on referral criteria and a section on diagnostic procedures. Its implementation consisted of a single publication in a Dutch medical journal, a book and a couple of courses.[3, 21] It is not known how many doctors are aware of the guideline and whether or not it changed medical practices.

In the present paper we wish to assess how many children were correctly referred to secondary health care according to the DCG, to evaluate the diagnostic work-up in secondary health care and to study the frequency of underlying medical disorders.

Material and methods

We performed a retrospective observational study in the outpatient clinics of the general paediatric departments of both a university hospital (Erasmus MC - Sophia Children's Hospital, Rotterdam) and a general hospital (Spaarne Hospital, Haarlem). In both clinics the DCG was well known and used during the study period. All new patients referred for short stature between January 1998 and December 2002 were identified retrospectively.

The children in whom the cause of growth retardation was already known were excluded. A previously described problem-orientated patient classification system[22] was used to identify the children in the university hospital. In the general hospital the children were identified by a local registration system, consisting of a hand written registry of reasons for referral of all new patients.

The following information was obtained from the medical records: date of birth, date of first presentation at the outpatient clinic, gender, ethnicity, perinatal information (birth weight, length, gestation, maternal obstetric problems etc.), family history, clinical presentation (symptoms and signs), information on puberty, longitudinal height measurements until the first presentation at the outpatient clinic, laboratory test results, radiological and pathological evaluations and final diagnosis. If the ethnicity was not recorded, it was assessed based on the patient's first and family name according to an algorithm reported earlier.[23]

The DCG addresses five stages in the analysis of short stature. First of all it focuses on seven auxological referral criteria (table 1). When a child is referred according to these criteria, the paediatrician is subsequently advised to follow four diagnostic steps:

- The patient's history, the physical examination, growth data and a hand radiograph should be collected to determine signs or symptoms that may indicate a specific disease.
- In the presence of specific clinical clues, appropriate further specific investigations are done. When there are no signs or symptoms leading to the suspicion of a certain disease, a list of laboratory investigations is advised for screening of several pathological conditions (table 2).
- Dependent on the abnormalities in the screening laboratory investigations further, more specific tests can be performed to establish the final diagnosis.
- If there is no indication of a certain disease after the preceding procedures the three following tests should still be considered: chromosomal analysis for Turner syndrome in girls, a biopsy to prove or rule out celiac disease and the determination of zinc to investigate zinc-deficiency in children with failure to thrive.[24]

For the evaluation of the diagnostic work up in this project all stages were taken into account. The auxological criteria as mentioned in the DCG were used to determine whether the children were correctly referred to the outpatient clinic. Since children under the age of three years may not yet show a stable growth pattern but are still seeking their individual growth channel (expressed as percentile or standard deviation score (SDS) position), most rules (1, 3-7) were not strictly applicable to this age group. Therefore it was decided to analyse this group separately. For the analyses we allowed a child to meet several criteria at the same time. Although plasma FSH in girls is only of diagnostic value in girls younger than 2 and older than 9 years, we analysed all ages in girls for this test, since there is no such specific recommendation in the current consensus.

Table 1. Seven auxological referral criteria taken from the Dutch Consensus Guideline.[3]

Description rule		Criteria	Rule nr.
Absolute height		HSDS* < -2.5	1
Clinical symptoms		HSDS* < -1.3 AND (dysmorphic features OR disproportions)	2
Persistent short stature after born SGA**		SGA** AND HSDS* < -1.88 after the age of 2 years	3
Short for target height and population (HSDScorr)	♂: < 10 yr and > 13.4 yr; ♀: < 9 yr and > 12.3 yr	HSDS* < -1.3 AND HSDS-THSDS§ < -1.3	4
	Pubertal age‡: ♂: 10 – 13.4 yr; ♀: 9 – 12.3 yr	HSDS* < -1.3 AND HSDS-THSDS§ < -1.3 With pubertal signs	5
Height deflection†	♂: < 10 yr and > 13.4 yr; ♀: < 9 yr and > 12.3 yr	T2 – T1 > 1 (SDS1 – SDS2)/(T2-T1) < -0.25 OR (SDS1 – SDS2)< -1	6
	Pubertal age‡: ♂: 10 – 13.4 yr; ♀: 9 – 12.3 yr	T2 – T1 > 1 (SDS1 – SDS2)/(T2-T1) < -0.25 OR (SDS1 – SDS2)< -1 With pubertal signs	7

* HSDS= Height Standard Deviation Score (Height – mean height for the same age and sex / SD for the same age and sex)

**SGA = Small for gestational age

§ THSDS= Target Height Standard Deviation Score (Target height = (height of mother (+height of father +13) + 4.5) / 2)

† Height deflection: Height deflection is formulated as Delta HSDS<-0.25 per year OR a delta HSDS <-1SDS over a longer period (not specified).

‡ Pubertal age: When a child does not show any pubertal signs (♂: genit ≥ Tanner stage 2 OR testis volume ≥ 4 ml; ♀: breast>= Tanner stage 2) at this age referral is not necessary.

Table 2. Laboratory investigations in the diagnostic work up according the DCG

Laboratory investigations	In order to diagnose	Category
Blood		
Hb, Ht, Leukocytes, Cell indices, Leukocyte differentiation, ESR (Ferritin)	Anemia / infections (and celiac disease and cystic fibrosis)	I
ALAT, ASAT, y GT	Liver diseases	II
Albumin, Creatinine, Sodium, Potassium, Calcium, Phosphate, Alkaline phosphatase, acid-base equilibrium	Renal diseases	III
IgA-anti endomysium, IgA- antigliadin, Anti-tissue glutaminase*, Total IgA	Celiac disease	IV
TSH, FT4	Hypothyroidism	V
IGF-I	Growth hormone deficiency	VI
FSH**	Turner syndrome	VII
Urine		
pH, glucose, protein, blood and sedimentation	Renal diseases	VIII

*At the moment the consensus meeting took place, anti tissue glutaminase as a diagnostic tool for celiac disease was not yet introduced nation wide.
**Only in girls.

All data were analysed in SPSS version 11. Height SDS was calculated using the 1997 Dutch reference growth data.[25] Small for gestational age (SGA) was defined as a birth weight and/or length SDS< -2 for gestational age, compared to recent Swedish reference values.[26] Differences between the two hospitals were calculated using the chi-square test.

Results

Patients

Between January 1998 and December 2002, 742 children were referred to the two hospitals for short stature (university hospital: n = 467, general hospital: n = 275) (see fig 1). Two hundred children were excluded either because the cause of growth retardation was already known before referral, the medical records were missing or there was another reason for referral than short stature. Hence, 542 cases were suitable for analysis. Fifty-nine children were under the age of 3 years at time of referral and were analysed separately. According to referral criteria mentioned in the DCG 76.4% (77.1% in the university and 73.9% in the general hospital) of the children older than 3 years were correctly referred (CR). In 5.6% children (5.7% in the university and 5.2% in the general hospital) there was insufficient information to assess whether the referral met the criteria (not classifiable (NC)) and in 18.0% the children did not meet the referral criteria (not correctly referred, NCR) according to the DCG (17.1% in the university and 20.9% in the general hospital).

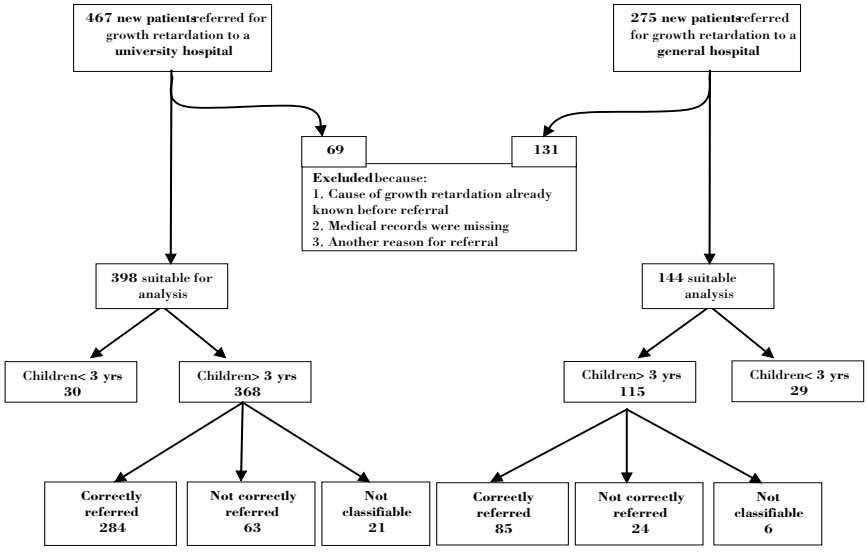


Fig. 1. Population description

Details of all patients are shown in table 3. The study groups were significantly different between the two hospitals for gender, ethnicity, height SDS (HSDS) at time of referral and target height.

Table 3. General characteristics of the study population in the university hospital (n=398) and the general hospital (n=144)

		University hospital	General hospital	Difference between 2 hospitals (p-value)
Gender Male: n (%)		219 (55%)	65 (45%)	0.04
Ethnicity N (%)	Dutch/European	291 (73.1%)	127 (88.2%)	
	Turkish	31 (7.8%)	6 (4.2%)	
	Moroccan	11 (2.8%)	1 (0.7%)	0.01
	Others:	54 (13.6%)	10 (6.9%)	
	Unknown	11 (2.8%)	0 (0%)	
Age at time of referral (yrs): mean (SD)		9.1 (4.0)	8.4 (4.7)	0.2
HSDS at time of referral: mean (SD)		-2.3 (0.8)	-1.9 (0.9)	<0.01
THSDS: mean (SD)		-0.7 (1.0)	-0.2 (0.9)	<0.01
HSDS - THSDS at time of referral: mean (SD)		-1.6 (0.8)	-1.7 (1.0)	0.7
Delta HSDS in last year before referral: mean (SD)		-0.08 (0.3)	-0.10 (0.3)	0.5
Dysmorphic features: n (%)		22 (5.5%)	2 (1.4%)	0.1
Disproportion: n (%)		15 (3.8%)	2 (1.4%)	0.08

HSDS= height standard deviation score; THSDS= target height standard deviation score

Referral criteria

Table 4 shows how many children in the correctly referred group complied with the 7 different referral criteria mentioned in the DCG (although longitudinal data were used

Table 4. Auxological criteria applicable to the correctly referred (CR) group of children > 3years old in both the university hospital (n=284) and
the general hospital (n=85) (multiple criteria per patient are possible).

Description rule	Rule nr.	University hospital n (%)	General hospital n (%)	Difference between 2 hospitals (p-value)
Absolute height	1.	173 (60.9)	34 (40.0)	0.01
Clinical symptoms	2.	23 (8.1)	3 (3.5)	0.1
Persistent short stature after born SGA	3.	55 (19.4)	13 (15.3)	0.3
Short for target height and population (HSDScorr)	♂: < 10 yr and > 13.4 yr; ♀: < 9 yr and > 12.3 yr	4. 210 (73.9)	75 (88.2)	0.04
	♂: 10 – 13.4 yr; ♀: 9 – 12.3 yr	5. 9 (3.2)	0 (0)	
Height deflection	♂: < 10 yr and > 13.4 yr; ♀: < 9 yr and > 12.3 yr	6. 58 (20.4)	18 (21.1)	0.9
	♂: 10 – 13.4 yr; ♀: 9 – 12.3 yr	7. 0 (0)	0 (0)	

for the analyses a child could only meet a specific referral criterion once). There was a significant difference in referral pattern between the two hospitals with respect to absolute height and "short for target height and population" (HSDScorr). In both hospitals HSDScorr is the criterion most complied with, followed by absolute height and height deflection.

Diagnostic work-up after referral (Table 5)

In 43 % of the correctly referred patients in the university hospital and 32% in the general hospital, no routine laboratory examination was done at all. In 52% and 49%, respectively, only some of the categories mentioned in the laboratory screening of the

Table 5. Diagnostic work up in correctly (CR) and not correctly referred (NCR) children > 3 years old. Percentages of patients with complete/partial evaluation are given (several test categories per patient).

		University hospital		General hospital		Difference in categories between 2 hospitals (p-value)
		CR (n=284) (%)	NCR (n=63) (%)	CR (n=85) (%)	NCR (n=24) (%)	
Routine laboratory investigations						
Anemia / infections		0.4 / 39.8	0.0 / 25.4	1.2 / 57.6	4.2 / 37.5	< 0.01
Liver diseases		22.5 / 4.2	2.8 / 0.0	14.1 / 21.2	8.3 / 25.0	0.03
Renal diseases (blood)		1.4 / 27.3	0.0 / 17.5	0.0 / 38.8	0.0 / 33.3	0.5
Celiac disease		21.1 / 15.8	11.1 / 3.2	49.4 / 4.7	25.0 / 4.2	<0.01
Hypothyroidism		37.0 / 3.2	2.5 / 0.0	45.9 / 3.5	29.2 / 8.3	0.02
Growth hormone deficiency		35.2	9.5	45.9	25	0.02
Turner syndrome *		17.2	6.5	14.0	18.1	1.0
Renal diseases (urine)		0.0 / 19.4	0.0 / 19.0	0.0 / 40.0	0.0 / 29.2	<0.01
Combined categories (at least one test category)		4.9 / 52.1	1.6 / 39.7	18.8 / 49.4	33.3 / 16.7	<0.01
Further and specific diagnostics						
Special investigations	Chromosomal analyses for Turner syndrome*	26.2	6.5	26.0	0.0	0.9
	Biopsy**	2.1	0.0	5.9	0.0	0.03
	Zinc-determination	0.4	0.0	0.0	0.0	0.6
Further, more specific tests	GH-tests	16.2	3.2	12.9	0.0	0.3
	Other tests***	8.8	3.2	28.2	25.0	<0.01

CR = Correctly referred; NCR = Not correctly referred

* These categories are only applicable to girls. The percentages are therefore calculated only on the female population.

** biopsy to rule out celiac disease.

*** other tests, like stool examinations, X-rays of the skeleton, ultrasounds of abdomen, hart, kidneys and thyroids, serum levels of steroids, genetic analyses, immunologic tests and allergic tests

DCG were covered and in only 5% and 19% respectively, all categories were covered. In none of the children a complete detailed routine diagnostic work up was performed. There was a significantly different approach towards the diagnostic workup between the two hospitals. In the general hospital more tests were performed, with less distinction between the correctly referred group and the non-correctly referred group. This difference was significant for all categories in the routine laboratory investigations except for the investigations for renal diseases in blood and screening for Turner syndrome. Significantly more biopsies to rule out celiac disease and other, more specific tests were done in the regional hospital. Less than a quarter of the girls was screened on FSH for Turner syndrome in the correctly referred group and in approximately 26% chromosomal analysis for Turner syndrome was performed. When the age rules recommended by paediatric endocrinologists (plasma FSH only <2 years and > 9 years, see material and methods) were applied the figures hardly changed. The determination of zinc was used only once in the diagnostic work up.

Outcome

In 80 children (14.8%) the diagnosis of persistent short stature after born SGA could be made on the basis of recorded birth size, although only 17 children (3.3%) were classified as such by the physicians. Pathologic causes of short stature were found in 27 children (5%) (see table 6). A large share of these were due to Turner, GHD, and celiac disease. Other pathological causes were: syndromes (n=2: Noonan syndrome, Leri Weill syndrome), anaemia (n=3), skeletal diseases (n=4) and emotional deprivation (n=1). Three children born SGA had also a pathologic cause for short stature (celiac disease, Turner syndrome and GHD). These three were classified under their pathologic cause and not under SGA in table 6.

Table 6. Diagnoses after diagnostic workup of short stature.

	University hospital				General hospital				Total
	Children	Children > 3 years			Children	Children > 3 years			
	< 3 years	CR	NCR	NC	< 3 years	CR	NCR	NC	
	n = 30	n = 284	n = 63	n = 21	n = 29	n = 85	n = 24	n = 6	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n = 542 (%)
GHD	1	6	0	0	0	0	0	0	7
CD	0	1	0	0	3	2	0	1	7
Turner	0	2	0	0	0	1	0	0	3
Other pathology	4	5	1	0	0	0	0	0	10
Total pathology	5 (16.7)	14 (5.2)	1 (5.7)	0 (0)	3 (10.3)	3 (3.4)	0 (0.0)	1 (16.7)	27 (5.0)
SGA only	4 (13.3)	54 (20.1)	3 (3.5)	4 (18.2)	1 (3.4)	13 (14.9)	0 (0.0)	1 (16.7)	80 (14.8)
Idiopathic	21 (70)	216 (74.7)	59 (90.8)	17 (81.8)	25 (86.2)	69 (81.6)	24 (92.1)	4 (66.8)	435 (80.2)

CR = Correctly referred; NCR = Not correctly referred; NC= Not classifiable (information to confirm CR was lacking);
SGA = Small for gestational age (with persistent short stature after two years); GHD = Growth hormone deficiency; CD = Celiac disease

Of all 27 children with pathologic outcome, seven were referred for other reasons (anaemia (2), coughing (2), delayed closure of fontanel (1), health check after adoption (1), poor weight gain (1) and poor food intake (1)) in addition to their short stature. Five children had dysmorphic features at the time of referral (2 children with Turner syndrome, 1 child with Noonan, 1 child with achondroplasia and 1 child with partial GHD) and 3 children were disproportionate (2 children with achondroplasia and 1 child with Leri- Weill syndrome). Six children had already been seen by a specialist before referral: 2 for short stature (they were referred for a second opinion), 1 for hydrocephalus, 1 for exostoses, 1 for neurofibromatosis and glioma of the medulla oblongata and 1 for ASD, but none of the children were previously investigated for short stature. For none of the children the family or medical history was helpful in determining the cause. Most of the correctly referred children with pathology complied with a deviant HSDScorr (83.4%), followed by absolute height (see table 7). The only child with a pathologic cause that was incorrectly referred, had a height SDS of –1.7 SDS at time of referral and was referred because of its short stature in combination with an undefined anaemia. The child turned out to have a beta-thalassemia.

Table 7. Auxological criteria applicable to children with pathology < 3 yrs (n=8, excluding SGA only) and correctly referred (CR) children with pathology >3 yrs (n=17, excluding SGA only) (multiple criteria per patient are possible).

Description rule		Rule nr.	<3 yrs n (%)	>3 yrs n (%)
Absolute height		1.	7 (87.5)	11 (64.7)
Clinical symptoms		2.	2 (25.0)	5 (29.4)
Persistent short stature after born SGA		3.	0 (0.0)	3 (17.6)
Short for target height and population (HSDScorr)	♂: < 10 yr and > 13.4 yr; ♀: < 9 yr and > 12.3 yr	4.	6 (75.0)	15 (88.2)
	♂: 10 – 13.4 yr; ♀: 9 – 12.3 yr	5.		
Height deflection	♂: < 10 yr and > 13.4 yr; ♀: < 9 yr and > 12.3 yr	6.	2 (25.0)	3 (17.6)
	♂: 10 – 13.4 yr; ♀: 9 – 12.3 yr	7.		

Discussion

This study was designed to evaluate consensus guidelines on poor growth in secondary health care and their outcome in terms of pathology. According to the referral criteria mentioned in the DCG 76.4% (284 in the university and 85 in the general hospital) of the children older than 3 years were correctly referred. In both hospitals "short for target height and population (HSDScorr)" appears to be the criterion most complied with, followed by absolute height and height deflection. The approach towards the diagnostic workup was significantly different between the two hospitals, but in none of the children a complete detailed routine diagnostic work up was performed. Pathologic causes for short

stature were found in 27 children (5%) and in 80 children (14.8%) the short stature was classified as persistent short stature after born SGA.

The Netherlands has a health care system based on referral, in which outpatient clinics of general paediatric departments mainly provide secondary health care to referred patients from the well organised national primary health care system. Consequently we believe that by identifying all children referred for short stature to outpatient clinics most children with short stature from the two geographical areas were gathered. The majority of the children older than 3 years were referred correctly according to the DCG. However, if the DCG had been followed strictly, more than 38% of the normal population of children would have been referred as van Buuren et al pointed out in their study.[27]

The 5 % of pathology found in our study concurs with previous reports.[4, 6, 28] In the Wessex growth study 8 children (4.4%) were identified as having an organic disease among the 180 children, whose height on screening at school entry was below the 3rd percentile.[6] In the Oxford study Ahmed et al reported 7 newly recognized children (3.0%) with organic disease among the 260 children whose height was below - 2 SDS, measured at the ages of 3 and 4.5 years.[4] In the Utah growth study[29] twenty-five out of 555 children (4.5%) were newly discovered as having GHD, hypothyroidism or Turner syndrome and another 53 children (9.5%) had other medical reasons for their poor growth (height below the 3rd percentile and/or growth rate below 5 cm/yr). In contrast to these population based studies Grimberg et al and Green et al found a higher percentage of newly diagnosed children with organic causes for their poor growth (23.7% (66 out of 278 children and 40% (79 out of 198), respectively).[20, 29] The children included in these studies were however referred to specialised growth centres because of short stature, without specific choices of anthropometric indicators or criteria for abnormality.

In both hospitals most children with pathology older than three years complied with the HSDScorr rule, followed by the absolute height rule and height deflection rule. This result is contrary to most findings in literature, where absolute height is referred to as the most important criterion for abnormal growth.[1, 2] It concurs however with the observation by Van Buuren et al that the best decision rule to detect children with Turner syndrome, one of the major causes of short stature, is the distance between height SDS and target height.[30] In the 8 children with pathology referred before the age of 3 years (CD (n=3), GHD (n=1), anaemia (n=2), skeletal diseases (n=2) and emotional deprivation (n=1)) both HSDScorr and absolute height seemed important criteria. According to the English consensus these children would however not have been diagnosed at this point, as it recommends a single measurement at the age of 5 years old.[2] As these children did not reach the age of 5 years in our study we are not able to evaluate whether they would have been picked up in the English system, but we can surely say that there would have been a delay. Especially in the children with GHD and celiac disease early diagnosis and treatment is important for its prognosis. In order to improve the referral criteria for growth monitoring with optimal cut-off points, we believe that more studies, similar to the recent report on Turner syndrome are required, with specific attention for children under the age of 3 years.

As far as we know, the DCG is the only published guideline on the general diagnostic work-up for short stature in secondary health care. Despite the fact that this consensus was well known in both hospitals participating in this study, in none of the children a complete detailed routine diagnostic work up as proposed in the DCG was performed and in 43 % of the patients in the university hospital and 32% in the general hospital no routine laboratory examination was done at all. The heterogeneity of tests used in the diagnostic work up, resulting in many missing data for the individual tests in this study, does unfortunately not allow us to construct an evidence-based decision rule for the general diagnostic work-up in children with short stature. We know however from a previous study that testing on celiac disease should be part of this work up, especially when there is no specific indication of another cause for short stature [31]. Likewise the diagnosis of Turner syndrome should be considered in any girl with unexplained short stature [32,33]. In contrast, the prior-probability of CF in infants or children with a low weight or length for age is very low and therefore a sweat test is not necessary in all children with short stature (Grote et al, submitted). Whether an acid-base equilibrium is necessary in every child with short stature to rule out renal acidosis will be addressed in a later study. In the meantime, the available evidence so far can be used to construct a new guideline with an expected acceptable efficacy and efficiency.

Conclusion

For the identification of children with abnormal growth accurate and well-defined referral criteria and a diagnostic work up are important. The current study shows that with the DCG, though only partially adhered to, at least 5 % pathologic growth failure could be detected. In a substantial part of these children (30%) there would at least have been a delay in diagnosis if the English consensus guideline would have been used. From previous studies it is known on the other hand that the DCG leads to too many referrals [27]. Therefore new guidelines are needed with a better sensitivity and specificity, in which target height should play a more prominent role and the implementation process receives more attention. Concerning the general diagnostic work up for short stature we emphasise the importance of testing for celiac disease in all children and for Turner syndrome in girls.

Acknowledgements

We acknowledge Hiske W. Wiersma, Carin H. Neuteboom and Lin Yiu Man, medical students for their great contribution to the study.
This publication was supported by an educational grant from Pfizer.

References

1. Grote F.K., Oostdijk W, de Muinck Keizer-Schrama SMPF, Dekker FW, Verkerk PH, Wit JM: Growth monitoring and diagnostic work-up of short stature: an international inventorisation. J Pediatr Endocrinol Metab 2005, 18:1031-1038.
2. Hall DM: Growth monitoring. Arch Dis Child 2000, 82:10-15.
3. de Muinck Keizer-Schrama SM: [Consensus 'diagnosis of short stature in children.' National Organization for Quality Assurance in Hospitals]. Ned Tijdschr Geneeskd 1998, 142:2519-2525.
4. Ahmed ML, Allen AD, Sharma A, Macfarlane JA, Dunger DB: Evaluation of a district growth screening programme: the Oxford Growth Study. Arch Dis Child 1993, 69:361-365.
5. Frindik JP, Kemp SF, Kearns FS, Hale B: Growth screening. A positive medical experience. Clin Pediatr (Phila) 1992, 31:497-500.
6. Voss LD, Mulligan J, Betts PR, Wilkin TJ: Poor growth in school entrants as an index of organic disease: the Wessex growth study. BMJ 1992, 305:1400-1402.
7. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. GH Research Society. J Clin Endocrinol Metab 2000, 85:3990-3993.
8. Hilken J: Uk audit of childhood growth hormone prescription, 1998. Arch Dis Child 2001, 84:387-389.
9. Juul A, Bernasconi S, Chatelain P, Hindmarsh P, Hochberg Z, Hokken-Koelega A, de Muinck Keizer-Schrama SM, Kiess W, Oberfield S, Parks J et al.: Diagnosis of growth hormone (GH) deficiency and the use of GH in children with growth disorders. Horm Res 1999, 51:284-299.
10. Juul A, Bernasconi S, Clayton PE, Kiess W, DeMuinck-Keizer SS: European audit of current practice in diagnosis and treatment of childhood growth hormone deficiency. Horm Res 2002, 58:233-241.
11. Wilson TA, Rose SR, Cohen P, Rogol AD, Backeljauw P, Brown R, Hardin DS, Kemp SF, Lawson M, Radovick S et al.: Update of guidelines for the use of growth hormone in children: the Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee. J Pediatr 2003, 143:415-421.
12. Cappa M, Loche S: Evaluation of growth disorders in the paediatric clinic. J Endocrinol Invest 2003, 26:54-63.
13. Duck SC: Identification and assessment of the slowly growing child. Am Fam Physician 1996, 53:2305-2312.
14. Fox LA, Zeller WP: Evaluation of short stature. Compr Ther 1995, 21:115-121.
15. Goldberg MJ, Yassir W, Sadeghi-Nejad A, Stanitski CL: Clinical analysis of short stature. J Pediatr Orthop 2002, 22:690-696.
16. Halac I, Zimmerman D: Evaluating short stature in children. Pediatr Ann 2004, 33:170-176.
17. Hermanussen M: The analysis of short-term growth. Horm Res 1998, 49:53-64.
18. Hindmarsh PC, Brook CG: Auxological and biochemical assessment of short stature. Acta Paediatr Scand Suppl 1988, 343:73-76.
19. Rosenfield RL: Essentials of growth diagnosis. Endocrinol Metab Clin North Am 1996, 25:743-758.
20. Green AA, Macfarlane JA: Method for the earlier recognition of abnormal stature. Arch Dis Child 1983, 58:535-537.
21. Diagnostiek kleine lichaamslengte bij kinderen. Van Zuiden Communications B.V.; 1998.
22. Van Steensel-Moll H.A., Jongkind C.J., Aarsen R.S.R., De Goede Bolder A., Dekker A., van Suijlekom-Smit L.W.A., Smit M., Kraayenoord S., Derksen-Lubsen G.: Een probleemgeorienteerd patientenclassificatiesysteem voor de algemene kindergeneeskunde II. Tijdschr Kindergeneeskunde 1996, 64:99-104.
23. Bouwmeester-Landweer MBR: Early home visitation in families at risk for maltreatment. PhD Thesis. Leiden University Medical Center; 2006.

24. Kaji M., Nishi Y.: Growth and minerals: Zinc. Growth, Genetics & Hormones 2006, 22:1-7.
25. Fredriks AM, Buuren van S, Burgmeijer RJF, Meulmeester JF, Beuker RJ, Brugman E, Roede MJ, Verloove-Vanhorick SP, Wit JM: Continuing positive secular growth change in the Netherlands 1955-1997. Pediatric Research 2000, 47:316-323.
26. Niklasson A, Ericson A, Fryer JG, Karlberg J, Lawrence C, Karlberg P: An update of the Swedish reference standards for weight, length and head circumference at birth for given gestational age (1977-1981). Acta Paediatr Scand 1991, 80:756-762.
27. Buuren van S, Bonnemaijer-Kerckhoffs DJ, Grote FK, Wit JM, Verkerk PH: Many referrals under Dutch short stature guidelines. Arch Dis Child 2004, 89:351-352.
28. Lindsay R, Feldkamp M, Harris D, Robertson J, Rallison M: Utah Growth Study: growth standards and the prevalence of growth hormone deficiency. J Pediatr 1994, 125:29-35.
29. Grimberg A, Kutikov JK, Cucchiara AJ: Sex differences in patients referred for evaluation of poor growth. J Pediatr 2005, 146:212-216.
30. Buuren van S, Dommelen van P, Zandwijken GR, Grote FK, Wit JM, Verkerk PH: Towards evidence based referral criteria for growth monitoring. Arch Dis Child 2004, 89:336-341.
31. Rijn van JC, Grote FK, Oostdijk W, Wit JM: Short stature and the probability of coeliac disease, in the absence of gastrointestinal symptoms. Arch Dis Child 2004, 89:882-883.
32. Davenport ML, Punyasavatsut N, Stewart PW, Gunther DF, Savendahl L, Sybert VP: Growth failure in early life: an important manifestation of Turner syndrome. Horm Res 2002, 57:157-164.
33. Moreno-Garcia M, Fernandez-Martinez FJ, Barreiro ME: Chromosomal anomalies in patients with short stature. Pediatr Int 2005, 47:546-549.

Part D

Improved referral criteria for growth monitoring

Chapter 8

Towards Evidence Based Referral Criteria for Growth Monitoring

S. van Buuren[1], P. van Dommelen[2], G.RJ. Zandwijken[3], F.K. Grote[4], J.M. Wit[5], P.H. Verkerk[6]

[1] Head, Dept. of Statistics, TNO Prevention and Health, Leiden
[2] Statistician, Dept. of Statistics, TNO Prevention and Health, Leiden
[3] Epidemiologist, Dutch Growth Foundation, Rotterdam
[4] MD, Dept. of Paediatrics, Leiden University Medical Center, Leiden
[5] Professor, Dept. of Paediatrics, Leiden University Medical Center, Leiden
[6] Head, Dept. of Child Health, TNO Prevention and Health, Leiden

Arch Dis Child 2004, 89:336-341.

Abstract

Objectives: To evaluate the performance of growth monitoring in detecting diseases. Turner Syndrome (TS) is taken as the target disease.

Design: Case-control simulation study. Three archetypal screening rules are applied to longitudinal growth data comparing a group with TS versus a reference group from birth to the age of 10 years.

Setting: Primary child health care.

Participants: Girls with diagnosed TS and a reference cohort.

Main outcome measures: Sensitivity, specificity and median referral age.

Results: Clear differences in performance of the rules were found. The best rule takes parental height into account. Combining rules could improve diagnostic accuracy.

Conclusion: Growth monitoring is useful to screen for TS. A combined rule that takes absolute height SDS, parental height and deflection in height velocity into account is the best way to do this. Similar research is needed for other diseases, populations and ages, and the results should be synthesised into evidence based referral criteria.

Introduction

Monitoring child growth and development is a routine part of child health care in many countries. In a typical scenario, the health care worker plots heights and weights on a reference diagram, and assesses whether the growth pattern of the child deviates from that of the reference population. If so, closer examination of the child might be needed. An important goal is to identify diseases and conditions that manifest themselves through abnormal growth. Examples include Turner Syndrome (TS), growth hormone deficiency, celiac disease, malnutrition, as well as many rare diseases.

In contrast to its widespread use, current knowledge about the diagnostic performance of growth monitoring is incomplete.[1, 2] Growth diagrams define the specificity of a single height measurement. The sensitivity of a single height measurement is unknown for even the most frequent diseases. Also, the sensitivity and specificity of measures involving two or more repeated observations, like height gain, are unknown. The current state of affairs unfortunately precludes an informed discussion about referral criteria. Referral criteria have been evaluated,[3, 4, 5, 6, 7] but these studies have not prevented the appearance of widely different guidelines. For example, the recent UK guideline is based on just one universal height measurement at age five.[8] In contrast, the Dutch consensus guidelines consist of multiple referral criteria covering infancy, childhood and adolescence.[9]
All in all, current practice differs among practitioners, and practices are not founded on evidence.

In order to make progress, we propose that all applications of growth monitoring should be judged along the conventional Wilson-Jungner criteria for screening tests.[10] Measures of diagnostic performance include sensitivity, specificity and median referral time. The latter measure is essential to account for the temporal aspect of the problem.

Of all diseases that might be detected by monitoring growth, TS is one of the most frequent, occurring in 1:2500 female live births. Only 20-40% of the affected individuals, usually the ones with typical clinical features and somatic abnormalities, are diagnosed in the newborn period.[11, 12] Diagnosis of the remaining patients is made during childhood (usually because of growth retardation) or later (because of lack of pubertal development [12]). This makes growth retardation the most important referral criterion in the screening process of TS. The average adult height of untreated women is about 20 cm lower than the mean of the population.[13] Early detection of TS permits the clinician to counsel the family about the consequences of TS, such as an increased risk for cardiac, renal, thyroid and auditory abnormalities associated with TS. Early detection also allows for the initiation of treatment with growth hormone, which increases final height substantially if started at a young age.[14,15] However, the diagnosis is often made too late,[11, 16] so that the results of growth hormone treatment are less favourable. Some work has been done to identify girls with TS earlier using height velocity,[17] but the diagnostic value appeared limited. The goal of the present study is to gain insight into the diagnostic performance of a broader set of referral criteria for auxological screening for TS in the open population.

Method

Table 1: Three archetypal screening rules for growth monitoring with their definition, scenario parameters, interpretation, default parameter values according to the Dutch consensus guidelines,[7] and the parameter values used in the simulation.

Screening rule	Definition	Parameter	Interpretation	Default value*	Simulation values
Absolute height SDS	For ages 0 to p years, refer if SDS < a.	a	SDS referral level before age p	-2.5	-1.5, -2, -2.5, -3, -3.5, -4
	For ages p to 10 years, refer if SDS < b.	b	SDS referral level after age p	-2.5	-1, -1.5, -2, -2.5, -3
		p	Age (in years) at which the referral level changes	Unspecified	1, 2, 3
Parental height corrected	For ages q to 10 years, refer if	c	SDS cut off level below which SDS must lie	-1.3	-1, -1.3, -1.5, -2, -2.5
	SDS < c, AND	d	Difference between target height SDS and SDS	-1.3	-1, -1.3, -1.5, -2, -2.5
	SDS - THSDS < d.	q	Age (in years) after which the rule is effective	0, 3**	1, 2, 3
Deflection	For any pair SDS_1 and SDS_2 measured at ages X_1 and X_2 (in years), refer if				
	$r \leq X_1 < X_2 < 10$, AND	e	Minimal interval (in years) between X_1 and X_2	1***	1, 2, 3
	$X_2 - X_1 \geq e$, AND	f	SDS cut off level below which SDS_2 must lie	Unspecified	10, 0, -1, -2, -2.5
	$SDS_2 < f$, AND	g	Height velocity change in SDS per year	-0.25	-0.20, -0.25,-0.33, -0.50
	$(SDS_2 - SDS_1)/(X_2-X_1) < g$	r	Age (in years) after which the rule is effective	0, 3**	3

* According to Dutch consensus guidelines

** The Dutch consensus guidelines are ambiguous

*** The Dutch consensus guidelines require that three measurements should have been taken, each at least one half a year apart

Screening rules

We investigated screening rules that are suitable for application within the setting of the child health care system. A child that is "screened in" will be referred to a physician for further investigation, eventually leading to the diagnosis of TS. We formulated three archetypal screening rules: an absolute height standard deviation score rule (HSDS), a parental height corrected rule, and a deflection rule (ΔHSDS). Based on the ***absolute HSDS*** rule a child is referred if HSDS is lower than some criterion value. The ***parental height corrected*** rule takes genetic height potential into account by comparing the HSDS of the child to its target height SDS. The target height (TH) is the expected adult height

given the heights of the biological parents and corrected for secular trend. For Dutch girls, the relevant formulas are TH = (maternal height + paternal height - 13)/2 + 4.5 and THSDS = (TH-170.6)/6.5.[18] The ***deflection*** rule signals whether an abnormal deflection in height occurs in terms of a change in HSDS per year. Table 1 gives the precise definition of each rule, the description of the free parameters, and default values of the parameters as used in the Dutch guidelines.[9]

Each screening rule was implemented in a computer program written in S-Plus,[19] and each rule was applied to longitudinal height data of children with and without TS. For each screening rule, we computed the sensitivity, specificity and median referral age for specific scenarios. A scenario is a combination of parameters. We defined scenarios by all possible parameter combinations. We first studied the properties of each screening rule separately. Given these results, we defined scenarios that combined the most promising elements of the separate rules, and computed the outcomes for combined scenarios.

Material

Longitudinal height curves from 777 girls with TS were collected from three sources. The National Registry of Growth Hormone Treatment in Children of the Dutch Growth Foundation contains data of all children in the Netherlands receiving growth hormone (GH) treatment. From this registry, 316 girls with TS, born between 1968 and 1996 were selected. In addition, data from 87 girls with TS, born between 1973 and 1988 from the Sophia Children's Hospital and the data of 374 Dutch girls described by Rongen ***et al.*** [13] were used. The first two sources contain data of girls that were treated with GH and other growth promoting treatment. For this analysis we used only height measurements before treatment. Karyotype, date of diagnosis TS, the presence of congenital anomalies and/or dysmorphic features and parental height were collected when available. The average numbers of measurements per year per child during the first 10 years were 2.2, 0.7, 0.6, 0.5, 0.5, 0.5, 0.5, 0.5, 0.5 and 0.5, respectively.

A reference sample of longitudinal height data was retrospectively obtained for a cohort of all girls (n=489) born in 1989 and 1990 in the municipality of Landgraaf, located in the south of the Netherlands. Data were collected from the records of the local child health care centre. These are routinely collected data, and they thus include all measurement errors that are being made in practice. The modal number of observations per girl was 17. Data were collected in 2001, so the oldest girls were about 11 years. The average numbers of visits per year per child during the first 10 years were 8.1, 2.2, 0.8, 0.8, 0.7, 0.7, 0.2, 0.1, 0.1 and 0.8. Table 2 contains additional information about the samples.

Table 2: Summary statistics for the Turner and reference samples.

	Turner		Reference	
	Count/Mean	S.D.	Count/Mean	S.D.
Total sample size (n)	777		489	
Total number of measurements	9660		7319	
Mean number of measurements per girl	12.4		15.0	
Mean height for age SDS (ages 0-10 year)	-2.44	1.13	-0.31	1.05
Mean weight for age SDS (ages 0-10 year)	-1.74	1.28	-0.12	1.05
Mean weight for height SDS (ages 0-10 year)	-0.06	1.29	0.12	1.04
Mean BMI for age SDS (ages 0-10 year)	-0.19	1.27	0.11	1.04
Height of both father and mother known	357		203	
Height of only one parent known	3		10	
Height of both parents unknown	417		276	
Mean father's height (cm)	179.4	7.50	178.4	7.57
Mean mother's height (cm)	166.4	6.29	166.7	7.38
Target height (cm)	169.7	5.89	170.6	5.70
Target height SDS	0.06	0.82	0.01	0.88
Gestational age (weeks)	38.9	2.07	39.7	1.61
Dysmorphic features (%) (N=145)				
Cubitus valgus	31			
Large inter-nipple distance	29			
Low hair implantation	21			
Webbed neck	19			
Karyotype (%) (N=327)				
45,X	62			
46,X,iX or 46,X,idic(X)	5			
45,X and 46,XX	5			
45,X and (46,X,iX or 46,X,idic(X))	12			
Other	16			
Median age of diagnosis of TS (years) (N=46)				
45,X (N=27)	6.9	4.94		
Other (N=19)	10.4	4.81		

Statistical analysis

HSDS was calculated with respect to the Dutch height reference data.[20] Parental heights were frequently missing (55% of the Turner group, 58% in the reference group). Deleting incomplete records would not only be wasteful, but would also lead to a selective subsample. Mean HSDS of girls with TS was –3.24 for the subsample with missing parental heights, compared to –2.53 for the subsample with known parental heights, but no such differences were found in the reference group. We imputed these data under the assumption that the data are missing at random[21] using ***mice***.[22] The method created multivariate imputations by applying sequential linear regressions, where each incomplete variable was imputed conditional on all other variables in an iterative fashion. The imputation model consisted of the last known HSDS, weight SDS, weight/height

SDS, BMI SDS, age, and the height of the other parent. The number of iterations was set to 15. Predictive mean matching was used to create parental heights imputations. The imputation method possesses important properties: it includes parameter uncertainty, preserves the multivariate structure in the data and has good coverage properties.[23] Figure 1 plots father's height against mother's height separately for the real and artificial data. It shows that the distribution is similar in both groups.

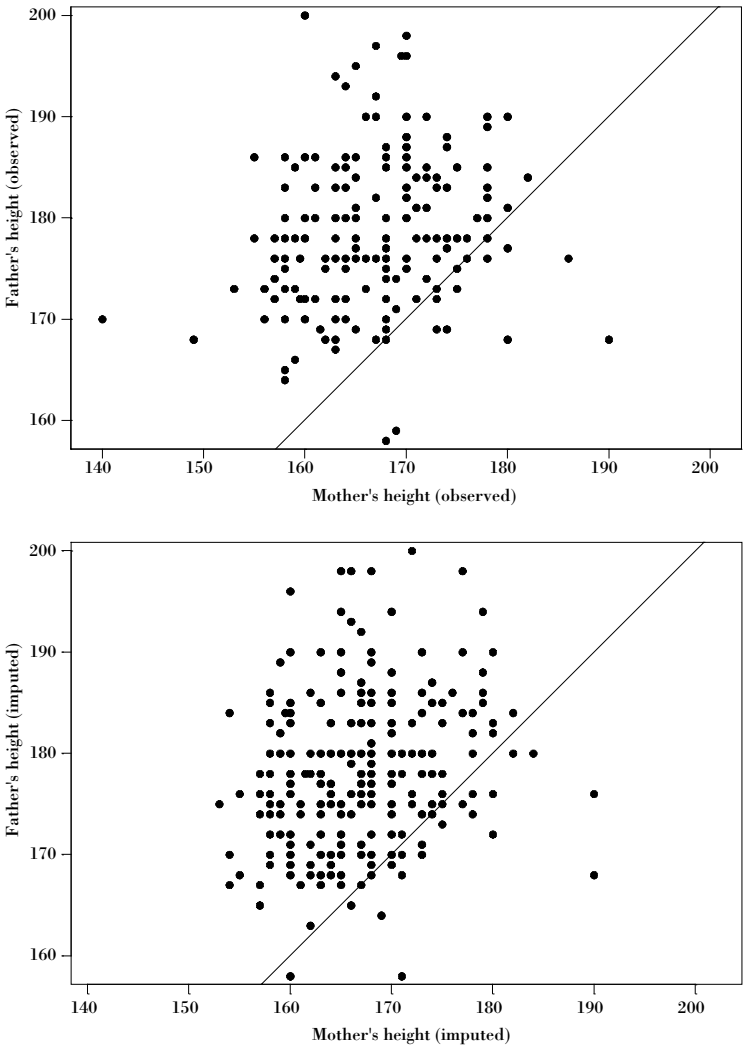


Figure 1: Father's height plotted against mother's height in the reference sample. The upper figure plots observed data from group in which both parental heights are known (n=203). The lower figure plots the imputed (artificial) data for cases where at least one parental height missing (n=286). The reference line indicates the location of equal parental heights.

We assumed that a child is referred ***the first time*** the growth pattern meets the criteria of a given screening rule. Multiple referrals by different rules were treated depending on the type of scenario under investigation. As long as we dealt with separate rules, the same child could be referred according to each rule, i.e., as if the screening rules operated in isolation, but in any combined scenario, multiple referrals were counted as one. The screening age of children that were not referred before the age of 10 years was taken as 10 years. TS girls with a referral age of 10 under a given scenario are missed, so the proportion of such girls is the false negative rate (1-sensitivity). The age of 10 years was chosen because treatment of TS, if indicated, could best be started before that age.

Finally, we synthesised our results by fitting linear regression models to the main outcome variables. These models can be used to predict sensitivity, specificity and median referral age (MRA) in intermediate cases that were not part of the simulation design.

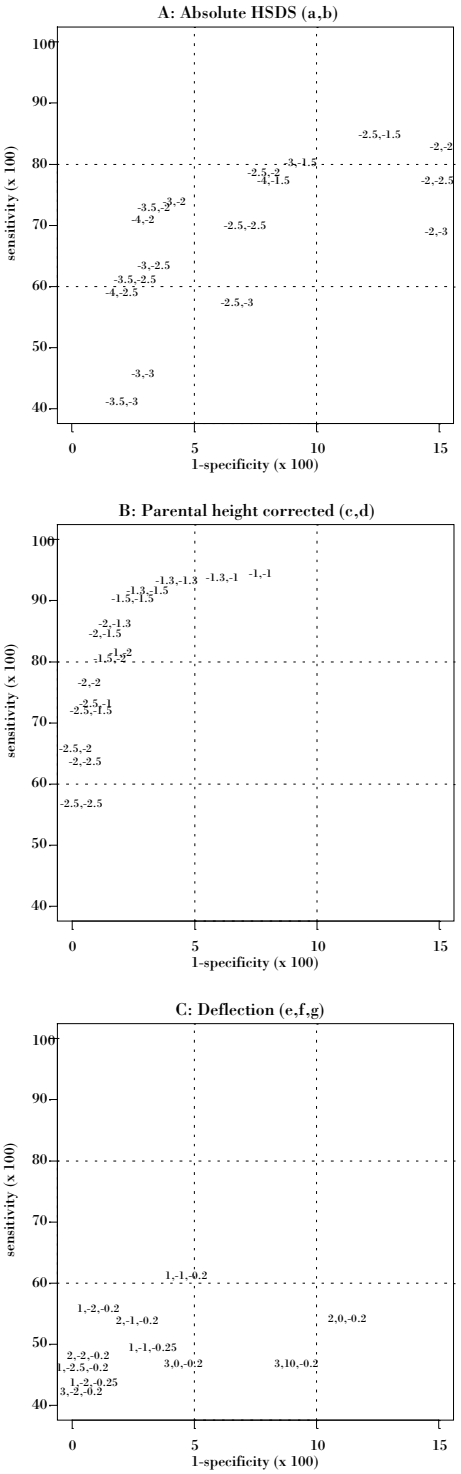
Results

Sensitivity and specificity

Figure 2a is the ROC-plot of scenarios under the absolute HSDS rule. Only scenarios with a true positive rate (sensitivity) of at least 40%, a false positive rate (1-specificity) of at most 15%, and with cut off age $p = 3$ are plotted. Under the default scenario "(-2.5, -2.5)" children are referred that have a HSDS < -2.5 ($a = -2.5$, $b = -2.5$, $p = 3$). Scenario "(-2.5, -2.5)" has a sensitivity of 70.2% and a specificity of 93.1%. Scenarios (-3, -2), (-3.5, -2) and (-4, -2) have better sensitivity and specificity for detecting TS. Specificity is, however, still on the low side for screening purposes (95 - 97%), thus these scenarios might lead to substantial numbers of false positives. Scenarios (-3.5, -2.5) and (-4, -2.5) cut down the number of false positives, at the expense of a loss of sensitivity. The influence of p on sensitivity and specificity was limited.

Performance of the parental height corrected rule was generally better (Figure 2b). The current Dutch guideline (-1.3, -1.3) pairs a high sensitivity of 93.5% with a specificity of 95.9%. Rules using more stringent cut off points reduce the number of false positive referrals at the expense of sensitivity. Examples of interesting scenarios are (-1.5, -1.5), (-2, -2) and (-2.5, -2.5). Note that for these cases $c=d$. The difference with the absolute SDS rule is the extra requirement that THSDS > (c-d), i.e., THSDS > 0 or taller than average parents.

Screening based on the deflection of the growth curve has low sensitivity for rules with a specificity of at least 85% (c.f. Figure 2c). Though not very sensitive, some deflection rules are highly specific. For example, the rule with $e=3$, $f=-2$ and $g=-0.25$ (not in Figure 2c) pairs a sensitivity of 23% with the maximal specificity of 100. It can be efficient to use such rules in conjunction with more sensitive rules.



Median referral age

Median referral age in the Turner group generally did not exceed 6 years under the absolute HSDS or the parental height corrected rule. Median referral age tends to be lower for higher sensitivity and lower specificity. Thus, more cases imply younger cases. This is especially true under scenarios that correct for parental height. The absolute HSDS rule provides the fastest detection of TS, primarily due to the fact that this is the only rule that takes measurements during infancy into account. Earlier detection of TS is possible at the expense of specificity, especially if done through the parental height rule.

Figure 2: ROC plot of different scenarios under three archetypal rules. Each scenario is labeled by its parameter values according to Table 1. For example, the label "(-3, -2)" in the left plot indicates the scenario with a = -3 and b = -2. Only scenarios with $p = q = r = 3$ (c.f. Table 1) are plotted.

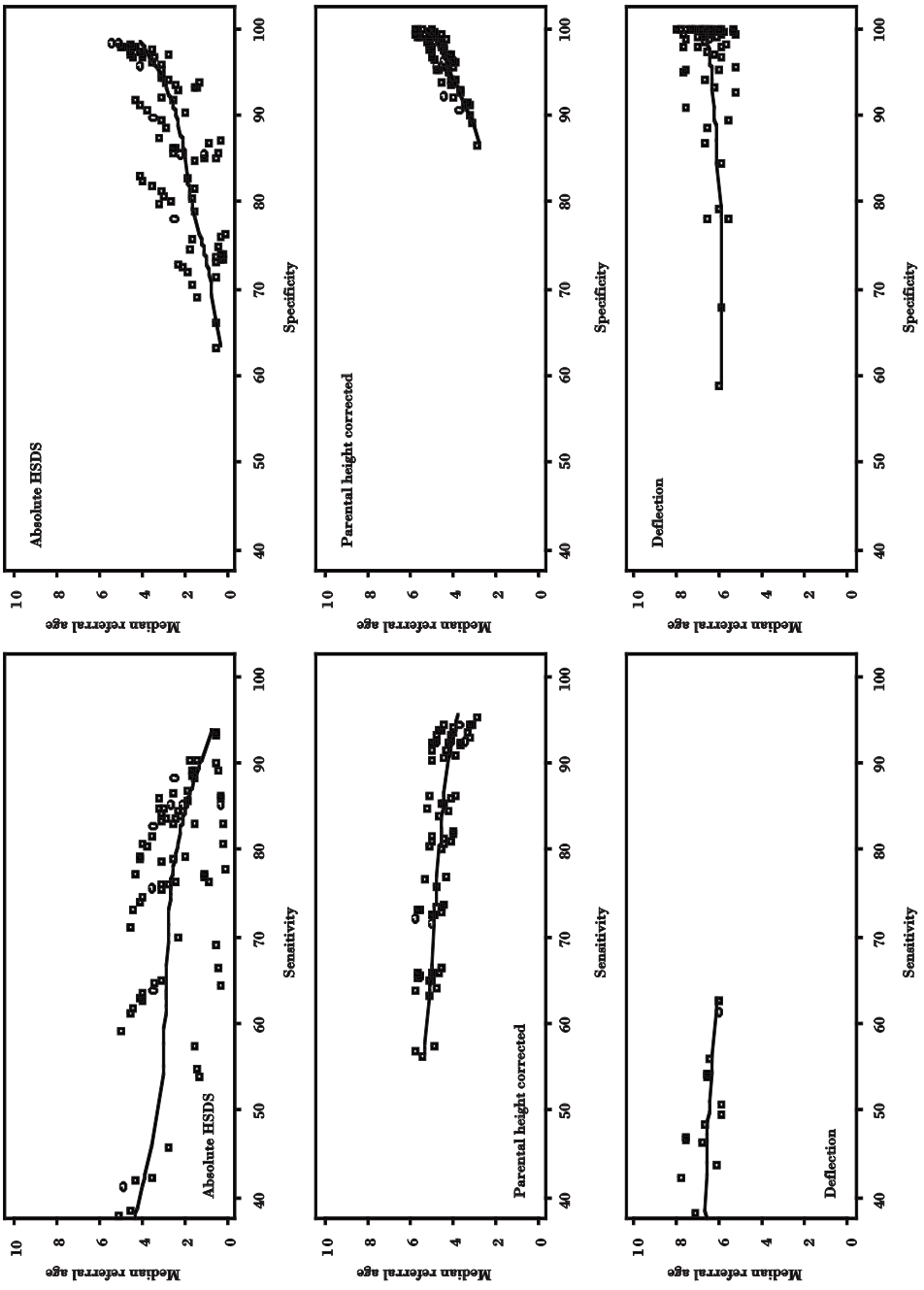


Figure 3: Median referral age of girls with TS as a function of sensitivity and specificity under each rule. Every dot corresponds to a scenario.

Predicting sensitivity, specificity and median referral age

Table 3 contains a synthesis of the results. It gives estimated coefficients of the linear regression for all outcomes. As the proportion of explained variance is generally high, the regression equations can be used to generate fairly accurate predictions for intermediate scenarios not listed in the table. As an example, the estimated sensitivity for scenario (-3, -2) for the absolute HSDS rule is equal to $97.5 - 3.62\boldsymbol{a} - 0.60\boldsymbol{b} - 6.04\boldsymbol{ab} = 73.3\%$. The observed values vary between 74.2% (for $\boldsymbol{p}$=3) and 76.5% (for $\boldsymbol{p}$=1). In this case, the differences between these observed and predicted values fall within one standard deviation of the residual variation (4.97%).

Table 3: Regression equations for predicting sensitivity, specificity and median referral age of the absolute HSDS (sds), parental height corrected (phc) and deflection (def) screening rules, the residual standard error, and the proportion of explained variance (r2).

Rule	Outcome	Predictive equation	Resid s.e.	r^2
sds	Sensitivity	97.5 – 3.62a – 0.60b – 6.04ab	4.97	0.89
	Specificity	58.4 – 3.55a – 2.32b + 1.20p + 2.00ab	4.56	0.79
	Median referral age	1.45 + 0.33a + 1.13b – 0.04p + 0.59ab – 0.32ap + 0.20bp	0.38	0.94
phc	Sensitivity	145 + 21.6c + 26.8d + 5.95cd	3.66	0.91
	Specificity	67.0 –11.0c - 11.3d +4.82q – 3.41cd + 1.06cq – 1.15dq	0.68	0.95
	Median referral age	– 1.09 – 1.76c –1.92d + 1.26q – 0.62cd + 0.26cq + 0.32dq + 0.11cdq	0.10	0.98
def	Sensitivity	89.9 – 8.59e + 0.40f + 145g	7.46	0.86
	Specificity	82.9 + 3.48e –1.05f – 21.1g	5.47	0.57
	Median referral age	5.63 + 0.82e – 0.02f + 2.28g	0.28	0.87

Combining rules

A child will be referred if she meets any of the rules. Sensitivity of a combined rule will be higher than that of its components, while its specificity will be lower. [24] Thus in order to create highly specific combinations, the component rules must have high specificity to start with.

Table 4 shows the diagnostic properties of two combinations. Combining the parental height corrected rule (-2, -2) with the absolute height corrected rule (-3.5, -3) increases sensitivity from 76.9% to 82.4%, decreases specificity from 99.4% to 97.5%, and lowers median referral age to 4.7 years. Observe that this combined rule is inferior to the parental height corrected rule (-2,-1.5) in terms of sensitivity and specificity. The story is different for the combination of the absolute rule with the deflection rule (3,-2,-0.25), which refers children with a HSDS below –2 and a deflection of at least 0.25 SDS per year during at least three years. While this rule detects only 23% of the TS group, there is not a single child in the reference group with this growth pattern. The rule picks up a few new cases. Sensitivity increases from 76.9% to 79.2%, whereas specificity remains at 99.4%. This combined rule is better than comparable parental height corrected rules.

Table 4: Combining rules using a high specificity strategy. Rows 1-3 list a parental height corrected (phc), an absolute sds (sds) and their combined (phc-sds) rule. Rows 4-6 list a parental height corrected (phc), a deflection (def) and their combined (phc-rule) rule. Row 7 is a single parental height corrected rule that is better than row 3 but not preferable to row 6. MRA = Median Referral Age.

Row	Rule	Scenario parameters							Sensitivity	Specificity	MRA
		a	b	c	d	e	f	g	(*100)	(*100)	
1	phc			-2.0	-2.0				76.9	99.4	5.2
2	sds	-3.5	-3.0						41.4	98.1	4.8
3	phc-sds	-3.5	-3.0	-2.0	-2.0				82.4	97.5	4.7
4	phc			-2.0	-2.0				76.9	99.4	5.2
5	def					3	-2.0	-0.25	23.3	100.0	7.7
6	phc-def			-2.0	-2.0	3	-2.0	-0.25	79.2	99.4	5.3
7	phc			-2.0	-1.5				84.9	98.8	5.1

Discussion

Growth monitoring is important for detecting TS, but until now no evidence has been available about the diagnostic quality of possible screening procedures. We estimated sensitivity, specificity and median referral age of TS for three screening rules, and for combinations of these rules. We found that these rules had different performance in discriminating TS. Rules that correct for parental height could identify TS better than rules using the absolute HSDS or rules based on the deflection of growth curves. Combining rules improved performance in particular cases.
The children in our control sample live in the southern part of the Netherlands, and are shorter on average (-0.31 HSDS) than the Dutch reference population. This means that the specificity for the Dutch reference population might be more favourable than estimates based on the shorter population. The equations in Table 3 can be used to estimate the size of the effect. For example, setting a=-2, b=-2.5 and p=1 yields a predicted specificity of 82.5%. Had the group been -0.31 shorter, then substituting a= -1.69, b= -2.19 and p=1 predicts a specificity of 78.1% for that group. So the actual specificity for a group that is 0.31 HSDS shorter is here 4.4% lower. In order to eliminate such biases, we added 0.31 HSDS to the measurements of the reference group. The existence of regional height differences implies that the actual false-positive rates can vary across the country. The parental height corrected rule and the deflection rule are less sensitive to such differences. Using the equations in Table 3, it is straightforward to compute the effect of regional differences on sensitivity and specificity. Region-specific screening rules can be created if the effect is substantial. Similar considerations apply to ethnic minority groups.

Diagnosis of TS is often unnecessarily delayed. Excluding the 20-40% of the patients identified in infancy, the median age of diagnosis is somewhere between 10 and 12 years [11, 16] Including 30% of the early cases into the calculation would lower the median age of diagnoses to the range of 7 to 8.4 years. By the time of diagnosis, patients were extremely short (mean –3.0 HSDS). We found that the median referral age of most screening rules

studied here is between 4 and 6 years. Some rules even identify 50% or more of the cases within the first year. The current policy in the Netherlands is that GH-Treatment in girls with TS is applied if HSDS < -1.5 and if the child is older than 6 years, but preferably younger than 9. Before the age of 6 years treatment is only started if HSDS < -2.5. Our results suggest that systematic growth monitoring is able to find the large majority of cases in time.

The occurrence of missing parental heights complicated the analysis. It is inappropriate to simply ignore the records with incomplete parental heights because the shorter TS girls drop out more frequently. This leads to sensitivity estimates that are too low. The effect is substantial. For example, using just the complete cases in scenario c=d=-1.3 and q=3 results in a sensitivity estimate of 88.7%, compared to 93.5% based on the imputed sample. As it would be unfair to exclude the incomplete cases only for the parental height rule, sensitivity estimates for other rules would also be affected. Imputation yields unbiased estimates for the TS group as a whole. The precision of these estimates is lower than found in the hypothetical case in which we would have had complete data, but it is higher than obtained in the inappropriate complete-case analysis just discussed.

Our results enable informed decisions about specific choices in screening rules for identifying TS. Although growth charts are also used to detect other anomalies, like growth hormone deficiency or celiac disease, growth monitoring should at least be able to detect TS. If monitoring cannot pick up TS, then it almost certainly will fail in more complicated cases where the effects on growth are less pronounced. It is likely that repeating our study for other diseases will lead to different estimates for sensitivity and specificity. Additional complexities will surface, for example, the lack of a gold standard for diagnosis of growth hormone deficiency. However, such studies would probably not lead to a different ranking among the three rules. We expect that rules that take parental height into account are generally preferable to rules that do not.

The findings appear to be only partially in harmony with published guidelines and proposals.[7, 9] As anticipated,[17, 25] we found that centile crossing has low sensitivity and specificity, and in this sense, the Dutch guidelines may need re-evaluation. Marked differences occur with respect to the correction for parental height. Hall dismissed a correction for parental target height on practical grounds,[8] whereas we found that it represents a substantial improvement, in line with earlier observations by Massa ***et al.***.[16]

We conclude that growth monitoring is useful to screen for TS. The parental height corrected rule will refer 60-77% of the girls with TS before the age of 10 at tolerable levels of false positives, i.e., at a maximum of 1%. We recommend the use of the combined rule "phc-def" listed in Table 4. This rule refers children older than age three if HSDS is below –2 and if either HSDS is more than 2 SD below the target HSDS, or HSDS shows a deflection of 0.25 SDS per year or more during a period of at least three years. This rule picks up almost 80% of the girls with TS, while it refers only 0.6% of the non-TS population. We also recommend that similar research should be done for other diseases, populations and ages. The results should be synthesised into general evidence based referral criteria.

References

1 Panpanich R, Garner P. Growth monitoring in children. Cochrane Database Syst Rev 2000; 2: CD001443.

2 Garner P, Panpanich R, Logan S. Is routine growth monitoring effective? A systematic review of trials. Arch Dis Child 2000; 82: 197-201.

3 Hindmarsh PC. Monitoring children's growth: Abnormal growth should also be defined by the crossing of height centiles (letter). BMJ 1996;312:122.

4 Paterson BA. A review of growth monitoring in Aboriginal school children in Australia. BMJ. com, electronic letter, 5 March 1999.

5 Mulligan J, Voss LD, McCaughey ES, Bailey BJR, Betts PR. Growth monitoring: testing the new guidelines. Arch Dis Child 1998;79:318-22.

6 Voss LD. Changing practice in growth monitoring. BMJ 1999;318:344-45.

7 Hall DMB. Growth monitoring. Arch Dis Child 2000; 82:10-5.

8 Hall DMD, Elliman D. Health for all children, 4th Ed. Oxford University Press, 2003.

9 de Muinck Keizer-Schrama SMPF. Consensus 'Diagnostiek kleine lichaamslengte bij kinderen' [Dutch consensus guidelines for short stature]. Ned Tijdschr Geneeskd. 1998; 142: 2519-25.

10 Wilson JM, Jungner G. Principles and practice of screening for disease. Geneva: World Health Organisation, 1968 (Public Health Paper Number 34).

11 Sävendahl L, Davenport ML. Delayed diagnoses of Turner's syndrome: Proposed guidelines for change. J Pediatr 2000; 137:455-9.

12 Gicquel C, Gaston V, Cabrol S, Le Bouc Y. Assesment of Turner's Syndrome by molecular analysis of the X chromosome in Growth retarded girls. J Clin Endocrinol Metab 1998; 83:1472-1476.

13 Rongen-Westerlaken C, Corel L, van den Broeck J, Massa G, Karlberg J, Albertsson-Wikland K, Naeraa RW, Wit JM. Reference values for height, height velocity and weight in Turner's syndrome. Swedish Study Group for GH treatment. Acta Paediatr. 1997; 86:937-42.

14 Sas TC, de Muinck Keizer-Schrama SM, Stijnen T, Jansen M, Otten BJ, Hoorweg-Nijman JJ, et al. Normalization of height in girls with Turner syndrome after long-term growth hormone treatment: results of a randomized dose-response trial. J Clin Endocrinol Metab 1999;84:4607-4612.

15 Reiter EO, Blethen SL, Baptista J, Price L. Early initiation of growth hormone treatment allows age-appropriate estrogen use in Turner's syndrome. J Clin Endocrinol Metab 2001;86:1936-1941.

16 Massa G, Vanderschueren-Lodeweyckx M. Age and height at diagnosis in Turner syndrome: influence of parental height. Pediatrics 1991; 88:1148-52.

17 Van den Broeck J, Hokken-Koelega A, Wit JM. Validity of height velocity as a diagnostic criterion for idiopathic growth hormone deficiency and Turner syndrome. Horm Res 1999;51:68-73.

18 Fredriks AM, van Buuren S, Burgmeijer RJF, Verloove-Vanhorick SP, Wit JM. Groeidiagrammen (2e, herziene en vermeerderde druk) [Growth diagrams, second edition]. Houten: Bohn Stafleu van Loghum, 2002.

19 Insightful Corp. S-Plus 2000 User's Guide. Seattle WA: Insightful, 2000.

20 Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E, Roede MJ, Verloove-Vanhorick SP, Wit JM. Continuing positive secular growth change in The Netherlands 1955-1997. Pediatr Res 2000;47: 316-23.

21 Little RJA, Rubin DB. Statistical analysis with missing data. Second Edition. Wiley: New York, 2002.

22 Van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. Stat Med 1999;18:681-94.

23 Brand JPL, van Buuren S, Groothuis-Oudshoorn CGM, Gelsema ES. A toolkit in SAS for the evaluation of multiple imputation methods. Stat Neerl 2003; 57, 36-45.
24 Macaskill P, Walter SD, Irwig L, Franco EL. Assessing the gain in diagnostic performance when combining two diagnostic tests. Stat Med 2002, 21, 2527-46.
25 Van Buuren S, Fredriks AM, Verkerk PH. Comment on "Consensus 'Diagnostiek kleine lichaamslengte bij kinderen" [Comment on Dutch consensus guidelines for short stature]. Ned Tijdschr Geneeskd 1999; 143, 1585-6.

Chapter 9

Which auxological characteristics are useful for the detection of Celiac disease?

P. van Dommelen[1#], F.K. Grote[2#], W. Oostdijk[2], S.M.P.F. de Muinck Keizer-Schrama[3], B. Boersma[4], G. Damen[5], C. Csizmadia[2], P.H. Verkerk[6], J.M. Wit[2], S. van Buuren[1,7].

[1] Dept. of Statistics, TNO Quality of life, Leiden, The Netherlands
[2] Dept. of Paediatrics, Leiden University Medical Center, Leiden, The Netherlands
[3] Dept. of Paediatrics, ErasmusMC - Sophia Children's Hospital, Rotterdam, The Netherlands
[4] Dept. of Paediatrics, Medical Center Alkmaar, Alkmaar, The Netherlands
[5] Dept. of Paediatrics, University Medical Center St Radboud, Nijmegen, The Netherlands
[6] Dept. of Child Health, TNO Quality of life, Leiden, The Netherlands
[7] Dept. of Methodology & Statistics, University of Utrecht, The Netherlands
[#] These authors contributed equally to this work

Submitted

Abstract

Objective: To study the diagnostic efficiency of several auxological criteria for the detection of children with celiac disease (CD).

Design: We studied various criteria concerning length and weight.

Patients: Longitudinal length and weight measurements up to 2.5 years of age from 3 groups of CD patients (two groups with clinical manifestations, one group diagnosed by screening) (n=134) and a reference group obtained from the Social Medical Survey of Children Attending Child Health Clinics (SMOCC) cohort (n=2,151) in The Netherlands.

Main outcome measures: Sensitivity, specificity and positive predictive value (PPV) for each criterion.

Results: The auxological criteria hardly discriminate between the screened CD group and the reference group. Criteria based on a decrease of body mass index (BMI) or weight standard deviation score (SDS) performed best for the groups with clinical manifestations. Thirty-four percent of the CD children and 2% of the reference children have a deflection in BMI SDS of at least -2.5 per year and a BMI SDS below -1.3 from the age of 0.5 year

Conclusion: Although the efficacy of growth monitoring for the detection of CD is modest, testing for CD deserves a place in the diagnostic work-up in young children with failure to thrive.

Keywords: growth monitoring, celiac disease

Introduction

Growth assessment is worldwide accepted and in many countries regularly integrated in a child health care system, despite the insufficient evidence to support this activity.[1] One of the most important goals of growth monitoring in developed countries is the detection of undiagnosed illnesses. There is nevertheless little consensus on referral criteria for children with growth retardation and the diagnostic performance of growth monitoring among countries.[2] Only recently, we reported on the predictive value of various auxological criteria for the detection of Turner's syndrome.[3] Since short stature is the main common physical characteristic of Turner's syndrome, we focused in that study on short stature and poor height gain. Growth retardation however does also imply failure to thrive in terms of poor weight gain.

Celiac disease (CD) is an illness in which both length (or height) deficit and poor weight gain might be the earliest signs of the disease. It is a gluten-sensitive enteropathy, characterized by subtotal villous atrophy of the small intestine and might be clinically diagnosed at an early age, when diarrhoea, belly distension and/or failure to thrive is present. In the Netherlands in 1994 the incidence of clinically diagnosed CD was 0.54 per 1000 live births.[4] However CD remains frequently unrecognized. Screening studies by means of detection of anti-endomysium antibodies have shown a much higher prevalence (1:300 to 1:100). The ratio clinically diagnosed versus screening detected CD is between 1:7 and 1:14.[5] A reduction in adult height, a higher prevalence of malignancies, adverse pregnancy outcome, neurological problems and osteomalacia are associated with CD. Early detection and treatment of CD may prevent these problems.

Mass screening for CD through specific antibodies in the general population probably will not be performed in the forthcoming years because of the uncertainty about the cost-benefit ratio. As there is a high incidence of CD (1.7 to 8.3%) in children with growth retardation without gastrointestinal symptoms and even higher (up to 59.1%) when other (endocrine) causes for short stature are excluded,[6] one could expect that a substantial proportion of infants and children with CD might be detected through growth monitoring.

In the Netherlands, nearly every child is monitored for height and weight from birth till the age of 16-18 years. Children with abnormal growth are referred to secondary health care according to certain criteria.[7] As in most of them no pathologic causes for short stature can be detected, in a current project the referral criteria are evaluated and adapted to minimize unnecessary referrals, without missing important diseases like CD, Turner's syndrome and endocrine diseases. This should result in evidence-based guidelines for growth monitoring. This project aims at determining optimal auxological referral criteria for detecting CD.

Method

Material

The longitudinal length and weight data of the patients with CD included in this study were collected from three different studies. The first study was a screening study on

unrecognised CD in children aged 2-4 years, visiting the Community Child Health Care Centres in the Dutch province of Zuid-Holland.[5] In this study 32 children with CD between May 1997 and June 1998 were detected. The second study was a retrospective study on catch up growth in patients with CD.[8] A written questionnaire including their symptomatology, duration of complaints before diagnosis, age at diagnosis, associated diseases in the past and parental heights was sent to all members of the Dutch Celiac Society in the early eighties. Growth data were collected from 74 children younger than 16 years. The third study was a prospective study on catch up growth.[9] All newly diagnosed childhood CD patients at two departments of paediatrics were included between April 1994 and September 1995 (n=28). We used all growth data before and at the start of the gluten-free diet and till the age of 2.5 years. The data was gathered retrospectively from child welfare clinics, paediatricians and general practitioners.

A reference sample was obtained from the Social Medical Survey of Children Attending Child Health Clinics (SMOCC) cohort, a nationally representative cohort of 2,151 children born in the Netherlands in 1988-1989.[10] This cohort consists of longitudinal data of length and weight of children up to the age of 2.5 years. Length and weight from birth to two years were previously described by Herngreen et al.[11]

Screening rules

For this study we formulated nine auxological rules for screening that could serve as criteria for referral to specialist care. We started with three archetypal rules of which the diagnostic performance to detect Turner's syndrome was reported by Van Buuren et al.[3] The first rule was the ***absolute Height Standard Deviation Score (HSDS) rule,*** which would lead to referral of a child if HSDS is lower than some simulation value. The second rule took genetic height potential into account by comparing the HSDS of the child to its target height SDS in combination with a HSDS below some simulation value (***parental height corrected rule***). The third rule signalled whether an abnormal deflection in height occurs in terms of change in HSDS per year in combination with a HSDS below some simulation value (***deflection rule***).

The present study expands these screening rules with analogical absolute SDS rules for weight, BMI and weight for length (i.e. refer when weight, BMI, weight for length, respectively, is lower than some simulation value), an analogical deflection rule for weight and BMI (i.e. refer when a change in weight or BMI SDS per year occurs and weight or BMI SDS is below some simulation value) and six other rules. The first of these other rules is a deflection rule that detects a child with a deflection in length, weight or BMI SDS/year without the restriction of having an SDS below some value (***unrestricted deflection rule***). The second rule refers if an absolute change in SDS occurs (***delta rule***). The third rule signals whether a deflection moves away from the child's target height (***parental height deflection rule***). The fourth rule is the ***combined weight and length deflection rule*** in which a deflection in length occurs after a deflection in weight. The fifth rule refers if the conditional weight gain SDS (SDS_{gain})[13] is below some value and weight SDS is below a simulation value (***conditional weight gain rule***). The sixth rule is similar to the

conditional weight gain rule without the restriction of having a weight SDS below some value (***unrestricted conditional weight gain rule***). Table 1a/b shows the definitions, parameters, interpretations and simulation values of the rules. It should be noticed that some parameters select a subset of the data and/or assume 2 or 3 measurements. The rules are only tested on children that comply with these assumptions.

Each screening rule was implemented using S-Plus version 7.0, and was applied to the longitudinal data of children. For the deflection, delta and conditional weight gain rules, all possible pairs of weights for each infant were used. We calculated sensitivity, specificity and positive predictive value (PPV) of different scenarios (a combination of parameters). The rules were ordered according to their sensitivity at high levels of specificity. A
higher sensitivity at the same level

of specificity, results in a better performance. Receiver Operating Characteristic (ROC) curves were constructed for the three best screening rules. Scenarios of rules with approximately 2% false-positive rate will be presented in detail as we assume that a false-positive rate of more than 2% would lead to too many referrals. PPV was calculated, assuming that the average incidence of CD is 0.54 per 1000 live births in the Caucasian population.[4]

Statistical analysis

Length, weight, BMI and weight for length were expressed as SDS, using the Dutch reference growth data.[13, 14] In preterm infants (gestational age < 37 weeks) length and weight SDS were corrected for gestational age. The intrauterine growth curve of the

Swedish reference population was used to express SDS till the age corresponding with 40 weeks of gestation.[15] Between 40 and 42 weeks an interpolation between the growth curve of the Swedish reference population and that of the Dutch reference population was used. From 42 weeks of gestation till the age of 2 years, SDS was calculated on ages corrected for gestation, using the Dutch reference growth data.
We assume that a child is referred if the growth pattern meets the criteria of a given screening rule for the first time. All rules were dealt with separately, meaning that the same child could be referred according to each separate rule. Because of the difference in presentation at diagnosis (screening versus symptomatic), the analyses were performed separately for CD-patients from group 1 (screened) and patients from group 2 and 3 (symptomatic).

Results

From the 134 children with CD, 12 were excluded from the analyses because of missing data (see figure 1). Table 2 contains general characteristics of the unscreened and screened CD groups. In the unscreened group mean SDS for weight was compromised most, followed by BMI SDS.

Table 1a Auxological criteria with their definitions, scenario parameters, interpretations and simulation values (part 1).

Screening rule	Definition	Parameter	Interpretation	Simulation values
Absolute SDS rule▲	For ages 0 to p years, refer if SDS < a, *AND*	a	SDS referral level before age p	-1,-1.3, -1.5, -2, -2.5, -3, -3.5
	For ages p to 2.5 years, refer if SDS < b	b	SDS referral level after age p	-1, -1.3, -1.5, -2, -2.5, -3
		p	Age (in years) at which the referral level changes	0, 0.5, 1
Parental height	For ages x to 2.5 years, refer if	x	Age (in years) after which the rule is effective	0, 0.5, 1
corrected rule	Length SDS < c, AND	c	Cut off level below which length SDS must lie	-1, -1.3, -1.5, -2, -2.5
	Length SDS – TH SDS < d	d	Difference between length SDS and target height SDS	-1, -1.3, -1.5, -2, -2.5
Deflection-rule ‡	For ages e_1 to 2.5 years, AND	e_1	Age (in years) after which the rule is effective	0, 0.5, 1
	$X_2 - X_1 \geq 1/12$ refer if		Minimal one month interval between ages X_1 and X_2	
	$SDS_2 < f$, AND	f	SDS cut off level below which SDS_2 must lie	-1,-1.3, -1.5,-2, -2.5
	$(SDS_2 - SDS_1)/(X_2-X_1) < g_1$	g_1	Change in SDS per year	-0.5,-1,-1.5,-2,-2.5
Unrestricted	For ages e_2 to 2.5 years, AND	e_2	Age (in years) after which the rule is effective	0, 0.5, 1
deflection-rule ‡	$X_2 - X_1 \geq 1/12$ refer if		Minimal one month interval between ages X_1 and X_2	
	$(SDS_2 - SDS_1)/(X_2-X_1) < g_2$	g_2	Change in SDS per year	-1.5,-2,-2.5,-3,-3.5,-4,-4.5,-5,-5.5
Delta-rule ▲	For ages e_3 to 2.5 years, AND	e_3	Age (in years) after which the rule is effective	0, 0.5, 1
	$X_2 > X_1$ refer if		Age X_2 after X_1	
	$(SDS_2 - SDS_1) < w$	w	Change in SDS	-0.5,-1,-1.5,-2,-2.5,-3
Parental height	For ages k_1 to 2.5 years, AND	k_1	Age (in years) after which the rule is effective	0, 0.5, 1
deflection rule	$X_2 > X_1$ refer if		Age X_2 after X_1	
	$(\text{Length } SDS_2 - \text{Length } SDS_1) < n_1$, AND	n_1	Change in length SDS	-0.5,-1,-1.5,-2,-2.5,-3
	$\lvert \text{Length } SDS_2 - \text{TH SDS} \rvert >$		Length SDS at age X_1 is closer to it's target height than	
	$\lvert \text{Length } SDS_1 - \text{TH SDS} \rvert$		Length SDS at age X_2	
Combined weight	For ages k_2 to 2.5 years, AND	k_2	Age (in years) after which the rule is effective	0, 0.5, 1
and length deflection	$X_3 > X_2 > X_1$, AND		Age X_3 after X_2 , X_2 after X_1 (ages for weight)	
rule	$Y_3 > Y_2 > Y_1$, refer if		Age Y_3 after Y_2 , Y_2 after Y_1 (ages for length)	
	$(\text{Weight } SDS_2 - \text{Weight } SDS_1) < n_2$, AND	n_2	Weight velocity change in Weight SDS	-0.25,-0.5,-1,-1.5,-2
	$(\text{Length } SDS_2 - \text{Length } SDS_1) < n_3$, AND	n_3	Length velocity change in Length SDS	-0.25,-0.5,-1,-1.5,-2
	$Y_1 > X_1$		Starting point length deflection after starting point weight deflection	

▲ This rule is calculated for length, weight, BMI and weight for length SDS.

‡ This deflection rule is calculated for length, weight and BMI SDS.

Table 1b Auxological criteria with their definitions, scenario parameters, interpretations and simulation values (part 2).

Screening rule	Definition	Parameter	Interpretation	Simulation values
Conditional weight gain rule† $	For ages h_1 to 2.5 years, AND $X_2 > X_1$ refer if	h_1	Age (in years) after which the rule is effective Age X_2 after X_1	0, 0.5, 1
	$SDSgain=(SDS_2 - r\ SDS_1)/(\sqrt{1-r^2}) < h2$, AND	h_2	Change in SDS	-0.5,-1,-1.5,-2,-2.5
	$SDS_2 < h_3$	h_3	SDS cut off level below which SDS2 must lie	-1,-1.3, -1.5,-2, -2.5
	with r=(exp(2z)-1)/(exp(2z)+1) and z=2.98-1.67log(gap)+ 0.251log(mean age)log(gap)-2.06/ gap+0.590log(mean age)- 0.104 (log(mean age) ^{2})			
Unrestricted conditional weight gain rule† $	For ages m_1 to 2.5 years, AND $X_2 > X_1$ refer if	m_1	Age (in years) after which the rule is effective Age X_2 after X_1	0, 0.5, 1
	$SDSgain=(SDS_2 - r\ SDS_1)/(\sqrt{1-r^2}) < m2$, AND with r=(exp(2z)-1)/(exp(2z)+1) and	m_2	Change in SDS	-1.5,-2,-2.5,-3,-3.5,-4,-4.5,-5,-5.5
	z=2.98-1.67log(gap)+ 0.251log(mean age)log(gap)-2.06/ gap+0.590log(mean age)- 0.104 (log(mean age) ^{2})			

† This rule is calculated for weight SDS.

$ SDS_{gain} summarises the child's weight gain over a period of time compared with the gain expected in an average child of the same initial weight, measured at the same two ages.

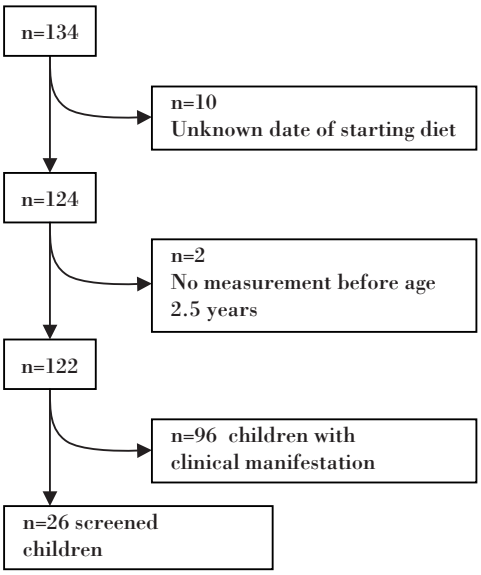


Figure 1 Flow chart of children with CD used in the study.

Table 2 General characteristics of the CD-population.

Characteristic		Screened (n=26)	Unscreened (n=96)
Gender (M)		50%	35%
Ethnicity	Dutch	92%	98%
	Others	8%	2%
Median (range) age in years at start diet		3.96 (2.94-6.06)	1.43 (0.41-20.7)
Mean (SD) length SDS*∞		-0.26 (0.98)	-0.89 (1.30)
Mean (SD) weight SDS*∞		-0.06 (0.81)	-1.54 (1.15)
Mean (SD) BMI SDS*∞		0.28 (0.57)	-1.28 (1.15)
Mean (SD) weight for length SDS*∞		0.14 (0.65)	-1.23 (1.13)
Mean (SD) target height SDS		0.41 (0.92)	0.00 (0.75)

* For the children in the screened group figures at diagnosis are given (also when diagnosis is after 2.5 years of age). For the unscreened children figures at the start of diet are given.

∞ Based on children with at least one measurement between 6 months before or 3 months after diet or diagnosis.

We tested the performance of all rules in distinguishing between the CD groups from the reference group. Sensitivity was almost similar to 1-specificity (the false-positive rate) for the group of CD children detected by screening. This indicates that the growth pattern of these patients does not differ much from the reference population. Figure 2 shows the ROC plots for the three best rules of the clinically suspected children with CD (groups 2 and 3). Only scenarios with a false-positive rate of less than 10% are plotted. The line for which sensitivity is equal to 1-specificity is given in the plot. Seventeen percent of

the CD children and almost none of the reference children have a change in BMI SDS of at least -1.5 from the age of 1 year. Thirty-seven percent of the CD children and 3.3% of the reference children have a deflection of at least -2.5 BMI SDS per year and a BMI SDS below -1 after the age of 0.5 year.

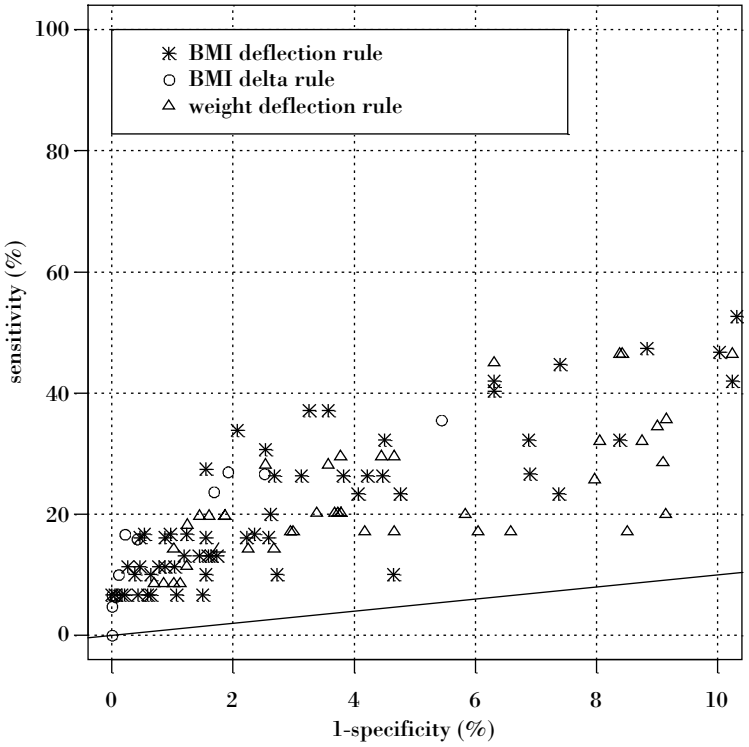


Figure 2 ROC plots of the three best auxological screening rules for the detection of CD in the unscreened groups (group 2 and 3). The rules are a deflection in BMI or weight SDS/year in combination with a BMI or weight SDS below some simulation value, and an absolute change in BMI SDS.

The properties of the three best rules for group 2 and 3, in terms of sensitivity and PPV at approximately 98% specificity, are presented in table 3. Thirty-four percent of the CD children and 2% of the reference children have a deflection in BMI SDS of at least -2.5 per year and a BMI SDS below -1.3 from the age of 0.5 year. In children with such deflection in BMI SDS the prior-probability of CD is 0.86%. After 0.5 year of age, 27% of the CD children versus 2% of the reference children have a BMI SDS change of -1.5. The weight deflection rule results in a sensitivity of 20% at a specificity level of 98%, and this result is similar for the conditional weight gain rule. For a higher specificity level, the weight deflection rule is slightly better than the conditional weight gain rule (18% versus 16% for 98.5% specificity).

Table 3 Properties of the best scenarios with approximately 2% false-positives (=98% specificity).

(unscreened) CD	Simulation values			Sensitivity	1-Specificity	PPV
BMI deflection rule	e_1=0.5	f=-1.3	g_1=-2.5	33.9%	2.1%	0.86%
BMI delta rule	e_3=0.5	w=-1.5		27.0%	1.9%	0.76%
weight deflection rule	e_1=0.5	f=-2.5	g_1=-0.5 to -1	19.7%	1.9%	0.56%

Discussion

This study shows that the overall performance of detecting CD with auxological criteria is modest. The auxological criteria hardly discriminate between the screened CD group and the reference group. In the patients with clinical suspicion of CD, rules that consider a change or deflection in BMI or weight SDS show the best performance.

The conditional weight gain rule is based on the concept of regression to the mean. The amount of regression to the mean depends on how highly correlated the weights are at the ages.[12] The correlations of the weights we used in this study are based on the UK 1990 weight reference.[20] To validate if these correlations can also be applied to Dutch children, we calculated if SDS_{gain} has a mean of zero and a SD of 1, and if it is uncorrelated with the first weight SDS. For the reference group of Dutch children, the mean (SD) SDS_{gain} is -0.05 (1.38) and its correlation with the first weight SDS is -0.22. As both SD and correlation are quite high, the conditional weight gain rule might perform better when using Dutch correlations of weights. However, at the moment these correlations are not available.

The CD data in our study were gathered retrospectively meaning that there was no fixed schedule of measurements in the CD-patients, resulting in a wide variation in the number of measurements between the individual patients. We tried to minimize the problem by gathering extra information about growth from school doctors in the Regional health centres, where nearly every child in the Netherlands is monitored for height and weight from birth till the age of 16-18 years.

As Csizmadia et al. reported earlier, the children with CD detected by screening had a normal weight and length at time of diagnosis.[5] We have now shown that all children in this group indeed had a normal growth pattern before diagnosis, which corresponds with the asymptomatic character of this silent form of CD. Therefore auxology seems not useful for the detection of silent CD.

Most of the patients in our study were females, as was reported in several other studies.[16] Bardella et al. hypothesized that males escape diagnosis, but that the two sexes are equally affected. This hypothesis is supported by the absence of differences in gender in the screening study (see table 2).

CD is often atypical or clinically silent and many children remain undiagnosed. However, since the widespread use of serologic testing and the increased awareness of CD in the late 1990s there has been an increase in incidence and a change in clinical presentation.[17, 18] Classical symptoms, like malabsorption and poor weight gain tend to start between the ages of 6-24 months and do no longer dominate the clinical picture. Instead, there is an increase of non-classical symptoms such as unusual intestinal complaints or extra-intestinal symptoms like short stature, involving older children.[20] Since our non-screened population was diagnosed before 1995, we were not able to study the effect of this change in clinical presentation on the performance of the auxological criteria. One may however assume that in the age-group studied in the present study the performance of the auxological criteria is similar for the present CD-population, since it is especially the delayed onset of the disease (the non-classical form) that has increased during the recent years, suggesting that the growth impairment becomes apparent much later.

In conclusion, the efficacy of growth monitoring for the detection of CD is modest in the first 2.5 years. As there is a high incidence of CD in children with growth retardation, the clinician may however consider testing for CD in a diagnostic work-up in young children with failure to thrive. The most sensitive auxological parameter is the deflection in BMI SDS.

Acknowledgements

We acknowledge Jeroen van Rijn for his great contribution to the study.
This publication was supported by an educational grant from Pfizer.

What is already known on this topic?

CD is a gluten-sensitive enteropathy, characterized by subtotal villous atrophy of the small intestine. In the Netherlands, the incidence of clinically diagnosed CD was 0.54 per 1000 live births. Length (or height) deficit and poor weight gain may be the earliest signs of the disease.

What this study adds

As far as we know, this is the first large evidence-based investigation on various types of auxological referral criteria for detecting children with CD.

References

1. Garner P, Panpanich R, Logan S. Is routine growth monitoring effective? A systematic review of trials. Arch Dis Child 2000;82:197-201.
2. Grote FK, Oostdijk W, de Muinck Keizer-Schrama SMPF, Dekker FW, Verkerk PH, Wit JM. Growth monitoring and diagnostic work-up of short stature: an international inventorisation. Pediatr Endocrinol Metab 2005;18:1031-8.
3. Buuren van S, Dommelen van P, Zandwijken GR, Grote FK, Wit JM, Verkerk PH. Towards evidence based referral criteria for growth monitoring. Arch Dis Child 2004;89:336-41.
4. George EK, Mearin ML, Franken HC, Houwen RH, Hirasing RA, Vandenbroucke JP. Twenty years of childhood coeliac disease in The Netherlands: a rapidly increasing incidence? Gut 1997;40:61-6.
5. Csizmadia CG, Mearin ML, von Blomberg BM, Brand R, Verloove-Vanhorick SP. An iceberg of childhood coeliac disease in the Netherlands. Lancet 1999;353:813-4.
6. Rijn van JC, Grote FK, Oostdijk W, Wit JM. Short stature and the probability of coeliac disease, in the absence of gastrointestinal symptoms. Arch Dis Child 2004;89:882-3.
7. de Muinck Keizer-Schrama SM. [Consensus 'diagnosis of short stature in children.' National Organization for Quality Assurance in Hospitals]. Ned Tijdschr Geneeskd 1998;142:2519-25.
8. Damen GM, Boersma B, Wit JM, Heymans HS. Catch-up growth in 60 children with celiac disease. J Pediatr Gastroenterol Nutr 1994;19:394-400.
9. Boersma B, Houwen RH, Blum WF, van Doorn J, Wit JM. Catch-up growth and endocrine changes in childhood celiac disease. Endocrine changes during catch-up growth. Horm Res 2002;58 Suppl 1:57-65.
10. Herngreen WP, Reerink JD, van Noord-Zaadstra B.M., Verloove-Vanhorick SP, Ruys JH. The SMOCC-study: Design of a representative cohort of live-born infants in the Netherlands. Eur J Public Health 1992;2:117-22.
11. Herngreen WP, van Buuren S, van Wieringen JC, Reerink JD, Verloove-Vanhorick SP, Ruys JH. Growth in length and weight from birth to 2 years of a representative sample of Netherlands children (born in 1988-89) related to socioeconomic status and other background characteristics. Ann Hum Biol 1994;21:449-63.
12. Cole TJ. Conditional reference charts to assess weight gain in British infants. Arch Dis Child 1995;73:8-16.
13. Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E et al. Continuing positive secular growth change in The Netherlands 1955-1997. Pediatr Res 2000;47:316-23.
14. Fredriks AM, van Buuren S, Wit JM, Verloove-Vanhorick SP. Body index measurements in 1996-7 compared with 1980. Arch Dis Child 2000;82:107-12.
15. Niklasson A, Ericson A, Fryer JG, Karlberg J, Lawrence C, Karlberg P. An update of the Swedish reference standards for weight, length and head circumference at birth for given gestational age (1977-1981). Acta Paediatr Scand 1991;80:756-62.
16. Bardella MT, Fredella C, Saladino V, Trovato C, Cesana BM, Quatrini M et al. Gluten intolerance: gender- and age-related differences in symptoms. Scand J Gastroenterol 2005;40:15-9.
17. Steens RF, Csizmadia CG, George EK, Ninaber MK, Hira Sing RA, Mearin ML. A national prospective study on childhood celiac disease in the Netherlands 1993-2000: an increasing recognition and a changing clinical picture. J Pediatr 2005;147:239-43.
18. Dewar DH, Ciclitira PJ. Clinical features and diagnosis of celiac disease. Gastroenterology 2005;128(4 Suppl 1):S19-S24.
19. Fasano A. Clinical presentation of celiac disease in the pediatric population. Gastroenterology 2005;128(4 Suppl 1):S68-S73.
20. Freeman JV, Cole TJ, Chinn S, Jones PRM, White EM, Preece MA. Cross sectional stature and weight reference curves for the UK, 1990. Arch Dis Child 1995;73:17-24.

Chapter 10

The value of auxological screening for Cystic Fibrosis

Floor K. Grote[1#], Paula van Dommelen[2#], Sabine M.P.F. de Muinck Keizer- Schrama[3], Wilma Oostdijk[1], Jan Bouquet[3], Johannes J.E. Hendriks[4], Jan Kouwenberg[5], Paul H. Verkerk[6], Stef van Buuren[2,7], Jan Maarten Wit[1]

[1] Dept. of Paediatrics, Leiden University Medical Center, Leiden, The Netherlands
[2] Dept. of Statistics, TNO Quality of life, Leiden, The Netherlands
[3] Dept. of Paediatrics, ErasmusMC - Sophia Children's Hospital, Rotterdam, The Netherlands
[4] Dept. of Paediatrics, University Hospital Maastricht, Maastricht, The Netherlands
[5] Juliana Children's Hospital, The Hague, The Netherlands
[6] Dept. of Child Health, TNO Quality of life, Leiden, The Netherlands
[7] Dept. of Methodology & Statistics, University of Utrecht, The Netherlands
[#] These authors contributed equally to this work

Submitted

Abstract

Aim: To study the diagnostic efficiency of several auxological criteria for the detection of Cystic fibrosis (CF).

Method: We studied the performance of various criteria concerning length, weight and body mass index (BMI), using longitudinal length and weight measurements up to 2.5 years of age from CF patients visiting three major CF clinics (n=216) and a reference group obtained from the Social Medical Survey of Children Attending Child Health Clinics (SMOCC) cohort (n=2,151) in The Netherlands.

Results: Within the first year weight is a better auxological tool for detecting CF than length.. At a false positive rate of 3 percent, 45% of children diagnosed within 1 year can be detected by weight Standard Deviation Score (SDS) deflection of -0.20 to -0.50 per year combined with a weight SDS below -2.5 (Positive predicted value (PPV)= 0.6%). Similarly 28% of children diagnosed after 1 year can be detected by BMI SDS deflection of –1 disregarding the time interval (PPV = 0.4%).

Conclusion: In the absence of a newborn screening program for CF, weight SDS deflection of -0.2 to -0.5 per year combined with weight SDS below -2.5 has the highest PPV for infants and BMI SDS decrease of -1 for older children.

Keywords: growth retardation, failure to thrive, Cystic Fibrosis, screening, early childhood

Introduction

Cystic fibrosis (CF) is one of the most common life-threatening autosomal recessive diseases in the Caucasian population, and early diagnosis is of great importance. Mostly symptoms start at an early age and include failure to thrive, persistent bronchopulmonary infections and exocrine pancreas insufficiency with malabsorption as a result.[1] The estimated incidence varies worldwide from 0.25 to 5 per 10.000 life births.[2] In Caucasian European newborns the incidence is 1:2000-3000 whereas in Caucasian North American newborns it is about 1:3500.[3] Although symptoms start at an early age, CF is not always timely diagnosed, because its presentation is variable.[4] In several countries Newborn screening (NBS) programs for CF have been introduced. In areas where there is no NBS program the diagnosis is made at an average age of 2 years.[1] In these countries growth monitoring is assumed to be instrumental in the early detection of at least part of the CF-population, since most of the CF-patients have presenting symptoms like failure to thrive and some even have failure to thrive as the only symptom.[1, 5-9]

Growth assessment is accepted worldwide and generally implemented in child health care systems although sufficient data to support this activity are lacking.[10] A diversity in the growth monitoring process and the diagnostic work-up of growth disorders is noticeable in industrialised countries.[11] Only a few guidelines have been published on referral criteria and diagnostic work-up for children with impaired growth.[12, 13] These guidelines emphasize height more than weight and are based on consensus meetings rather than on experimental evidence. Even for failure to thrive, often used in infancy and early childhood to describe growth impairment, consensus on the choice of anthropometric indicators or their criteria for abnormality is lacking.[14] Recently, Van Buuren et al reported on the predictive value of various auxological criteria for the detection of Turner syndrome.[15] The present study aims to explore the diagnostic efficiency of several auxological criteria (including both weight and length) for the detection of children with CF.

Method

Material

Longitudinal length- and weight measurements were collected retrospectively from CF patients visiting three major CF clinics in The Netherlands: Erasmus MC - Sophia Children's Hospital in Rotterdam (n=166), University Hospital Maastricht (n=30) and Juliana Children's Hospital in The Hague (n=20). The data were collected from existing patient data files. Additional data were obtained, with permission from the patient or his or her parents, from the school doctors in the regional health centres.

The following information was obtained: date of birth, date of diagnosis, gender, ethnicity, perinatal information (birth weight, length, gestation), date of diagnosis of CF, DNA-mutation and height of biological parents. If the ethnicity was not recorded, it was assessed based on the patient's first and family name according to an algorithm reported earlier.[16]

A reference sample was obtained from the Social Medical Survey of Children Attending Child Health Clinics (SMOCC) cohort, a nationally representative cohort of 2,151 children born in the Netherlands in 1988-1989.[17] This cohort consists of longitudinal data of length and weight up to the age of 2.5 years. Length and weight from birth to two years were previously described by Herngreen et al.[18]

Screening rules

For this study we formulated seven auxological rules for screening, that could serve as criteria for referral to specialist care. We started with the three archetypal rules of which the diagnostic performance to detect Turner's syndrome was reported by Van Buuren et al.[15] The first rule was the ***absolute Height Standard Deviation Score (HSDS) rule***, which would lead to referral of a child if HSDS is lower than some simulation value. The second rule took genetic height potential into account by comparing the HSDS of the child to its target height in combination with a HSDS below some simulation value (***parental height corrected rule***). The third rule signalled whether an abnormal deflection in height occurs in terms of change in HSDS per year in combination with a HSDS below some simulation value (***deflection rule***).

The present study expands these screening rules with analogical absolute SDS rules for weight, BMI and weight for length (i.e. refer when weight, BMI, weight for length respectively is lower than some simulation value), an analogical deflection rule for weight (i.e. refer when a change in weight SDS per year occurs and weight SDS is below some simulation value) and four other rules. The first of these other rules is a deflection rule that detects a child with a deflection in length or weight SDS/year without the restriction of having an SDS below some value (***deflection rule 2***). The second rule refers if a change in SDS occurs disregarding time (***delta rule***). The third rule signals whether a deflection moves away from the child's target height (***parental height deflection rule***). The fourth rule is the ***combined weight and length deflection rule*** in which a deflection in length occurs after a deflection in weight. Table 1 shows the definitions, parameters, interpretations and simulation values of the rules.

Each screening rule was implemented using S-Plus version 7.0, and was applied to the longitudinal data of children. We calculated sensitivity, specificity and positive predictive value (PPV) of different scenarios (a combination of parameters). The rules were ordered according to their sensitivity at high levels of specificity. A higher sensitivity at the same level of specificity, results in a better performance. Receiver Operating Characteristic (ROC) curves were constructed for the four best screening rules. Scenarios of rules with approximately 3% false-positive rate will be presented in detail as we assume that a false-positive rate of more than 3% would lead to too many referrals. PPV was calculated assuming that the average incidence of CF is 1:3000 in the Caucasian population.[3]

Statistical analysis

Length, weight, target height, body mass index (BMI) and weight for length were expressed as SDS, using the Dutch reference growth data.[19, 20] In preterm infants (gestational age < 37 weeks) length and weight SDS were corrected for gestational age. The intrauterine

Table 1 Auxological criteria with their definitions, scenario parameters, interpretations and simulation values

Screening rule	Definition	Parameter	Interpretation	Simulation values
Absolute SDS rule▲	For ages 0 to p years, refer if SDS < a, *AND*	a	SDS referral level before age p	-1,-1.3, -1.5, -2, -2.5, -3, -3.5
	For ages p to 2.5 years, refer if SDS < b	b	SDS referral level after age p	-1, -1.3, -1.5, -2, -2.5, -3
		p	Age (in years) at which the referral level changes	0, 1
Parental height	For ages x to 2.5 years, refer if	x	Age (in years) after which the rule is effective	0, 1
corrected rule	Length SDS < c, AND	c	Cut off level below which length SDS must lie	-1, -1.3, -1.5, -2, -2.5
	Length SDS – TH SDS < d	d	Difference between length SDS and target height SDS	-1, -1.3, -1.5, -2, -2.5
deflection-rule 1‡	For ages e_1 to 2.5 years, AND	e_1	Age (in years) after which the rule is effective	0, 1
	$X_2 - X_1 \geq 1/12$ refer if		Minimal one month interval between ages X_1 and X_2	
	$SDS_2 < f$, AND	f	SDS cut off level below which SDS_2 must lie	-1,-1.3, -1.5,-2, -2.5
	$(SDS_2 - SDS_1)/(X_2-X_1) < g_1$	g_1	Change in SDS per year	-0.20,-0.25,-0.33, -0.50,-1,-1.5,-2,-2.5
deflection-rule 2‡	For ages e_2 to 2.5 years, AND	e_2	Age (in years) after which the rule is effective	0, 1
	$X_2 - X_1 \geq 1/12$ refer if		Minimal one month interval between ages X_1 and X_2	
	$(SDS_2 - SDS_1)/(X_2-X_1) < g_2$	g_2	Change in SDS per year	-0.20,-0.25,-0.33, -0.50,-1,-1.5,-2,-2.5
delta-rule▲	For ages e_3 to 2.5 years, AND	e_3	Age (in years) after which the rule is effective	0, 1
	$X_2 > X_1$ refer if		Age X_2 after X_1	
	$(SDS_2 - SDS_1) < w$	w	Absolute change in SDS	-0.50,-1,-1.5,-2,-2.5,-3
Parental height	For ages k_1 to 2.5 years, AND	k_1	Age (in years) after which the rule is effective	0, 1
deflection rule				
	$X_2 > X_1$ refer if		Age X_2 after X_1	
	$(\text{Length } SDS_2 - \text{Length } SDS_1) < n_1$, AND	n_1	Length velocity change in HSDS	-0.50,-1,-1.5,-2,-2.5,-3
	$\lvert \text{Length } SDS_2 - \text{TH SDS} \rvert >$		Length SDS at age X_1 is closer to it's target height than	
	$\lvert \text{Length } SDS_1 - \text{TH SDS} \rvert$		Length SDS at age X_2	
Combined weight and	For ages k_2 to 2.5 years, AND	k_2	Age (in years) after which the rule is effective	0, 1
length deflection rule				
	$X_3 > X_2 > X_1$, AND		Age X_3 after X_2 , X_2 after X_1 (ages for weight)	
	$Y_3 > Y_2 > Y_1$, refer if		Age Y_3 after Y_2 , Y_2 after Y_1 (ages for length)	
	$(\text{Weight } SDS_2 - \text{Weight } SDS_1) < n_2$, AND	n_2	Absolute weight change in Weight SDS	-0.1,-0.25,-0.5,-1,-1.5,-2
	$(\text{Length } SDS_2 - \text{Length } SDS_1) < n_3$, AND	n_3	Absolute length change in Length SDS	-0.1,-0.25,-0.5,-1,-1.5,-2
	$Y_1 > X_1$		Starting point length deflection after starting point weight deflection	

▲ The rule is the calculated for length, weight, BMI and weight for length SDS.

‡ These deflection rules were calculated for length and weight SDS.

growth curve of the Swedish reference population.[21] was used to express SDS till the age corresponding with 40 weeks of gestation. Between 40 and 42 weeks an interpolation between the growth curve of the Swedish reference population and that of the Dutch reference population was used. From 42 weeks of gestation till the age of 2 years, SDS was calculated on ages corrected for gestation, using the Dutch reference growth data.

Parental height was missing in 31% of the CF-patients. We imputed these data under the assumption that the data were missing at random using Multivariate Imputation by Chained Equations (MICE).[22] The method created multivariate imputations by applying sequential linear regressions, where each incomplete variable was imputed conditionally on all variables in an iterative fashion. The imputation model consisted of the height SDS at the age of 5 years (or closest to the age of 5 years), weight SDS, weight for height SDS, BMI SDS, age, age at diagnosis, gender, the height of the other parent and hospital. Height SDS at the age of 5 was chosen for the imputation model, because in most children the catch-up growth has resulted in a normal height at this age.[23] The number of iterations was set to 15. Predictive mean matching was used to create parental height imputations. The imputation method includes parameter uncertainty, preserves the multivariate structure in the data and has good coverage properties.[24]

We divided the CF-population into a group diagnosed within 1 year and a group diagnosed after 1 year and compared this with two different datasets from the reference group (one with data up to 1 year of age and one with data up to 2.5 years of age). This was done to minimize the variation in number of measurements between CF children caused by the variability in age at diagnosis.

Calculations were based on the assumption that a child is referred if the growth pattern meets the criteria of a given screening rule for the first time. All rules were dealt with separately, meaning that the same child could be referred according to each separate rule. The analyses were done separately for children, who were diagnosed before the age of 1 year and for children who were diagnosed after the age of 1 year. Children diagnosed before the age of 1 year were compared with the reference sample with measurements up to 1 year of age.

Results

From the 216 children with CF, 93 were excluded from the analyses because of missing data (see figure 1). Almost 80% of the children are diagnosed within 2.5 years of age. Table 2 contains general characteristics of the CF group. Mean SDS for weight was compromised most, followed by an index of weight for length (weight-for-length or Body Mass Index (BMI)) and length SDS.

We tested the performance of all rules in distinguishing between the CF group and the reference group. ROC plots of scenarios under the four best rules (according to their sensitivity and specificity) are shown in figure 2. Only scenarios with a false-positive rate of less than 10% are plotted. The line for which sensitivity is equal to 1-specificity

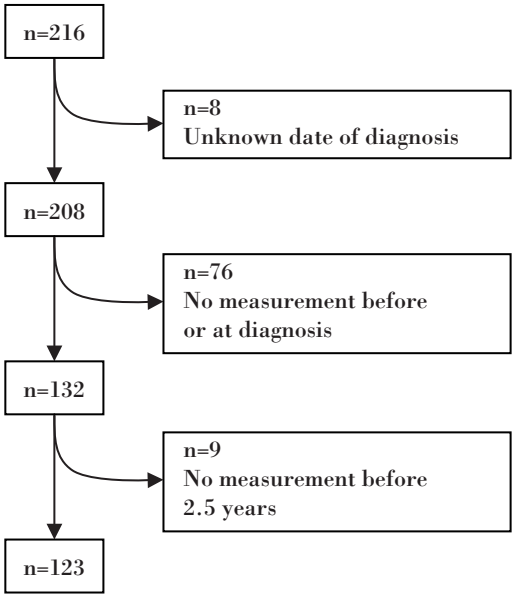


Figure 1 Flow chart of children with CF used in the study.

Table 2 General characteristics of the CF-population.

Characteristic		
Gender (M)		51%
Ethnicity	Dutch/European	91%
	Turkish	2%
	Moroccan	1%
	Others	4%
	Unknown	2%
Median (range) age in years at time of diagnosis		0.59 (0-15)
Mean (SD) length SDS at time of diagnosis$^{\infty}$		-1.08 (1.13)
Mean (SD) weight SDS at time of diagnosis$^{\infty}$		-1.60 (1.35)
Mean (SD) BMI SDS at time of diagnosis$^{\infty}$		-1.13 (1.79)
Mean (SD) weight for length SDS at time of diagnosis$^{\infty}$		-1.31 (1.74)
Mean (SD) target height SDS		0.21 (0.64)
DNA	Homozygous for dF508	47.2%
	Heterozygous for dF508*	20.3%
	Others*	3.3 %
	Unknown	29.3%

* mutations other than dF508 were: 'A455E', 'G542X', 'N1303K', 'R1162X', 'R553X', '1717-1G>A' 'IVS17bTA', 'Q552P', 'R1066C', 'S1251N', 'G542x', '1677d', 'G178R', 'Q493X' and '3659delC'.

$^{\infty}$ Based on children with at least one measurement between 6 months before or 3 months after diagnosis.

is given in the plots. The ROC curves show that the performance of the rules of children with CF diagnosed within 1 year (Figure 2A) is better than that of children diagnosed after 1 year (Figure 2B). The length deflection rule, BMI delta rule and absolute weight SDS rule result in a sensitivity of 18-26% at a specificity level of 99% for the CF group diagnosed within 1 year. For the CF group diagnosed after 1 year, the BMI delta rule and the absolute BMI SDS rule show a sensitivity of 23% at a specificity of 98.3%.

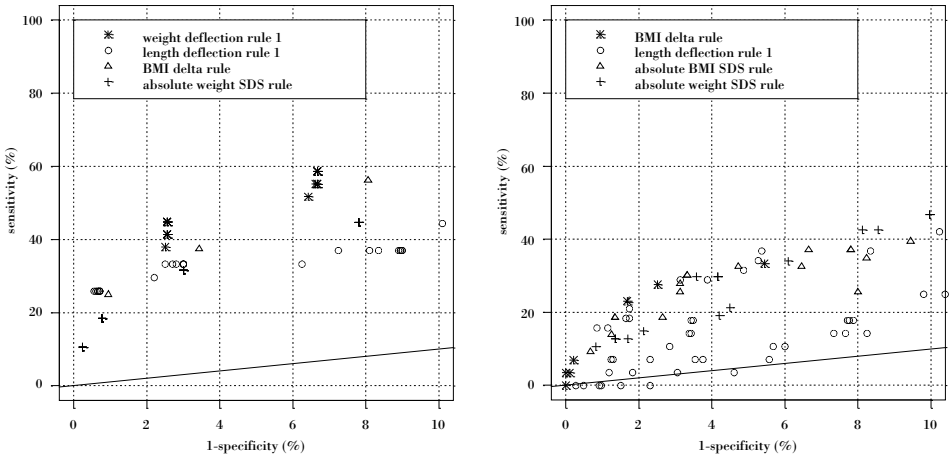


Figure 2 ROC plots of the four best auxological screening rules for the detection of CF.
A. Optimal ROC curves for CF diagnosed < 1 year. The rules are a deflection in weight or length SDS per year in combination with a weight or length SDS below some simulation value, an absolute change in BMI SDS, and a weight SDS below a value.
B. Optimal ROC curves for CF diagnosed >= 1 year. The rules are an absolute change in BMI SDS, a deflection in length SDS per year in combination with length SDS below some simulation value, and a BMI or weight SDS below a value.

The properties of the four best rules, in terms of sensitivity and PPV at approximately 97% specificity, are presented in table 3. The upper part shows the results of the children with CF diagnosed within 1 year and a reference group with measurements until the age of 1 year. Almost 45% of the CF children diagnosed within 1 year and 2.6% of the reference children have a weight SDS below -2.5 and a change in weight SDS per year between 0.2 and 0.5 (weight deflection rule 1: e1=0, f=-2.5 and g1=-0.2 to -0.5). In children with such change in weight SDS the prior-probability of CF is 0.57%. When this rule would be applied, median referral age would be 0.19 years, which is on average 1.3 months earlier than the real age of diagnosis.
The lower part of table 3 shows the results of the rules of children with CF diagnosed after the age of one year and all measurements of the reference children. Almost 28% of the CF children diagnosed after the age of one year and approximately 2.5% of the reference children have a change in BMI SDS of at least -1 between 1 and 2.5 years (BMI delta rule: e3=1,w=-1), resulting in a PPV of 0.37%. Median referral age would then be 2.0 years, which is 21 months earlier than the observed age at diagnosis. The length deflection rule

and the absolute BMI and weight SDS rule result in a sensitivity between 28 to 30% at a specificity level between 96.4 and 96.9%.

Table 3 Properties of the best scenarios with approximately 3% false-positives (=97% specificity).

CF diagnosed < 1 year	Simulation values			Sensitivity	Specificity	PPV
Weight deflection rule 1	e1=0	f=-2.5	g1= -0.20 to -0.50	44.8%	97.4%	0.57%
Length deflection rule 1	e1=0	f=-2	g1= -2	33.3%	97.5%	0.44%
BMI delta rule	e3=0	w=-2.5		37.5%	96.6%	0.37%
Absolute weight SDS rule	a=all	b=-2.5	p=0	31.6%	97.0%	0.35%
CF diagnosed >= 1 year	Simulation values			Sensitivity	Specificity	PPV
BMI delta rule	e3=1	w=-1		27.6%	97.5%	0.37%
Length deflection rule 1	e1=0	f=-2	g1= -2.5	28.9%	96.9%	0.31%
Absolute BMI SDS rule	a=-3	b=-2	p=1	27.9%	96.9%	0.30%
Absolute weight SDS rule	x=-2.5	c=-3	d=1	29.8%	96.4%	0.28%

Discussion

We studied if auxological criteria can be of practical value for the detection of cystic fibrosis (CF) and showed that the overall performance of detecting CF with such parameters is moderate. Especially in the first year of life, weight seems to be a better auxological tool for the detection of CF than length and deflection is more important than a single measurement. Almost 45% of the CF children diagnosed within 1 year would be detected by a certain weight deflection (PPV = 0.57%) and almost 28% of the CF children diagnosed after 1 year by an absolute change in BMI SDS (PPV = 0.37%). The performance of the rules of children with CF diagnosed within the first year of life is better than that of children diagnosed later. The better performance of the rules in infants than in older children may be associated with the higher likelihood of being diagnosed sooner when the disease is more severe.
Growth status at the time of diagnosis of CF, as well as methods to classify failure to thrive have previously been described, but results vary widely, partially due to the diversity in criteria used.[25-27] In agreement with other studies we found an abnormal mean absolute length and weight at time of diagnosis.[7, 28-32] Based on these studies we estimated that the predictive value of such criteria is limited.[33] By gathering longitudinal growth data of CF-patients before diagnosis, we were able to study not only growth status at certain moments but also the deflection of the growth curve.

The CF data in our study were collected retrospectively, which implies that there was no fixed schedule of measurements in the CF-patients, resulting in a wide variation in the number of measurements between the individual patients. We tried to minimize the problem by gathering additional information about growth from school doctors in the "Regional health centres", where nearly every child in the Netherlands is monitored for height and weight from birth till the age of 16-18 years. The data can therefore be considered as representative of the situation in daily practice.

Newborn screening has shown beneficial effects on the prognosis of CF and has been implemented in several countries.[34-36] In the absence of a newborn screening program, however, the clinician may consider to test for CF in a diagnostic work-up in children with failure to thrive, since CF is a severe disease representing itself sometimes with monosymptomatic FTT and still up to 45% of the children can be detected within the first year using auxology. In this case the observation of weight impairment is more useful than length impairment and deflection of the growth curve is a relevant parameter.
A weight SDS deflection of -0.20 to -0.50 per year in combination with a weight SDS below -2.5 has the highest PPV for children under the age of one year and a BMI SDS decrease of -1 for older children. These screening rules can form the basis for future computer algorithms in child welfare clinics.

Acknowledgements

We acknowledge Wendelien Planten for her great contribution to the study, all the members of the CF team of the ErasmusMC - Sophia Children's Hospital, with Dr. H.A.W.M. Tiddens as coordinator, for gathering the information, Dorien Holtslag for her help gathering all information in Maastricht. This publication was supported by an educational grant from Pfizer.

References

1. Giglio L, Candusso M, D'Orazio C, Mastella G, Faraguna D. Failure to thrive: the earliest feature of cystic fibrosis in infants diagnosed by neonatal screening. Acta Paediatr 1997;86:1162-5.
2. Lewis PA. The epidemiology of cystic fibrosis. In Hodson ME, Geddis DM, eds. Cystic fibrosis, pp 1-13. London: Chapman & Hall, 1995.
3. Bobadilla JL, Macek M, Jr., Fine JP, Farrell PM. Cystic fibrosis: a worldwide analysis of CFTR mutations--correlation with incidence data and application to screening. Hum Mutat 2002;19:575-606.
4. Kharrazi M,.Kharrazi LD. Delayed diagnosis of cystic fibrosis and the family perspective. J Pediatr 2005;147:S21-S25.
5. Armstrong DS, Grimwood K, Carzino R, Carlin JB, Olinsky A, Phelan PD. Lower respiratory infection and inflammation in infants with newly diagnosed cystic fibrosis. BMJ 1995;310:1571-2.
6. Oliveira MC, Reis FJ, Chagas AJ, Brasileiro FG, Bahia M, Silva LD, Penna FJ. [Study of intestinal malabsorption diseases as cause of monosymptomatic short stature]. J Pediatr (Rio J) 1998;74:213-6.
7. Ranganathan SC, Stocks J, Dezateux C, Bush A, Wade A, Carr S, Castle R, Dinwiddie R, Hoo AF, Lum S, Price J, Stroobant J, Wallis C. The evolution of airway function in early childhood following clinical diagnosis of cystic fibrosis. Am J Respir Crit Care Med 2004;169:928-33.
8. Tepper RS, Hiatt P, Eigen H, Scott P, Grosfeld J, Cohen M. Infants with cystic fibrosis: pulmonary function at diagnosis. Pediatr Pulmonol 1988;5:15-8.
9. Wesley AW, Horne AM, Elliott RB. Problems in diagnosis of cystic fibrosis. N Z Med J 1984;97:773-5.
10. Garner P, Panpanich R, Logan S. Is routine growth monitoring effective? A systematic review of trials. Arch Dis Child 2000;82:197-201.
11. Grote FK, Oostdijk W, de Muinck Keizer-Schrama SMPF, Dekker FW, Verkerk PH, Wit JM. Growth monitoring and diagnostic work-up of short stature: an international inventorisation. J Pediatr Endocrinol Metab 2005;18:1031-8.
12. Hall DM. Growth monitoring. Arch Dis Child 2000;82:10-5.
13. de Muinck Keizer-Schrama SM. [Consensus 'diagnosis of short stature in children.' National Organization for Quality Assurance in Hospitals]. Ned Tijdschr Geneeskd 1998;142:2519-25.
14. Wilcox WD, Nieburg P, Miller DS. Failure to thrive. A continuing problem of definition. Clin Pediatr (Phila) 1989;28:391-4.
15. van Buuren S, van Dommelen P, Zandwijken GR, Grote FK, Wit JM, Verkerk PH. Towards evidence based referral criteria for growth monitoring. Arch Dis Child 2004;89:336-41.
16. Landsmeer-Beker EA, Bouwmeester-Landweer MBR, Korbee-Haverhoek HD, Kousemaker NPJ, Baartman HEM, Wit JM, Dekker FW. Non-response on a postal questionnaire adressing risk factors for child maltreatment. In: Bouwmeester-Landweer MBR. Early home visitation in families at risk for maltreatment. Thesis, Leiden University Medical Center, 2006
17. Herngreen WP, Reerink JD, van Noord-Zaadstra B.M., Verloove-Vanhorick SP, Ruys JH. The SMOCC-study: Design of a representative cohort of live-born infants in the Netherlands. Eur J Public Health 1992;2:117-22.
18. Herngreen WP, van Buuren S, van Wieringen JC, Reerink JD, Verloove-Vanhorick SP, Ruys JH. Growth in length and weight from birth to 2 years of a representative sample of Netherlands children (born in 1988-89) related to socioeconomic status and other background characteristics. Ann Hum Biol 1994;21:449-63.
19. Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E, Roede MJ, Verloove-Vanhorick SP, Wit JM. Continuing positive secular growth change in The Netherlands 1955-1997. Pediatr Res 2000;47:316-23.

20. Fredriks AM, van Buuren S, Wit JM, Verloove-Vanhorick SP. Body index measurements in 1996-7 compared with 1980. Arch Dis Child 2000;82:107-12.
21. Niklasson A, Ericson A, Fryer JG, Karlberg J, Lawrence C, Karlberg P. An update of the Swedish reference standards for weight, length and head circumference at birth for given gestational age (1977-1981). Acta Paediatr Scand 1991;80:756-62.
22. van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. Stat Med 1999;18:681-94.
23. Karlberg J, Kjellmer I, Kristiansson B. Linear growth in children with cystic fibrosis. I. Birth to 8 years of age. Acta Paediatr Scand 1991;80:508-14.
24. Brand J, van Buuren S, van Mulligen EM, Timmers T, Gelsema E. Multiple imputation as a missing data machine. Proc Annu Symp Comput Appl Med Care 1994;303-6.
25. Lai HC, Kosorok MR, Sondel SA, Chen ST, FitzSimmons SC, Green CG, Shen G, Walker S, Farrell PM. Growth status in children with cystic fibrosis based on the National Cystic Fibrosis Patient Registry data: evaluation of various criteria used to identify malnutrition. J Pediatr 1998;132:478-85.
26. Raynor P,.Rudolf MC. Anthropometric indices of failure to thrive. Arch Dis Child 2000;82:364-5.
27. Wright JA, Ashenburg CA, Whitaker RC. Comparison of methods to categorize undernutrition in children. J Pediatr 1994;124:944-6.
28. Farrell PM, Kosorok MR, Rock MJ, Laxova A, Zeng L, Lai HC, Hoffman G, Laessig RH, Splaingard ML. Early diagnosis of cystic fibrosis through neonatal screening prevents severe malnutrition and improves long-term growth. Wisconsin Cystic Fibrosis Neonatal Screening Study Group. Pediatrics 2001;107:1-13.
29. Haeusler G, Frisch H, Waldhor T, Gotz M. Perspectives of longitudinal growth in cystic fibrosis from birth to adult age. Eur J Pediatr 1994;153:158-63.
30. Kraemer R, Aebi C, Casaulta AC, Gallati S. Early detection of lung disease and its association with the nutritional status, genetic background and life events in patients with cystic fibrosis. Respiration 2000;67:477-90.
31. Waters DL, Wilcken B, Irwing L, Van Asperen P, Mellis C, Simpson JM, Brown J, Gaskin KJ. Clinical outcomes of newborn screening for cystic fibrosis. Arch Dis Child Fetal Neonatal Ed 1999;80:F1-F7.
32. Accurso FJ, Sontag MK, Wagener JS. Complications associated with symptomatic diagnosis in infants with cystic fibrosis. J Pediatr 2005;147:S37-S41.
33. Grote F.K., Planten W.A., Oostdijk, W., Dekker, F. W., and Wit, J. M. The probability of Cystic Fibrosis in infants and children with failure to thrive. Arch Dis Child . 2006. In Press
34. Lai HJ, Cheng Y, Farrell PM. The survival advantage of patients with cystic fibrosis diagnosed through neonatal screening: evidence from the United States Cystic Fibrosis Foundation registry data. J Pediatr 2005;147:S57-S63.
35. Sims EJ, McCormick J, Mehta G, Mehta A. Neonatal screening for cystic fibrosis is beneficial even in the context of modern treatment. J Pediatr 2005;147:S42-S46.
36. Dankert-Roelse JE,.Merelle ME. Review of outcomes of neonatal screening for cystic fibrosis versus non-screening in Europe. J Pediatr 2005;147:S15-S20.

Part E

Radiographic evaluation

Chapter 11

Radiographic evaluation of children with growth disorders

S.G. Kant[1], F. Grote[2], M.H. de Ru[1,2], W. Oostdijk[2], H.M. Zonderland[3], M.H. Breuning[1], J.M. Wit[2]

[1] Center for Human and Clinical Genetics, Department of Clinical Genetics
[2] Department of Pediatrics
[3] Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands.

Submitted

Abstract

Short stature as well as tall stature can have a wide variety of causes. Tall stature is usually experienced as a less important problem than short stature, but for both clinical presentations it is important to make a correct diagnosis as to etiology. The identification of the diagnosis frequently relies on radiological criteria. However, no international uniformity exists with respect to the radiographic evaluation of children with growth problems. We recommend that in patients with a possible diagnosis of a skeletal dysplasia a skeletal survey must be performed. In patients with a proportionate stature radiographic analysis of the hand and wrist will be sufficient in most cases. However, whenever there are clinical abnormalities with a possible underlying bone anomaly, a modified skeletal survey is appropriate. The combination of clinical and biochemical features and an appropriate skeletal survey can often make the correct diagnosis and/or guide the subsequent molecular analysis.

Introduction

Growth disorders are a major concern for parents and their children, and it can be the first sign of a pathologic condition. A height more than 2.0 standard deviations (SD) below or above the mean, corrected for sex and age, is considered as short stature and tall stature respectively, but these limits are arbitrary. Tall stature is frequently associated with positive qualities of character and high social status, and is generally seen as a less serious problem than short stature, although tall girl often face social problems. Nevertheless, for both clinical presentations it is important to search for the cause of the growth problem, in order to know the therapeutical options and the natural course of the disorder, and for genetic counseling.

Many causes of growth disorders are known, and are usually classified as primary growth disorders, secondary growth disorders and idiopathic short or tall stature.[1, 2] Whenever a child has a growth disorder, it is important to measure body proportions. Body proportions can best be described as the ratio between sitting height and total height. This ratio is dependent on the age of the child. Several age references have been published.[3-6] Relating arm span to heigth can also be considered, but one has to keep in mind that in a patient with short limbs total height is affected by the shortened legs. The ratio between arm span and height can therefore be normal, while clinically there is clear disproportion. Disproportion is usually defined as an abnormal ratio between the length of the trunk and the length of the limbs. When the child has a disproportionate short stature there is a high suspicion of a skeletal dysplasia. In most cases this means relatively short legs compared to the trunk, but a disproportion can also consist of a normal or short trunk with relatively long legs and/or arms.

In order to differentiate familial or constitutional growth problems from pathologic growth disorders, the patient's history, the family history and parental heights, physical examination and reviewing of growth charts is needed. Further examinations generally consist of a radiograph of the left hand and wrist to define bone age. When there is still no indication for a particular disorder laboratory measurements in blood are performed to search for infectious diseases, anemia, systemic disorders or gastrointestinal and endocrine abnormalities.[7]
More specialized examinations, like chromosome analysis or growth hormone stimulation tests, are needed if a specific disorder is suspected. Whenever there is a suspicion of a skeletal dysplasia, radiographic analysis (especially worthwhile in the growing child) is important to get to a more precise diagnosis, or to narrow down the number of possibilities.

The aim of this review is to make an inventory of what is known about the skeletal survey that is needed with respect to the different growth problems: short or tall stature, with or without disproportion. For this purpose, we searched for relevant literature in the biomedical literature databases PubMed and Embase, and in standard texts, in order to come up with advice on this subject for physicians dealing with children with growth disorders.

Radiographic evaluation in children with short stature

Radiographic evaluation in children with short stature is usually meant to confirm a suspected skeletal dysplasia, and to help differentiate between the many types that are known. Various guidelines for radiographic analysis of disproportionate short stature (table 1) are available.[8-13]

Table 1 Reported guidelines for skeletal survey in children with disproportionate short stature

		ESDN (2003) [8]	ISDR (2004) [9]	ACR (2001) [10]	Lachman (1998) [11]	Mortier (2001) [12]	Offiah (2003) [13]
Skull	- AP	-	+	+	+[d]	+	+
	- lateral	-	+	+	+	+	+
Spine	- AP	+	+[b]	+	+	+	+[g]
	- lateral	+	+	+	+[e]	+	+
Thorax	- AP (ribtechnique)	+	+	+[c]	+	+	+
Pelvis (including hips) - AP		+	+	+	+	+	+
Upper limb - AP		-	+	+, bi	+	+	+
Hand/wrist (left) - AP or PA		+	+, bi	+, bi	+, bi	+	+
Lower limb - AP		+[a], bi	+	+, bi	+	+[f]	+
Foot	- AP	-	+, bi	+, bi	+, bi	-	-

ESDN = European Skeletal Dysplasia Network
ISDR = International Skeletal Dysplasia Registry (of the Cedars-Sinai Medical Center)
ACR = American College of Radiology
bi = bilateral

[a] only a view of the knee recommended, AP and lateral
[b] from the cervical spine only a lateral view recommended
[c] also a lateral view of the thorax recommended
[d] also a Towne's projection recommended to ascertain the size of the foramen magnum and the base of the skull
[e] separate flexion-extension views of the cervical spine recommended to evaluate the odontoid and C1-C2 dislocation
[f] lateral view of the knee recommended to view the patella
[g] only a view of the thoracolumbar spine recommended

The significance of the radiographs of different parts of the skeleton has been commented on in many reports.[11, 13-19] and is summarized below.

Skull

A radiograph of the skull can provide supplementary information that supports the diagnosis. Clinical features like microcephaly or macrocephaly, or craniosynostosis can be confirmed with a radiograph. The size of the fontanels is important to record, because it is known that these can be rather large with delayed closure in cleidocranial dysplasia.

Spine and ribs

Radiographs of the whole spine, including the cervical region, are made for a good view of the position of the spine, to define a possible scoliosis, kyphosis or pronounced lumbar lordosis. Besides, the width of the spinal canal is measured. Progressive caudal narrowing of the interpedicular distance and stenosis of the lumbar spinal canal might be an indication for achondroplasia or hypochondroplasia. Finally, the shape and size of all the vertebra is observed. For instance, platyspondyly (flattening of the vertebra) is typical for osteogenesis imperfecta or spondyloepiphyseal dysplasia.
A frontal view of the thorax is useful when abnormalities of the ribs are suspected. Besides, the scapulae and clavicles can be viewed in such a radiograph.

Pelvis

The pelvis is often abnormal in skeletal dysplasias, especially the size and shape of the iliac wings and the ossification pattern. In most neonatal chondrodystrophies delayed ossification of the pubic bones is seen.

Long bones

Radiographs of the long bones are made to enable the measurements of the different bone lengths, in order to differentiate between rhizomelic (proximal segment or upper arm/leg), mesomelic (middle segment or under arm/leg) or acromelic (distal segment or hand/foot) shortening. Besides, it can be established whether the problem is located in the epiphysis, metaphysis or diaphysis.

Hands and feet

A radiograph of the left hand and wrist is generally made to establish bone age. It is assumed that the shape and development of the phalanges and metacarpals on this radiograph reflect the development of those bones that define total body height (vertebra and long bones in the legs). However, a radiograph of the hand and wrist is also important when looking for morphologic abnormalities, for instance a trident hand as an indication for achondroplasia. Furthermore, one should look for fusion of the phalanges, oligodactyly or polydactyly. For example, syndactyly can occur in Holt-Oram syndrome.
Radiographs of the feet rarely contribute to the diagnostic process in short stature, because mostly the same abnormalities are seen in the hands and and many more variations of normal ossification occur in the feet.

According to some of the reported guidelines radiographic evaluation of the long bones can be restricted to one side of the body, unless the child has body asymmetry.[12, 13] Others are less explicit on this subject [8, 9, 11] and the ACR guideline [10] advise radiographs of both upper limbs and both lower limbs for complete evaluation. The evaluation can be repeated, mostly with an interval of two years, because some features become clearer when a child grows older.[13, 20]
In the fetus or newborn frontal and lateral views of the total body ("babygrams") often suffice for most diagnoses, but carefully positioned separate films are preferred, or as an adjunct at least separate films of the hands.[11, 13, 16]

In patients with proportionate short stature a radiograph of the left hand and wrist, in order to define skeletal maturation (bone age), will usually be sufficient.[11,19] An extensive skeletal survey is not considered useful in these patients, because abnormalities of the skeleton are not expected. In order to define bone age the different bones in the hand are compared to reference radiographs.[21, 22] In this way it is also possible to make a rough estimation of the expected final height.[22, 23] This will be most reliable from the age of 6-8 years, depending on the method used.[24]

Short stature with normal proportions is usually not related to a skeletal dysplasia, but there are several exceptions. This means that in a child with short stature and normal body proportions, it is still important to look for dysmorphic features and/or congenital anomalies. A cleft palate can be part of Stickler syndrome, specific toe abnormalities can indicate Otopalatodigital syndrome, while the Madelung deformity is a strong indication for Leri-Weill dyschondrosteosis. Such abnormal findings can warrant targeted extension of radiographic analysis.

In some instances a radiograph of the hand is used for metacarpophalangeal pattern profile (MCPP) analysis. Determining the MCPP is a method to standardize the length of the phalangeal and metacarpal bones in the form of a Z-score. This score is defined by the difference in length between one of the hand bones and a reference length for this bone, corrected for sex and age, divided by the standard deviation of the used reference length.[25, 26] These Z-scores for the 19 hand bones are plotted in graphics, which shows that different syndromes have different patterns. Specific MCPP's have, among others, been published for achondroplasia, Robinow syndrome, Noonan syndrome, Turner syndrome and Leri-Weill dyschondrosteosis.[27-31] In most cases an MCPP analysis is used to help support a certain diagnosis, especially when molecular analysis to confirm the diagnosis is not possible.

Radiographic evaluation in children with tall stature

No guidelines exist for radiographic analysis of tall stature. Generally, a skeletal survey is not necessary, because the suspicion of a skeletal dysplasia in the case of tall stature is low. Whenever children with tall stature have clinical abnormalities suggesting skeletal abnormalities, the accompanying clinical features lead to a targeted radiographic analysis, instead of a routine skeletal survey. For instance in sclerosteosis [32] radiographs of the skull and hands will be sufficient, while a more extended series of radiographs is needed in the case of one specific form of spondyloepiphyseal dysplasia.[33] This policy is comparable to that for children with proportionate short stature who have accompanying abnormalities.

The most important radiograph in children with tall stature is an X-ray of the left hand and wrist, in order to define skeletal maturation (bone age) [21, 22] and predict final height.[22, 23] Children with tall stature often have an advanced skeletal maturation. This is seen in constitutional or familial tall stature, but also in some endocrine disorders (precocious puberty, adrenal hyperplasia) and in several overgrowth syndromes (Sotos syndrome,

Weaver syndrome). A delayed skeletal maturation is rarely seen in patients with tall stature, but does exist for example in cases of hypogonadism.[34]

A radiograph of the hand can also be used to notice possible osteoporosis in patients with tall stature based on a sex chromosome abnormality, like Klinefelter syndrome (47,XXY). Androgen deficiency in boys and men with Klinefelter syndrome is an important risk factor for osteoporosis. Treatment with testosterone supplements increases the bone mineral density, and should be started preferably at the beginning of puberty.[35] However, a radiograph of the hand and wrist may only provide an indication of osteoporosis. Bone mineral density is best measured by bone densitometry.

MCPP's with a specific pattern have also been published for some syndromes with tall stature, like Sotos syndrome and Marfan syndrome.[36, 37] Since molecular analysis is possible for both syndromes in respectively the NSD1 and FBN1 gene, the clinical relevance is not very high. However, not in all clinically distinct cases of Sotos or Marfan syndrome can a gene abnormality be identified. In these patients an MCPP is useful to support the clinical diagnosis.

To define arachnodactyly the metacarpal index (MCI) can be used. This index represents the ratio of the mean length to the mean width of the second to fifth metacarpal bones. In arachnodactyly the index is more than 8.5, while normally the index is less than 7.9. Arachnodactyly is a typical feature in Marfan syndrome, but is also reported in homocystinuria, osteogenesis imperfecta, dystrophia myotonica, Ehlers-Danlos syndrome, contractural arachnodactyly (Beals syndrome), and constitutional tall stature.[38, 39]

Discussion

Owing to the fast development and implementation of molecular genetics in recent years, it is nowadays possible to diagnose various growth disorders by DNA analysis. Because of the high costs that go with molecular investigations, it is advisable to ask for a targeted gene analysis. This is why radiographic analysis is still of eminent importance in the analysis of growth disorders. Results of radiographic analysis can guide molecular analysis, and therefore can contribute to an efficient approach to diagnosing growth disorders.[40]

Recommendations for conventional radiographic analysis are different for children with short and tall stature. Particularly in children with ***disproportionate short*** stature a series of radiographs known collectively as a skeletal survey is indicated.[11, 13, 19] Various skeletal surveys with different contents have been suggested (table 1).[8-13] Guidelines for pediatricians in The Netherlands were published in 1998.[41] These guidelines were based on consensus and consisted of a radiograph of the left hand and wrist, a radiograph of the lumbar spine, humerus and femur. In our experience these series of radiographs have turned out to be too limited in clinical practice. Other, more extended guidelines that are recommended also lack scientific evidence. Most of these are based on clinical experience and the philosophy that visualization of both the axial skeleton and the long and short

tubular bones enables a reliable differentiation between the different skeletal disorders.[2, 12, 13, 16, 17]

Uniformity in its application will enable research to define sensitivity and specificity of the different radiographs in the future. Looking at the overlap between the different skeletal surveys in table 1, and taking into account the reported relevance of each radiograph , we recommend to use a series of radiographs as noted in table 2. This skeletal survey matches almost completely with the ones recommended by Mortier [12] and Offiah.[13] Further research is needed to collect scientific evidence for the usefulness of this series of radiographs.

Table 2. Recommendations for radiographic analysis in children with growth disorders

Short stature		Tall stature
Disproportionate	Proportionate	Disproportionate/proportionate
Skull (PA and lateral)	Left hand/wrist (PA)	Left hand/wrist (PA)
Spine (AP and lateral)		
Thorax (AP)	Further films dictated by clinical	Further films dictated by clinical
Pelvis (AP)	features	features
Upper limb (AP)		
Left hand and wrist (PA)		
Lower limb (AP)		

PA = posteroanterior view AP = anteroposterior view lateral = lateral view

In children with a ***proportionate*** stature, whether short or tall, a radiograph of the left hand and wrist is often sufficient, to define skeletal maturity and predict final height. A modified skeletal survey is appropriate only whenever clinical abnormalities suggest skeletal anomalies. In children with ***disproportionate tall*** stature radiographic analysis is also defined by the clinical abnormalities observed.

One has to keep in mind that the methods used to define skeletal maturation are based on data from normal children, and are not demonstrated to be accurate in children with growth abnormalities. Besides, the normal rate of skeletal maturation differs between males and females, and between different ethnic groups.[42] Even though the data on which skeletal maturation is based originate from the 1930's, they are still applicable nowadays.[43]

In children, of course, radiation dose must be kept as low as possible. The skeletal survey we propose consists of conventional radiographs, of which the radiation dose in the course of years has diminished, as a result of progressive modernizing of equipment. Radiation dose in this series of radiographs can therefore be considered as low.[44] By choosing a systematic approach, the number of radiographs can be reduced to a minimum and irrational radiographs of several parts of the skeleton are avoided. In this way conventional radiographs are a safe and valuable contribution to the diagnosis of growth disorders.

References

1. Reiter EO, Rosenfeld RG: Normal and aberrant growth; in Larsen PR, Kronenberg HM, Melmed S, Polonsky KS (eds.): Williams Textbook of Endocrinology. Philadelphia, Saunders, 2003, pp 1003-1114.
2. Drop SL, Greggio N, Cappa M, Bernasconi S; International Workshop on Management of Puberty for Optimum Auxological Results: Current concepts in tall stature and overgrowth syndromes. J Pediatr Endocrinol Metab 2001;14 Suppl 2:975-984.
3. Dangour AD, Schilg S, Hulse JA, Cole TJ: Sitting height and subischial leg length centile curves for boys and girls from Southeast England. Ann Hum Biol 2002;29:290-305.
4. Prader A, Largo RH, Molinari L, Issler C: Physical growth of Swiss children from birth to 20 years of age. First Zurich longitudinal study of growth and development. Helv Paediatr Acta Suppl.1989;52:1-125.
5. Gerver WJ, De Bruin R: Relationship between height, sitting height and subischial leg length in Dutch children: presentation of normal values. Acta Paediatr 1995;84:532-535.
6. Fredriks AM, Van Buuren S, van Heel WJM, Dijkman-Neerincx RHM, Verloove-Vanhorick SP, Wit JM : Nation-wide age references for sitting height, leg length and sitting height/height ratio and their diagnostic value for disproportionate growth disorders. Arch Dis Child 2005;90:807-812.
7. Grote FK, Oostdijk W, de Muinck Keizer-Schrama SMPF, Dekker FW, Verkerk PH, Wit JM: Growth monitoring and diagnostic work-up of short stature: an international inventorization. J Ped Endocrinol Metab 2005;18:1031-1038.
8. European Skeletal Dysplasia Network. Radiographs required. 2003. www.esdn.org/radiographs.html.
9. The International Skeletal Dysplasia Registry. Cedars-Sinai Medical Centre, Los Angeles, USA 2000-2004. www.csmc.edu/3810.html.
10. ACR practice guideline for skeletal surveys in children. The American College of Radiology, 2001. www.acr.org.
11. Lachman RS: Radiologic and imaging assessment of the skeletal dysplasias; in Kelnar CJH, Savage MO, Stirling HF and Saenger P (eds.): Growth disorders. Pathophysiology and treatment. London, Chapman & Hall, 1998, pp 251-264.
12. Mortier GR: The diagnosis of skeletal dysplasias: a multidisciplinary approach. Eur J Radiol 2001;40:161-167.
13. Offiah AC, Hall CM: Radiological diagnosis of the constitutional disorders of bone. As easy as A, B, C? Pediatr Radiol 2003;33:153-161.
14. Lachman RS: The cervical spine in the skeletal dysplasias and associated disorders. Pediatr Radiol 1997;27:402-408.
15. Mortier GR, Rimoin DL, Lachman RS: The scapula as a window to the diagnosis of skeletal dysplasias. Pediatr Radiol 1997;27:447-451.
16. Macpherson RI, Pai GS: Evaluation of newborns with skeletal dysplasias. Indian J Pediatr 2000;67:907-913.
17. Vanhoenacker FM, Van Hul W, Gielen J, De Schepper AM: Congenital skeletal abnormalities: an introduction to the radiological semiology. Eur J Radiol 2001;40:168-183.
18. Glass RBJ, Fernbach SK, Norton KI, Choi PS, Naidich TP. The infant skull: a vault of information. Radiographics 2004; 24: 507-22.
19. Lachman RS: Skeletal dysplasias; in Kuhn JP, Slovis TL, Haller JO (eds.): Caffey's pediatric diagnostic imaging. Philadephia, Mosby/Elsevier, 2004, pp 2122-2180.
20. Giedion A : The weight of the fourth dimension for the diagnosis of genetic bone disease. Pediatr Radiol 1994;24:387-391.
21. Greulich WW, Pyle SJ: Radiographic atlas of skeletal development of the hand and wrist, ed 2, California, Stanford University Press, 1959.

22. Tanner JM, Healy MJR, Goldstein H, Cameron N (eds): Assessment of skeletal maturity and prediction of adult height (TW3-method), ed 3, London, WB Saunders, 2001.
23. Bayley N, Pinneau SR: Tables for predicting adult height from skeletal age: revised for use with the Greulich-Pyle hand standards. J Pediatr 1952;40:423-441.
24. Clark PA, Rogol AD: Somatic growth and its regulation; in Kostyo JL and Goodman HM (eds): Handbook of physiology, section 7: the endocrine system, volume V: hormonal control of growth, ed 1, New York/Oxford, Oxford University Press, 1999, pp 37-59.
25. Poznanski AK, Garn SM, Nagy JM, Gall JC: Metacarpophalangeal pattern profiles in the evaluation of skeletal malformations. Radiology 1972;104:1-11.
26. Butler MG, Meaney FJ, Kaler SG: Metacarpophalangeal pattern profile analysis in clinical genetics: an applied anthropometric method. Am J Phys Anthropol 1986;70:195-201.
27. Ingemarsson S, Fenger K: Metacarpophalangeal relations in 21 Danish patients with achondroplasia. Dan Med Bull 1988;35:104-107.
28. Butler MG, Gale DD, Meaney FJ, Wadlington WB, Robinow M: Metacarpophalangeal pattern profile analysis in Robinow syndrome.
Am J Med Genet 1987;27:219-223.
29. Butler MG, Kumar R, Davis MF, Gale DD, Dahir GA, Meaney FJ: Metacarpophalangeal pattern profile analysis in Noonan syndrome.
Am J Med Genet 2000;92:128-131.
30. Laurencikas E, Söderman E, Davenport M, Jorulf H, Sävendahl L: Metacarpophalangeal pattern profile analysis as a tool for early diagnosis of Turner syndrome. Acta Radiol 2005;46:424-430.
31. Laurencikas E, Söderman E, Grigelioniene G, Hagenäs L, Jorulf H: Metacarpophalangeal pattern profile analysis in Leri-Weill dyschondrosteosis.
Acta Radiol 2005;46:200-207.
32. Hamersma H, Gardner J, Beighton P: The natural history of sclerosteosis. Clin Genet 2003;63:192-197.
33. Bleasel JF, Holderbaum D, Mallock V, Haqqi TM, Williams HJ, Moskowitz RW: Hereditary osteoarthritis with mild spondyloepiphyseal dysplasia--are there "hot spots" on COL2A1? J Rheumatol 1996;23:1594-1598.
34. Leung AK, Robson WL: Evaluating tall children. Can Fam Physician 1995;41:457-458, 461-462, 465-468.
35. Smyth CM, Bremner WJ: Klinefelter syndrome. Arch Intern Med 1998;158:1309-1314.
36. Dijkstra PF, Cole TR, Oorthuys JW, Venema HW, Oosting J, Nocker RE: Metacarpophalangeal pattern profile analysis in Sotos and Marfan syndrome.
Am J Med Genet 1994;51:55-60.
37. Butler MG, Meaney FJ, Kittur S, Hersh JH, Hornstein L: Metacarpophalangeal pattern profile analysis in Sotos syndrome. Am J Med Genet 1985;20:625-629.
38. Walker BA, Beighton PH, Murdoch JL : The Marfanoid hypermobility syndrome. Ann Intern Med 1969;71:349-352.
39. Nelle M, Tröger J, Rupprath G, Bettendorf M : Metacarpal index in Marfan's syndrome and in constitutional tall stature. Arch Dis Child 1994;70:149-150.
40. Lachman RS, Krakow D, Cohn DH, Rimoin DL : MED, ***COMP***, multilayered and NEIN: an overview of multiple epiphyseal dysplasia. Pediatr Radiol 2005;35:116-123.
41. de Muinck Keizer-Schrama SMPF, Boukes FS, Oostdijk W, Rikken B (red.): Diagnostiek kleine lichaamslengte bij kinderen, ed 1, Alphen aan den Rijn, Van Zuiden Communications B.V., 1988.
42. Rosenfeld RG, Cohen P: Disorders of growth hormone/insulin-like growth factor secretion and action, in Sperling MA (ed): Pediatric Endocrinology, ed 2, Philadelphia, Saunders, 2002, pp 211-216.

43. van Rijn RR, Lequin MH, Robben SG, Hop WC, van Kuijk C: Is the Greulich and Pyle atlas still valid for Dutch Caucasian children today? Pediatr Radiol 2001;31:748-752.
44. Brugmans MJ, Buijs WC, Geleijns J, Lembrechts J: Population exposure to diagnostic use of ionizing radiation in The Netherlands. Health Phys 2002;82:500-509.

Part F

New guideline

Chapter 12

Evidence-based guideline for the referral of children with short stature

Floor K. Grote[1#], MD, Paula van Dommelen[2#], Msc, Wilma Oostdijk[1], MD, PhD, Sabine M.P.F. de Muinck Keizer- Schrama[3], MD, PhD, Paul H. Verkerk[4], MD, PhD, Jan Maarten Wit[1], MD, PhD, Stef van Buuren[2,5], Msc, PhD

[1] Dept. of Paediatrics, Leiden University Medical Center, Leiden, The Netherlands
[2] Dept. of Statistics, TNO Quality of life, Leiden, The Netherlands
[3] Dept. of Paediatrics, ErasmusMC - Sophia Children's Hospital, Rotterdam, The Netherlands
[4] Dept. of Child Health, TNO Quality of life, Leiden, The Netherlands
[5] Dept. of Methodology & Statistics, University of Utrecht, The Netherlands
[#] These authors contributed equally to this work

Submitted

Abstract

Objective: To establish evidence-based guidelines for growth monitoring on a population basis.

Study design: Several auxological referral criteria were formulated and applied to longitudinal growth data of four different patient groups, as well as three samples from the general population.

Results: Almost 30 % of pathology can be detected by height standard deviation score (HSDS) below -3 or at least two observations of HSDS below -2.5 at a low false-positive rate (<1%) in 0-3 year old infants. For 3-10 year olds, a rule concerning distance to target height of >2 SD in combination with HSDS < -2.0 has the best predictive value. In combination with a rule concerning severe short stature (<-2.5 SDS) and a minor contribution of a rule concerning height deflection, 85.7% of children with Turner's syndrome and 76.5% of short children due to various disorders are detected at a false-positive rate of 1.5-2%.

Conclusion: The proposed guidelines for growth monitoring show a good sensitivity at an acceptably low false-positive rate in 3-10 year old children. Distance to target height is the most important criterion. Below the age of 3 years the sensitivity is considerably lower. The resulting algorithm appears suitable for industrialized countries, but requires further testing in other populations.

Introduction

Growth monitoring in infancy and childhood has been part of preventive child health programs since more than a century, and short stature or growth retardation is regarded as a relatively early sign of poor health. Despite this longstanding and wide acceptance of growth monitoring, there is little evidence for its effectiveness and efficiency.[1] In developing countries, growth monitoring is primarily aimed at detecting malnutrition. In industrialized countries, where malnutrition is rare, the major purpose of growth monitoring is early detection of growth disorders, such as Turner's syndrome (TS), Growth Hormone deficiency (GHD) and celiac disease (CD).

For early identification of children with abnormal growth one needs good growth monitoring systems as part of preventive child health programs; well-defined and accurate referral criteria; and good diagnostic work-ups after referral. Although most industrialized countries have a child health program including regular growth monitoring, there is a wide diversity in protocols used for growth monitoring and diagnostic work-up of growth disorders, and a virtual absence of experimental studies on the efficacy of these screening and diagnostic procedures.[2] Only few guidelines have been published on referral criteria and diagnostic work-up for children with impaired growth and these are based on consensus meetings rather than on experimental evidence.[3, 4] In the few experimental studies on growth monitoring various referral criteria have been used.[5-7] For failure to thrive, a common term for growth impairment in infants, the situation is even more complicated as there is considerable confusion about the definition and choice of anthropometric indicators.[8]

For a rational approach of growth monitoring, one has first to determine cut-off points of auxological criteria to be used in the decision whether growth-retarded children should be referred for further investigations. In the Netherlands, a consensus meeting was held in the mid nineteen nineties to establish such referral criteria.[3] Three auxological parameters were chosen: height standard deviation score (HSDS), change in HSDS (HSDS deflection), and distance between height and target height SDS. Additional criteria included clinical signs (disproportion or dysmorphism), specific symptoms (as those associated with emotional deprivation), or previous history of low birth weight and/or length (small for gestational age, SGA). Thereafter, however, it was shown that applying the criteria would lead to far too many referrals.[9]

Consequently we started a project aimed at producing evidence-based guidelines for growth monitoring, with high positive predictive values (PPV's) at acceptable false-positive rates. The first step in this process was to study the predictive value of various auxological criteria for the detection of TS.[10] We then studied the auxological parameters of patients with various causes of growth failure referred to the paediatric clinic in two hospitals (Chapter 7). Subsequently, we analysed the percentage of infants and children in three random samples from the general population that would comply with the various screening rules. In the present report we describe the performance of the best auxological parameters in terms of sensitivity and specificity in four groups of patients with growth

disorders and in three supposedly normal population samples, and propose that these can be used in growth monitoring protocols.

Method

Material

For the analysis longitudinal height and weight data from four different patient groups were included, as well as three samples from the general population. Each group was analysed separately. For the patient groups only measurements before or at age of diagnosis or start diet (CD-population) were taken into account.

The first group of patients consisted of 777 girls with TS, collected from three sources and previously described by van Buuren et al.[10] The second group was a group of new patients referred for short stature to the outpatient clinics of the general paediatric departments of two hospitals (Erasmus MC - Sophia Children's Hospital, Rotterdam and Spaarne Hospital, Haarlem) between January 1998 and December 2002 (Chapter 7). Out of 542 children referred to the clinic, 27 children with pathology were found: 7 with GHD, 7 with CD, 3 with TS and 10 with other pathological causes (syndromes (n=2: Noonan's syndrome, M. Leri-Weill), anaemia (n=3), skeletal diseases (n=4) and emotional deprivation (n=1)). Only these 27 children were included in the analyses. The third group consisted of CF patients collected from three major CF clinics in The Netherlands: Erasmus MC - Sophia Children's Hospital in Rotterdam (n=166), University Hospital Maastricht (n=30) and Juliana Children's Hospital in The Hague (n=20) (Chapter 10). The last group was a group of CD-patients consisting of two separate subgroups: 1) a retrospective study described by Damen ***et al.***, in which they studied the catch up growth in patients with celiac disease,[11] and 2) a prospective study on catch up growth by B. Boersma ***et al.***[12]

The relevance for testing the new guidelines varied between the groups. TS is particularly relevant for determining the sensitivity of screening rules as TS is one of the main medical conditions detectable only by growth monitoring. Moreover, it can be well defined (by chromosomal analysis) and growth data from a relatively large group were at our disposal. Another group that was relevant to test the sensitivity was the mixed pathology group (n=27). We observed that growth monitoring is less successful in detecting CF and CD (Chapter 9 and 10). Also, these conditions could be screened and diagnosed in other ways than growth only. Therefore, the proposed guideline was particularly aimed at detecting a high percentage of pathology in the first two patient groups.

For the determination of the specificity of the proposed guidelines, three different reference populations were used. The first reference sample was obtained from the Social Medical Survey of Children Attending Child Health Clinics (SMOCC) cohort, a nationally representative cohort of 2,151 children born in the Netherlands in 1988-1989, consisting of longitudinal data of length and weight up to the age of 2.5 years.[13] The second reference population is a cohort of all children born in the years 1989 and 1990 in Landgraaf and Kerkrade, located in the southern part of The Netherlands ("LIMBURG",

n = 970).[9] The third population is a random sample of children born between 01-01-1985 and 31-12-1988, attending school doctors between 1998 and 2000 in Leiden and Alphen aan den Rijn, the Netherlands ("ZHN", n = 400) (Grote et al, in preparation).

Screening rules

By combining evidence found in previous studies, three auxological referral criteria were formulated. Only criteria of practical value for child health programs were considered.

The first rule takes genetic height potential into account by comparing the HSDS of the child to its target height in combination with a HSDS below a certain cut-off. In our earlier study on TS [10] as well as in a study on a mixed population of short children (Grote et al, in preparation) we found that this combination offers the best predictive value. We calculated the test characteristics for a distance between HSDS and target height of more than 2 SDS with cut-off points for height SDS of -2, –1.5, or –1.0 SDS. This rule is labelled "***short for target height and population***" (further called "***short for target height***"). In TS the combination of distance to target height SDS of >2 and HSDS<-2 led to the best sensitivity (76.9%) and specificity (99.4%).[10]

The second rule concerns HSDS for the appropriate reference population. HSDS is generally considered as one of the most important referral criteria, especially when parental height is not available.[2, 4] In order to keep the percentage of false-positives low, we chose a cut-off of -2.5 (~ 0.4th percentile). This cut-off was chosen for historical and pragmatic reasons, as it is the lowest line on the Dutch and various other growth charts. If this rule would be applied irrespective of age and of ethnic origin, it would lead to approximately 6% of referrals,[9] but if only applied to children older than three years using the ethnically appropriate growth charts the referrals decline considerably to approximately 2% (Grote et al, in preparation). This rule is labelled "***very short***".

The third rule applies to deviation of the individual growth curves from the expected growth channels, either expressed as height velocity (cm/year or SDS for age) or as a change of HSDS. The HSDS change is thought to be more suitable, because it better reflects the deviation from canalisation of the growth curve, and because height velocity depends not only on age but also on HSDS position. A low growth velocity has long been considered as the most important growth parameter, and many clinicians can show examples of cases where deflection of growth curve is the only indication of a growth disorder, e.g. an acquired form like GH deficiency caused by a brain tumour or primary hypothyroidism by Hashimoto disease. However, its usefulness for growth screening appears limited. Voss et al found that height velocity did not distinguish short stature due to pathology from normal short stature.[7] We have shown this earlier for children with growth hormone deficiency.[14] Van Buuren et al found that a height deflection of more than 0.25 SDS would lead to a large number of false-positives.[9] The predictive value of deflection can be improved if one demands a continuous deflection over 3 years (e.g. 0.25 SDS/yr during at least 3 years),[10, 14] a larger deflection over an undefined time interval (e.g. a deflection of >1.0 SDS), or in combination with an absolute HSDS<-2. In the present analysis we combined various expressions of height deflection (per year

or cumulative) with various cut-off points for HSDS (<-2.0, <-1.5 or <-1.0). This decision rule is labelled "***height deflection and short for population***" (further called "***height deflection***"). We decided that deflection with a cut-off of 1.0 SDS over an undetermined time interval would be most practical, as this should detect both a slow and fast bend of the growth curve, and most growth reference diagrams include lines with a distance of 1 SDS.[15]

Analytic procedure

Length, height, weight, target height, body mass index (BMI) and weight for length or height were expressed as SDS, using recent Dutch, Turkish and Moroccan reference data.[16-19] All criteria were first analysed for all age-groups. As growth curves in the first three years can cross SDS lines when birth length SDS is far from target height SDS, and length measurements are less accurate, specificity of the various rules is expected to be lower than in later years, leading to too many referrals.[9] We therefore performed separate analyses in two age groups (0-3 and 3-10 years), and calculated test characteristics for different cut-off values (HSDS -3.0, -2.5, -2.0, -1.5 and -1.0) and other additive parameters.

Parental height was frequently (4-58%) missing in the various data sets. We imputed these data under the assumption that data were missing at random using Multivariate Imputation by Chained Equations (MICE).[20] The method created multivariate imputations by applying sequential linear regressions, where each incomplete variable was imputed conditionally on all variables in an iterative fashion. The imputation model consisted of the last known HSDS (except for the CF-population where we chose the HSDS closest to the age of 5 years instead), HSDS, weight SDS, weight for height SDS, BMI SDS, gender (except for the TS group as these are all girls), HSDS of the father and/or HSDS of the mother (if available), ethnicity (except for the TS and Limburg cohort) and for CF and CD age at diagnosis or start diet. For CF HSDS at the age of 5 was chosen for the imputation model instead of the last known height, because in most children catch-up growth has resulted in a normal height at this age.[21] The number of iterations was set to 15. Predictive mean matching was used to create parental height imputations. The imputation method includes parameter uncertainty, preserves the multivariate structure in the data and has good coverage properties.[22]

Calculations were based on the assumption that a child is referred if the growth pattern meets the criteria of a given screening rule for the first time. All rules were analysed separately as well as in combination with the others. A false-positive rate of <1% for the separate rules and < 2% for the combined rules was assumed to be acceptable from the perspective of preventive child health care.

Results

As the data were gathered retrospectively, there was no fixed schedule of measurements, resulting in a varying number of measurements per individual child. Table 1 shows the number of children per age group and the mean number of measurements.

Table 1. Number of children (N) and mean number of measurements (n) per child in each group

		Limburg N=970	ZHN N=400	SMOCC N= 2151	Turner's syndrome N= 777*	Short stature due to pathology N= 27	Cystic Fibrosis N=216	Celiac disease N=120
Age group	Number of measurements	N (n)	N (n)	N (n)	N (n)	N (n)	N (n)	N (n)
0-3	≥1 AND at least 1 weight measurement before 0.1 years†	931 (11)	341 (11)	1942 (8)	353 (4)	23 (6)	89 (5)	86 (7)
	≥2 with 0.5-1 year interval AND at least 1 weight measurement before 0.1 years†	810 (12)	321 (14)	1835 (9)	158 (8)	15 (9)	32 (10)	66 (12)
3-10	≥1	958 (3)	361 (4)	0	524 (5)	17 (3)	25 (2)	22 (4)
	≥2	893 (4)	339 (4)	0	472 (6)	13 (3)	14 (3)	16 (5)

* 492 children had measurements under the age of 3 years.

† At least 1 weight measurement before 0.1 years is necessary to be able to exclude children with a birth weight < 2500 grams or a first measurement within 0.1 year (5 weeks) with weight SDS< -2 if no birth weight available, and gestational age <37 weeks (or not available) (see table 2)

Applying the three auxological criteria to all age groups resulted in a high number of referrals in the general population (presumably false positives) (data not shown). This was primarily due to referrals in the 0-3 year group: the ***height deflection*** and ***short for target height*** rules would produce a high false-positive rate. By adding extra criteria under the age of 3 years and varying the cut-off points, the performance of the different rules were then tested in the two age groups. Scenarios with the best test performance are shown in table 2 and the yield of these best scenarios in terms of sensitivity (true-positives) and 1-specificity (false-positives) are shown in tables 3 and 4, respectively.

Table 2. Referral criteria with the best test characteristics

A.

0-3 years	Criteria	Rule nr.
Repeatedly very short	HSDS_1 < -2.5 and HSDS_2 < -2.5 AND 0.5≤Age_2-Age_1<1 year AND [birth weight >=2500 grams or if no birth weight available than first measurement within 0.1 year (5 weeks) with weight SDS≥ -2, and gestational age ≥37 weeks (or not available)]	1.
Extremely short	HSDS < -3 AND [birth weight ≥2500 grams or if no birth weight available than first measurement within 0.1 year (5 weeks) with weight SDS ≥ -2, and gestational age ≥37 weeks (or not available)]	2.
Combination of rule 1+2		3.

B.

3-10 years	Criteria	Rule nr.
Short for target height and population	HSDS-THSDS < -2 AND HSDS < -2	1.
Very short	HSDS < -2.5	2.
Height deflection (and short for population)	Delta HSDS < -1 AND HSDS < -2	3.
Combination of rule 1+2+3		4.

Table 3. Sensitivity (%) of several auxological rules for four different patient-groups (true-positives)

		Turner's syndrome	Short stature due to pathology	Cystic Fibrosis	Celiac disease
0-3 years	Repeatedly very short*	7.1%	14.8%	0.0%	1.2%
	Extremely short	13.0%	26.1%	6.7%	4.7%
	Combination	14.7%	26.1%	6.7%	4.7%
3-10 years	Short for target height and population	76.9%	58.8%	8.0%	27.3%
	Very short	74.0%	58.8%	4.0%	18.2%
	Height deflection (and short for population)**	13.4%	17.6%	0.0%	18.2%
	Combination	85.7%	76.5%	8.0%	27.3%

Note: if a child has only 1 measurement, the child cannot be referred according to the repeatedly very short rule and the absolute height deflection rule.

* In the subgroup with ≥2 measurements the percentage of referrals would be 15.8% for Turner's syndrome, 26.7% for mixed pathology, and 1.5% for celiac disease

** In the subgroup with ≥ 2 measurements the percentage of referrals would be 14.8% for Turner's syndrome, 23.1% for mixed pathology, and 25.0% for celiac disease.

Table 4. Estimated percentages of referrals in three reference populations (false-positives)

		Limburg	ZHN	SMOCC
0-3 years	Repeatedly very short*	0.2%	0.0%	0.4%
	Extremely short	0.2%	0.6%	0.7%
	Combination	0.3%^	0.6%	0.9%^
3-10 years	Short for target height and population	0.7%	1.1%	NA
	Very short	0.9%	0.8%	NA
	Height deflection (and short for population)**	0.1%	0.8%	NA
	Combination	1.5%#	1.9%#	NA

NA=not available

Note: if a child has only 1 measurement, the child cannot be referred according to the repeatedly very short rule and the absolute height deflection rule.

* Based on subgroup with ≥2 measurements percentage referrals is 0.2% Limburg and 0.4% SMOCC

**Based on subgroup with ≥2 measurements percentage referrals is 0.1% Limburg and 0.9% ZHN

^ No significant difference between Limburg and SMOCC for the combined rule 0-3 years (χ^2 (1)=2.79, p=0.10)

No significant difference between Limburg and ZHN for the combined rule 3-10 years significant (χ^2 (1)=0.38, p=0.54)

For children under the age of three years the true positive rate for pathology is modest, if the false-positive rate has to be kept low. The best rule consists of an HSDS <-2.5 at least twice within 1 year (***very short repeated***) or an HSDS <-3 (***extremely short)*** rule, confined to infants born at or after 37 weeks of gestational age (or when information on gestational age is not available) and born with a weight >= 2500 g (if birth weight was not available, the first measurement within 0.1 year (5 weeks) with a weight SDS >= -2 was used). With this rule 14.7% of the children with TS can be detected, at a false positive rate of <1%. This is probably an underestimation, because the percentage of 7.1% for a repeated HSDS <-2.5 increased to 15.8% by assessing only the subgroup of children with more than 2 measurements. The ***short for target height*** rule did not result in acceptable test characteristics.

Above the age of 3 years a total of 85.7% of children with TS and 76.5% of the children with mixed pathology can be detected by the combination of the ***short for target height*** rule, the ***very short*** rule and the ***height deflection*** rule.

If a stepwise approach would be taken for 3-10 year old children, the ***very short*** rule would add 42 patients (7.7%) to the 76.9% of the girls with Turner syndrome who complied with the ***short for target height*** rule. For the group of children with short stature due to mixed pathology 3 persons (17.7 %) would be added to the 58.8% of children who complied with the ***short for target height*** rule. The addition of this rule would increase the false-positive rate by 0.3 % (1 child) in the ZHN cohort and 0.7% (7 children) in the Limburg cohort. Applying the ***height deflection*** rule after the two other rules would only add few extra patients (4 patients (0.8%) for TS, none for the children with mixed pathology), while the false-positive rate would increase by 0.6% (2 children).

Discussion

In an effort to establish evidence-based guidelines for growth monitoring on a population basis, we studied the performance of a set of decision rules in four groups of patients and three samples from the general population, aiming at a combination of a high sensitivity with an acceptably low false-positive rate. In 0-3 year old infants, after exclusion of babies born preterm and with a low birth weight, we found that a HSDS <-3 or at least two observations of a HSDS <-2.5 within 1 year, has the best performance at a low false-positive rate (<1%). However, only 14.7% of the children with TS and 26.1% of children with other growth disorders can be detected with these rules. For 3-10 year old children the ***short for target height*** rule in combination with the ***very short*** rule and a minor contribution of the ***height deflection*** rule detects 85.7% of children with TS and 76.5% of short children due to various disorders, at a false-positive rate of 1.5-2%. A graphical representation of the algorithm is shown in fig 1.

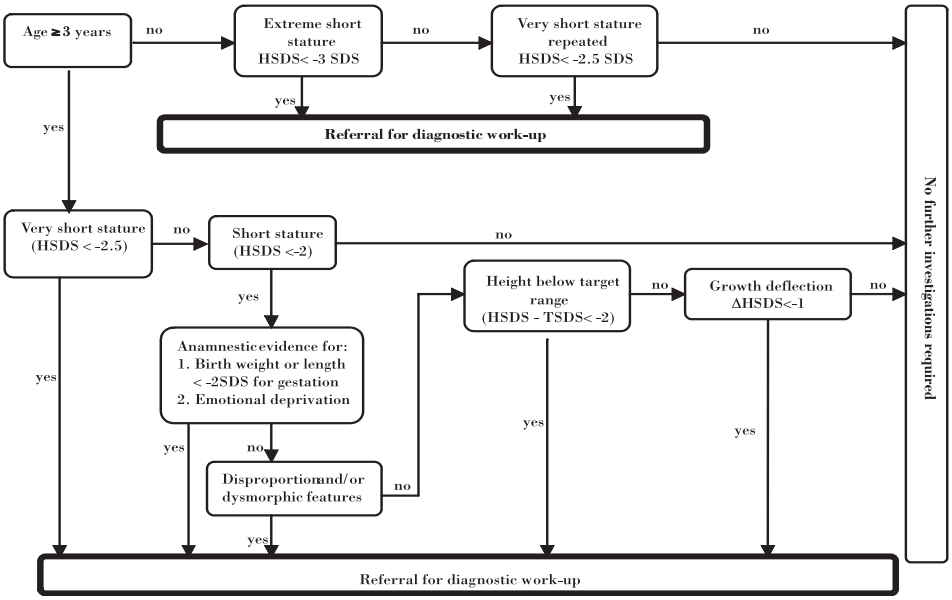


Fig 1. Flowdiagram of proposed criteria for referral of children with growth disorders.
HSDS= Height Standard Deviation
THSDS= Target Height Standard Deviation

The low efficacy and efficiency of growth monitoring between 0-3 years, particularly of rules involving target height and length deflection, is probably mainly caused by the well-established fact that correlation between length and midparental height is low at birth, and rapidly increases during the first 3 years of life.[23] Crossing SDS lines in this age period is therefore not unusual. This is in line with our observation that referral based on a low length velocity or a large distance to target height would lead to too many referrals in this age group, and confirms our earlier data.[9] For this age group the only useful referral rule was based on an extremely low or repeatedly low HSDS. Still, only 15-26% of the growth disorders studied were detected, and even less infants with CF or celiac disease. This is in concurrence with our previous studies on CF and CD, in which we found that weight is a better auxological tool than length at this young age.

In concurrence with our earlier observations in TS,[10] we found that also in a mixed set of growth disorders diagnosed in a pediatric clinic the best decision rule to detect children with pathology older than three years is the ***short for target height*** rule. This result contrasts with earlier speculations that this parameter might be too inaccurate because of the uncertainty of parental height.[4] From a preventive health care perspective the ***height deflection*** rule is of little use. Still, we propose to keep this rule in the algorithm, as it is important that the rare cases with growth deflection due to acquired growth disorders are detected timely. In order to keep the false-positive rate low, we combined HSDS deflection with a HSDS<-2.0, but a severe deflection irrespective of the HSDS reached should be considered as an alarming signal.

There are a number of methodological issues that can be discussed. First, as our data were gathered retrospectively, there was no fixed schedule of measurements, resulting in a variation in the number of measurements between the individual children. In some children only one measurement was available. The deflection could therefore not be calculated or used as a potential referral rule. We assumed for our analyses that these children did not meet the criteria concerning deflection or repetition. This may have led to an underestimation of the suitability of the deflection rule. However, since for the vast majority of the children more than one measurement was available, this underestimation is probably small.

For the algorithm not only auxologic rules are important, but also a number of clinical symptoms and signs. If medical history reveals that birth weight and/or length was low, and HSDS is <-2.0 from the age of approximately 3 years, the diagnosis of persistent short stature after SGA can be made. It is known that approximately 10% of these children do indeed remain short, and do not achieve normal adult height.[24] Referral to a growth clinic is needed for further diagnostic tests and for the decision on growth hormone treatment. As catch-up can emerge within the first 2 years but sometimes between the age of two and three, we set the age limit for catch-up at three years. An important, but fortunately rare, issue in the medical history is to check for symptoms of emotional deprivation (psychosocial short stature).[25-27] Obviously, a thorough physical examination should be carried out, and special attention should be given to body proportions and dysmorphic features. Abnormal body proportions are important signs of skeletal dysplasia and dysmorphic features can direct the attention to various primary growth disorders ("syndromes"). We propose that combining a HSDS<-2.0 with any of these clinical symptoms and signs is sufficient reason for referral.

In conclusion, the proposed guidelines for growth monitoring show a good sensitivity at an acceptably low false-positive rate in 3-10 year old children. Distance to target height is the most important criterion. Below the age of 3 years the guidelines can only detect a small percentage of pathology at an acceptably low false-positive rate, and are therefore of limited use, even if the rules are restricted to children born at term with a normal birth size. The auxological part of the flow diagram can be included into a computer program to assist medical personnel. Besides auxological rules, clinical issues taken form the medical history and physical examination can offer important guidance in taking the decision to refer patients for further tests. The resulting algorithm appears suitable for industrialized countries, but requires further testing in other populations. Finally, no algorithm can fully replace clinical judgement of the physicians, and in case of an unusual growth pattern even if it would not comply with the rules for referral, physicians should still be free to follow their clinical judgement.

Acknowledgements

This study was possible with a grant from ZonMw (grant no. 2100.0050) and supported by an educational grant from Pfizer.

References

1. Garner P, Panpanich R, Logan S. Is routine growth monitoring effective? A systematic review of trials. Arch Dis Child 2000;82:197-201.
2. Grote F.K., Oostdijk W, de Muinck Keizer-Schrama SMPF ***et al.*** Growth monitoring and diagnostic work-up of short stature: an international inventorisation. J Pediatr Endocrinol Metab 2005;18:1031-8.
3. de Muinck Keizer-Schrama SM. [Consensus 'diagnosis of short stature in children.' National Organization for Quality Assurance in Hospitals]. Ned Tijdschr Geneeskd 1998;142:2519-25.
4. Hall DM. Growth monitoring. Arch Dis Child 2000;82:10-5.
5. Ahmed ML, Allen AD, Sharma A, Macfarlane JA, Dunger DB. Evaluation of a district growth screening programme: the Oxford Growth Study. Arch Dis Child 1993;69:361-5.
6. Frindik JP, Kemp SF, Kearns FS, Hale B. Growth screening. A positive medical experience. Clin Pediatr (Phila) 1992;31:497-500.
7. Voss LD, Mulligan J, Betts PR, Wilkin TJ. Poor growth in school entrants as an index of organic disease: the Wessex growth study. BMJ 1992;305:1400-2.
8. Wilcox WD, Nieburg P, Miller DS. Failure to thrive. A continuing problem of definition. Clin Pediatr (Phila) 1989;28:391-4.
9. Van Buuren, S, Bonnemaijer-Kerckhoffs DJ ***et al.*** Many referrals under Dutch short stature guidelines. Arch Dis Child 2004;89:351-2.
10. Van Buuren S, van Dommelen P, Zandwijken GR ***et al.*** Towards evidence based referral criteria for growth monitoring. Arch Dis Child 2004;89:336-41.
11. Damen GM, Boersma B, Wit JM, Heymans HS. Catch-up growth in 60 children with celiac disease. J Pediatr Gastroenterol Nutr 1994;19:394-400.
12. Boersma B, Houwen RH, Blum WF, van Doorn J, Wit JM. Catch-up growth and endocrine changes in childhood celiac disease. Endocrine changes during catch-up growth. Horm Res 2002;58 Suppl 1:57-65.
13. Herngreen WP, Reerink JD, van Noord-Zaadstra B.M., Verloove-Vanhorick SP, Ruys JH. The SMOCC-study: Design of a representative cohort of live-born infants in the Netherlands. Eur J Public Health 1992;2:117-22.
14. Van den Broeck J, Hokken-Koelega A, Wit J. Validity of height velocity as a diagnostic criterion for idiopathic growth hormone deficiency and Turner syndrome. Horm Res 1999;51:68-73.
15. Use and interpretation of anthropometric indicators of nutritional status. WHO Working Group. Bull World Health Organ 1986;64:929-41.
16. Fredriks AM, van Buuren S, Burgmeijer RJ ***et al.*** Continuing positive secular growth change in The Netherlands 1955-1997. Pediatr Res 2000;47:316-23.
17. Fredriks AM, van Buuren S, Wit JM, Verloove-Vanhorick SP. Body index measurements in 1996-7 compared with 1980. Arch Dis Child 2000;82:107-12.
18. Fredriks AM, van Buuren S, Jeurissen SE ***et al.*** Height, weight, body mass index and pubertal development reference values for children of Turkish origin in the Netherlands. Eur J Pediatr 2003;162:788-93.
19. Fredriks AM, van Buuren S, Jeurissen SE ***et al.*** Height, weight, body mass index and pubertal development references for children of Moroccan origin in The Netherlands. Acta Paediatr 2004;93:817-24.
20. Van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. Stat Med 1999;18:681-94.
21. Karlberg J, Kjellmer I, Kristiansson B. Linear growth in children with cystic fibrosis. I. Birth to 8 years of age. Acta Paediatr Scand 1991;80:508-14.
22. Van Buuren S, Brand JPL, Groothuis-Oudshoorn CGM, and Rubin DB. Fully conditional specification in multivariate imputation. Journal of Statistical Computation and Simulation accepted for publication. 2006. Journal (Full)

23. Gibson AT, Carney S, Cavazzoni E, Wales JK. Neonatal and post-natal growth. Horm Res 2000;53 Suppl 1:42-9.
24. Hokken-Koelega AC, De Ridder MA, Lemmen RJ ***et al***. Children born small for gestational age: do they catch up? Pediatr Res 1995;38:267-71.
25. Doeker B, Simic S, Hauffa BP, Andler W. [Psychosocially stunted growth masked as growth hormone deficiency]. Klin Padiatr 1999;211:394-8.
26. Gohlke BC, Khadilkar VV, Skuse D, Stanhope R. Recognition of children with psychosocial short stature: a spectrum of presentation. J Pediatr Endocrinol Metab 1998;11:509-17.
27. Gohlke BC, Frazer FL, Stanhope R. Growth hormone secretion and long-term growth data in children with psychosocial short stature treated by different changes in environment. J Pediatr Endocrinol Metab 2004;17:637-43.

Chapter 13

General discussion

General discussion

The aim of this thesis was to collect evidence for establishing new guidelines for the assessment of short stature in children. In this assessment one can distinguish two parts: 1) auxological screening in the general population; and 2) diagnostic work up in children referred to the specialist. In this chapter we will first discuss the new evidence-based guideline for the auxological part of the assessment of short children, based on the evidence that was collected in the various parts of this project. Thereafter we will discuss the assembled evidence for the diagnostic work up in children with short stature and offer suggestions for a new guideline. Finally, we will discuss the plans for the implementation process of the new guideline in the Netherlands and present proposals for future research.

Auxological screening

As mentioned earlier in this thesis, little experimental evidence can be found in the literature on which schemes for growth monitoring and auxological screening can be based. Various auxological criteria have been used for growth failure in experimental studies, and also in the few consensus-guidelines that have been published on growth monitoring different criteria were proposed for referral of short children.[1-5]

As a first step in this project aimed at establishing evidence based-guidelines we made enquiries among paediatric endocrinologists in Europe and other industrialised countries, as well as among general practitioners and Primary Health Care physicians in the Netherlands, about the referral criteria used for growth monitoring (see part B of this thesis). Height for age, either expressed as centile position or as standard deviation score, was mostly used in industrialized countries with referral protocols for children with short stature, followed by the deviation of height, either expressed as height velocity or delta height SDS. The distance to target height appeared to be used less frequently. Primary Health Care physicians in the Netherlands reported that the distance to target height, as well as height for age, were the most relevant criteria. They thought that clinical signs and symptoms (e.g. disproportion or dysmorphic features) and extreme short stature were the most important referral criteria. They further thought that height deflection would lead to too many referrals. This is in partial agreement with the arguments given by Hall et al in their Consensus statement, i.e. that absolute height is the best referral criterion, and that deflection and the distance to target height are often unreliable.[4]

Subsequently we evaluated the auxological rules of the existing guidelines in practice (Chapter 6) in part C. We confirmed the results of Van Buuren et al [6] that the current Dutch Consensus Guideline would lead to too many referrals (approximately 80%), mainly due to the deflection of length during the first 3 years of life. This is, however, in sharp contrast to the much lower number of referrals for deflection that was expected at the time of the consensus meeting (175 children each year).[7] The discrepancy between the expected and observed specificity can be explained by various factors. First, in this context measurement error is a relevant issue, which for example can become visible as a single low value in between normal measurements. Voss et al reported that in the Wessex study imprecision in auxological assessment was not uncommon and that especially

height velocity over a short period of time is prone to this phenomenon.[8] Second, ethnic variety is an important factor, given the considerable differences in mean height between different ethnic groups. In the original consensus guideline and the study of Van Buuren one population reference was used, while it is now well documented that the "original" Dutch population is considerably longer/taller than for example Moroccan, Turkish and Asian children), and that the growth charts for children with these origins have to be used.[9, 10] Third, the inclusion of growth data from early infancy, where a low length shortly after birth will rapidly increase/decrease into the direction of target height SDS, has presumably a negative effect on specificity. The correlation between length and midparental height is low at birth, and rapidly increases during the first 3 years of life.[11] Crossing SDS lines in this age period is therefore not unusual.

We additionally found that the UK Consensus Guideline leads to far less referrals, but is expected to be relatively insensitive to several clinically relevant growth disorders, as it disregards target height, whereas we found that especially that criterion was most complied with by children with pathology in our evaluation study in secondary health care (***chapter 7***).

To improve the referral pattern of children with short stature we chose in part D three patient groups to determine cut-off points of auxological criteria to be used in the decision whether growth-retarded children should be referred for further investigations. While a great diversity of congenital or acquired conditions can cause short stature, only Turner syndrome (TS), cystic fibrosis (CF) and celiac disease (CD) were taken into account as these are the biggest and most important groups to be detected next to Growth Hormone

Deficiency. As Growth Hormone Deficiency is heterogeneous in its clinical presentation and diagnosed partially on the basis of growth pattern, while no gold standard test is available, we did not consider this group suitable for the determination of appropriate auxological screening criteria for short stature.[12]

We found that growth monitoring is useful to screen for TS. The best decision rule to detect children with TS is the distance between height SDS and target height (the so-called parental height corrected rule). Application of this rule would lead to the referral of 60-77% of girls with TS before the age of 10 years, at acceptable levels of false positives. We recommended the use of a combined rule, i.e. to refer children older than 3 years if HSDS is below –2 and if either HSDS is more than 2 SD below the target HSDS, or HSDS shows a deflection of 0.25 SDS per year or more during a period of at least three years. This rule picks up almost 80% of the girls with TS, while it refers only 0.6% of the non-TS population.

In contrast, the overall performance of detecting CD or CF with auxological criteria is modest. Nevertheless, testing for CD deserves a place in the diagnostic work-up in young children (within the first 2.5 years) with failure to thrive, since it is especially the delayed onset of the disease (the non-classical form) that has increased during the recent years, suggesting that the growth impairment becomes apparent later than previously. Likewise the clinician may consider to test for CF in a diagnostic work-up in children with failure to thrive in the absence of a newborn screening program, since CF is a severe disease

representing itself sometimes with monosymptomatic failure to thrive and up to 45% of the children can be detected within the first year using auxology. Evidently, a much better tool to detect CF at an early age is newborn screening, which has shown beneficial effects on the prognosis of CF and has now been implemented in several countries.[13-15] For the detection of both disorders (CF and CD) rules that consider a deflection of BMI or weight SDS show the best performance and can form the basis for future computer algorithms in child welfare clinics.

Finally, we established a new guideline in part F, by working out the performance of the best auxological parameters in terms of sensitivity and specificity in four groups of patients with growth disorders and in three supposedly normal population samples. The low efficacy and efficiency of growth monitoring between 0-3 years, particularly of rules involving target height and length deflection, led to the only useful referral rule that was based on an extremely low or repeatedly very low HSDS. Still, only 15-26% of the growth disorders studied were detected, and even less infants with CF or CD. This is in concurrence with our previous studies on CF and CD, in which we found that weight is a better auxological tool than length at this young age (***part D***).
Like in our study in TS, we found that also in a mixed set of growth disorders diagnosed in a pediatric clinic the best decision rule to detect children with pathology older than three years is the rule that takes target height into account. We derived that the distance should be more than 2.0 SD, instead of the –1.3 cut-off used in the 1996 Consensus guideline,[7] and combined it with a HSDS <-2.0 in order to limit the number of false positive results. This combined rule resulted also in one of the best combinations of sensitivity and specificity for the detection of TS (***chapter 8***).

Height SDS (HSDS) for age is still considered as one of the most important referral criteria, especially when parental height is not available.[4, 16] A HSDS of -2.5 SD (~ 0.4th percentile) was chosen as cut-off since this leads to an acceptable false-positive rate, while it is the lowest line on most growth charts and therefore suitable for practical use.

Although British investigators have shown that growth velocity over a period of 1 year is of little use as a screening tool,[3] and despite our observations that the change in HSDS per year leads to too many referrals (***chapter 6***), we propose to keep a parameter of growth deflection rule in the algorithm, as it is important that (rare) acquired growth disorders which present primarily with growth deflection are detected timely. By putting the cut-off point at 1 SDS and by omitting the time-limit, we created a practical deflection rule, which detects both a slowly deviating growth curve (for example in girls with Turner syndrome) and a rapid growth retardation, such as seen for example in children with a malignant brain tumor or other acquired growth disorders. Still, in order to keep the false-positive rate low, we combined HSDS deflection with a HSDS<-2.0 for screening purposes, but a severe deflection irrespective of the HSDS attained should also be considered as an alarming signal.

Besides auxological rules, a number of clinical symptoms and signs are important for the algorithm for the referral of children with short stature. As it is known that approximately 10% of children born with a low birth weight and/or length (small for gestational age,

SGA) remain short, and do not achieve normal adult height,[17] the diagnosis of persistent short stature after SGA can be made, if medical history reveals that birth weight and/or length was low, and HSDS is <-2.0 from the age of approximately 3 years. As catch-up usually occurs within the first 2 years but sometimes continues in the third year of life, we set the age limit for catch-up at three years. Likewise the medical history should be checked for symptoms of emotional deprivation (psychosocial short stature). [18-20] Finally, abnormal body proportions are important signs of skeletal dysplasia and dysmorphic features can direct the attention to various primary growth disorders ("syndromes"). We propose that combining a HSDS<-2.0 with any of these clinical symptoms and signs is sufficient reason for referral. The resulting algorithm is presented in fig 1.

Diagnostic work up by the medical specialist

A proper auxological screening for short stature should be followed by an evidence-based diagnostic work-up in secondary health care. However, we could not find experimental evidence supporting the use of a certain diagnostic procedure. The only information in the literature on this issue comes from expert opinion papers on specific guidelines for the diagnosis of growth hormone deficiency in childhood and adolescence,[7, 21, 22] and from the Dutch Consensus Guideline.[7] In addition, we have shown in ***part C, chapter 4*** that while there is agreement among paediatricians in Europe,that some biochemical, radiological and genetic tests have to be used, there is no full consensus on which tests should be preferred. For the presentation of our new recommendations for the diagnostic work up based on the evidence found in our project, we shall follow the various steps suggested by the Dutch Consensus Guideline.

Table 1. Laboratory investigations in the diagnostic work up according the DCG

Laboratory investigations	In order to diagnose	Category
Blood		
Hb, Ht, Leukocytes, Cell indices, leukocyte differentiation, ESR, (Ferritin)	Anemia / infections (and celiac disease and cystic fibrosis)	I
ALAT, ASAT, γGT	Liver diseases	II
Albumin, Creatinine, Sodium, Potassium, Calcium, Phosphate, Alkaline phosphatase, acid-base equilibrium	Renal diseases	III
IgA-anti endomysium, IgA- antigliadin, Anti-tissue glutaminase*, Total IgA	Celiac disease	IV
TSH, FT4	Hypothyroidism	V
IGF-I	Growth hormone deficiency	VI
FSH**	Turner syndrome	VII
Urine		
pH, glucose, protein, blood and sedimentation	Renal diseases	VIII

*At the moment the consensus meeting took place, anti-tissue glutaminase as a diagnostic tool for celiac disease was not yet introduced nation wide.
**Only in girls.

When there are no signs or symptoms leading to the suspicion of a certain disease, the Dutch Consensus Guideline proposes a list of laboratory investigations for screening of several pathological conditions (table 1). Dependent on the abnormalities in the screening laboratory investigations further, more specific tests, like a sweat test for Cystic Fibrosis, can be performed to establish the final diagnosis. However, if no indication of a certain disease is present after the preceding procedures, the three following tests should still be considered according to the Dutch Consensus Guideline: chromosomal analysis for Turner syndrome in girls, a biopsy to prove or rule out celiac disease and the determination of zinc levels in plasma or hairs to investigate zinc deficiency in children with failure to thrive.[23]

We found that although this consensus guideline was not well followed in the two hospitals in which we performed the study, at least 5 % pathologic growth failure could be detected.. This concurs with previous reports.[1, 3, 24] In the Wessex growth study 8 children (4.4%) were identified as having an organic disease among the 180 children, whose height on screening at school entry was below the 3rd percentile.[3] In the Oxford study Ahmed et al reported 7 newly recognized children (3.0%) with organic disease among the 260 children whose height was below - 2 SDS, measured at the ages of 3 and 4.5 years.[1] In the Utah growth study twenty-five out of 555 children (4.5%) were newly discovered as having growth hormone deficiency (GHD), hypothyroidism or Turner syndrome and another 53 children (9.5%) had other medical reasons for their poor growth (height below the 3rd percentile and/or growth rate below 5 cm/yr). [29] In contrast to these population based studies Grimberg et al and Green et al found a higher percentage of newly diagnosed children with organic causes for their poor growth (23.7% (66 out of 278 children and 40% (79 out of 198), respectively).[25, 26] The children included in these studies were, however, referred to specialized growth centers because of short stature, without specific choices of anthropometric indicators or criteria for abnormality.

Laboratory investigations in the diagnostic work up

There was considerable heterogeneity in the amount of diagnostic work up carried out in our evaluation study. In none of the children referred for short stature a complete detailed routine diagnostic work up as proposed in the Dutch Consensus Guideline was performed and in 43 % of the patients in the university hospital and 32% in the general hospital no routine laboratory examination was done at all (***part C, chapter 7***), resulting in many missing data for the individual tests. Therefore, these results did unfortunately not allow us to construct an evidence-based decision rule for the general diagnostic work-up in children with short stature. New recommendations will therefore depend on a combination of various factors: the prevalence of the disease; the frequency in which the disorder presents itself with growth retardation only; the sensitivity and specificity of the test; the costs of the test; and the implications for the patients. In the remainder of this paragraph we will suggest new recommendations based on the evidence found in this thesis, following the categories of the consensus guideline (see table 2).

The first laboratory category exists of hematological parameters, cell indices, leukocyte differentiation and erythrocyte sedimentation rate (ESR). Its main aim is to detect or

exclude anemia and infectious or inflammatory diseases. Our international inquiry showed that these tests were recommended in most countries with guidelines for diagnostic work up (***chapter 4***). We did not perform a thorough literature search on the prevalence of short stature in combination with anemia, but the available literature shows that there is a strong relationship between thalassemia, sickle cell disease and growth retardation.[27-30] Likewise, Stephenson et al showed evidence of the association between infectious diseases in general and linear growth.[31] Anemia and infection can also be the first signs of other growth related disorders like inflammatory bowel diseases (IBD), celiac disease (CD) or cystic fibrosis (CF). Also the ESR is an important parameter in detecting IBD. In ***chapter 2*** we concluded that all children with short stature should be evaluated for CD. However, this category of laboratory investigations is not very specific for the detection of CD in contrast to category IV, which will be discussed later.
In ***chapter 3*** we found that the prior probability of CF in infants or children with a low weight or length for age is too low for a reliable result of a sweat test. The same conclusion might be drawn for the infectious parameters, but experimental data are lacking. However, as anemia and infectious parameters are important for the detection of other growth related disorders, and as they are noninvasive for the patient and relatively cheap, we recommend these parameters to be kept in the routine diagnostic work up of short children.

The second category of the routine diagnostic work up exists of parameters to exclude liver diseases. Especially ASAT and ALAT were recommended in more than 50% of the countries with an existing guideline for the assessment of short stature (***chapter 4***), but yGT was usually considered optional. Although Sokol et al concluded that growth retardation is common in children with chronic liver disease,[32] not any asymptomatic short child in whom liver function tests revealed a liver disorder, is encountered in more than 30 years of experience. Therefore we believe that it is extremely unlikely that the sole presenting sign of a liver disorder is growth retardation. However, we have not been able to perform an extensive literature search on the prevalence of monosymptomatic short stature at diagnosis in children with liver disorders and further research has to be performed to collect experimental evidence on the issue. At present, we considere it justified to remove these parameters from the routine diagnostic work up of short stature.

The third category, in combination with the parameters in the urine-sample mentioned in category VIII (see table 1), is aimed at detecting renal diseases, calcium/phosphate disorders and malabsorption. More than 50% of the countries with a guideline for a diagnostic work up in children with short stature recommended to evaluate electrolytes, albumin and creatinine (***chapter 4***). This concurs with the literature that shows that several renal diseases are in fact associated with short stature and that growth retardation is often present at diagnosis while other clinical symptoms are still absent.[33-35]. An acid base equilibrium measurement, an easy and cheap test to screen for kidney diseases such as renal acidosis, was only recommended in 32% of the countries with guidelines and was seldom done in the hospitals familiar with the Dutch Consensus Guideline (***chapters 4 and 5***). Probably the main reason for skipping this test was that an extra capillary blood sample is necessary, besides the routine venous blood sample to rule out other diseases.

Currently we are still working on a study that addresses this issue and we hope to provide stronger evidence for the value of this parameter in the diagnostic work-up of children with short stature. Preliminarily, we can already say that, in accordance with previously published data, several patients with distal renal tubular acidosis show failure to thrive as the first and main symptom.[36-40] Therefore, for the time being we recommend to keep this test in the diagnostic work-up, besides the other parameters mentioned in category III and VII.

Category IV is a specific category to rule out CD. Although less than 50% of the children with short stature were screened for CD in secondary health care (***chapter 5***), we concluded in ***chapter 2*** that children with short stature should be evaluated for CD, as in 2% to 8% of the children with short stature and no gastrointestinal symptoms, CD may be the underlying cause, and the risk increases to 19% to 59% if other causes for short stature are excluded. At the time of the consensus meeting in the Netherlands, IgA-anti endomysium, IgA- antigliadin, and total IgA were used for screening for CD. However, at present screening with anti-tissue transglutamase antibodies or anti-endomysium is the best way to identify patients at risk.[41] For a proper interpretation of the results of these tests total IgA remains important, as 7-10% of the CD patients have IgA-deficiency.[42]

There seems to be international consensus on testing TSH and FT4 to diagnose or rule out hypothyroidism in the diagnostic work up in children with short stature (***chapter 4)***. Nevertheless, not every child was screened for hypothyroidism in our evaluation study in secondary health care. Although a systematic literature search was not performed, clinical experience combined with the prevalence of hypothyroidism is in favour of including these tests in the work-up.[43]

As growth hormone deficiency is one of the most important conditions to be detected by auxological screening, it is obvious that IGF-I should be kept in the diagnostic work-up. This opinion is shared by most of the countries with current guidelines (***chapter 4***).

FSH is only recommended as screening tool for Turner syndrome in the diagnostic work up for short stature in 50% of the countries with guidelines. In our study, FSH was determined in less than a quarter of the girls in the correctly referred group of children to secondary health care (***chapter 5***). When the age rules recommended by pediatric endocrinologists (to measure plasma FSH only in girls <2 years and > 9 years) were applied, the figures hardly changed. From the literature, as well as from clinical experience, we know that the diagnosis of Turner syndrome should be considered in any girl with unexplained short stature.[44, 45] Therefore, we believe that irrespective of the FSH result, a chromosomal analysis should be carried out in each girl in whom the initial laboratory screening has not shown an abnormality.

More specific tests in the diagnostic work up

Although anti-tissue transglutamase and anti-endomysium antibodies have a relatively good sensitivity and specificity, the gold standard for the definite diagnosis of CD remains

an intestinal biopsy. As children with short stature should be evaluated for CD, this test should always be considered if no indication of a certain disease is present after the routine diagnostic work up, especially in children with an IgA deficiency and in children younger than 2 years in whom the sensitivity of the serologic screening tests is relatively low. This is even more indicated, if haematological investigations provide additional support for CD.

As we pointed out earlier, the diagnosis of Turner syndrome should be considered in any girl with unexplained short stature. Nevertheless chromosomal analysis for Turner syndrome was only performed in approximately 26% of the correct referred population in our evaluation study, and only 50% of the countries with guidelines recommend it for the diagnostic work up. As stated above, we believe that in any girl with unexplained short stature a karyotype has to be performed.

The determination of zinc was used only once in the diagnostic work up of the children referred for short stature to secondary health care (***chapter 5***), in contrast to the guideline. Reasons to consider zinc (Zn) deficiency as cause of short stature are that Zn is essential for somatic growth in children and that even in developed countries marginal to moderate Zn deficiency is not unusual.[23] Therefore, there are certainly arguments in favour of testing children with unexplained short stature for Zn deficiency. On the other hand, the prevalence of Zn deficiency in western countries is unknown. Furthermore, there are no data on sensitivity and specificity of the various tests, but apparently the available tests are suboptimal. For example, the plasma Zn concentration as recommended in the Dutch Consensus Guideline is not the accurate way to determine Zn deficiency, as the Zn levels may respond to metabolic conditions unrelated to the Zn status.[46, 47] Further research is necessary to find a reliable marker for Zn deficiency, and to collect data on the importance of Zn status for growth in western societies.

Besides the tests described in the Dutch Consensus Guideline, we found evidence that performing a sweat test in an infant with a low length or weight for age does not give a reliable result, as the prior probability of CF is less than 1%. Although a weight SDS deflection of -0.2 to -0.5 per year combined with a weight SDS below -2.5 for infants and a BMI SDS decrease of -1 for older children showed a better performance, the positive predictive value was still less than 1%. If clinical symptoms or signs suggestive for CF are found in combination with growth faltering, further diagnostic steps are warranted, as the prior probability is then expected to be higher.

Radiographic evaluation in the diagnostic work up

Although various guidelines for radiographic analysis of disproportionate short stature are available,[8-13] no international uniformity exists with respect to the radiographic evaluation of children with growth problems. We recommend that in patients with a possible diagnosis of a skeletal dysplasia a skeletal survey (Skull (PA and lateral); Spine (AP and lateral); Thorax (AP); Pelvis (AP); Upper limb (AP); Left hand and wrist (PA); Lower limb (AP), with PA = posteroanterior view, AP = anteroposterior view and lateral

= lateral view) must be performed. In patients with proportionate stature radiographic analysis of the hand and wrist is sufficient in most cases. However, whenever there are clinical abnormalities with a possible underlying bone anomaly, a modified skeletal survey is appropriate. The combination of clinical and biochemical features and an appropriate skeletal survey can guide the subsequent molecular analysis.

Genetic analyses in the diagnostic work up

As many growth related disorders have a genetic aetiology, chromosome and molecular analysis are indispensable in the diagnostic work up of children. This was also supported by representatives from countries with guidelines for the assessment of short stature (***chapter 4***). However, few of these disorders present with an isolated growth retardation. Therefore, genetic analysis usually takes plays only if additional signs and symptoms suggestive for a certain syndrome are present. For a systematic diagnostic approach we refer to a review by Kant et al,[48] in which they give an overview of the different genetic causes of short stature and propose a flow chart for molecular analyses. For a recent review on the diagnostic procedures to detect genetic disorders in the growth hormone – Insulin-Like Growth Factor-I axis we refer to the paper by Walenkamp et al.[49]

Implementation

Enquiries in general practice and primary health care have shown that the Dutch Consensus Guideline on the referral of children with short stature is used by very few general practitioners and by approximately 50% of the child health physicians. This fits the earlier observations that an increasing awareness of guidelines among doctors is not automatically accompanied by a wider implementation of the underlying procedures, specifically not with respect to non-evidence based guidelines.[50-52] As we look into the main determinants of a good innovation process (dissemination, adoption, implementation and continuation),[53] we can conclude that the implementation of the Dutch Consensus Guideline failed in several aspects. First, its dissemination only consisted of a single publication in a Dutch medical journal, a book that was made available to paediatricians, and several postgraduate courses.[5,7] Second, even if the guideline was known to the doctor, the auxological rules were scarcely adopted in the field, as many doctors found it difficult to work with and expected too many referrals due to the auxological rules (***chapter 5***). Third, the implementation process was not supported by the professional health organisations in the different fields. As the new guideline is based on evidence we now have a better starting point, but still a thorough implementation procedure will be needed, with sufficient personal and financial investment during the various stages of the process, in order to achieve an acceptable level of implementation.

Concluding remarks and proposals for future research

From this thesis we learned that there is little international consensus on the referral and diagnostic work-up of children with short stature. Our literature studies and biometrical studies have resulted in an algorithm for the referral of children with short stature and

recommendations for the diagnostic work up after referral. However, no algorithm can fully replace the clinical judgment of the physicians, and in case of an unusual growth pattern, certainly if associated with clinical symptoms or signs, even if it would not comply with the rules for referral or the recommendations, physicians should still be free to follow their clinical judgment.

The resulting algorithm for the referral of short stature (fig 1) appears suitable for industrialized countries, but requires further testing in other populations. Moreover, as there is a low efficacy and efficiency of growth monitoring between 0-3 years, particularly of rules involving target height and length deflection, further research is necessary to define auxological rules for failure to thrive in this age group. In the UK it has been suggested to perform frequent weight measurements and calculate the Thrive Index (TI), which is a measure of the discrepancy between a child's predicted and actual weight. The TI can be assessed on Cole's conditional charts to detect children with failure to thrive (FTT).[54-56] As a threshold for referral these authors use a TI of < -1.48 SDS. The authors admit, however, that more study is needed before this can be recommended as a formal screening program.

As the diagnostic work-up reported in our evaluation study (chapter 7) was carried out incompletely in most cases, and as the frequency of (varying) pathology is in the order of 5%, we were not able to construct an evidence-based decision rule for the general diagnostic work-up in children with short stature at this point. Further research is necessary to find evidence for the continuation of testing of liver diseases in the diagnostic work up. Whether an acid-base equilibrium is necessary in every child with short stature to rule out renal acidosis is currently being investigated and will be presented later.

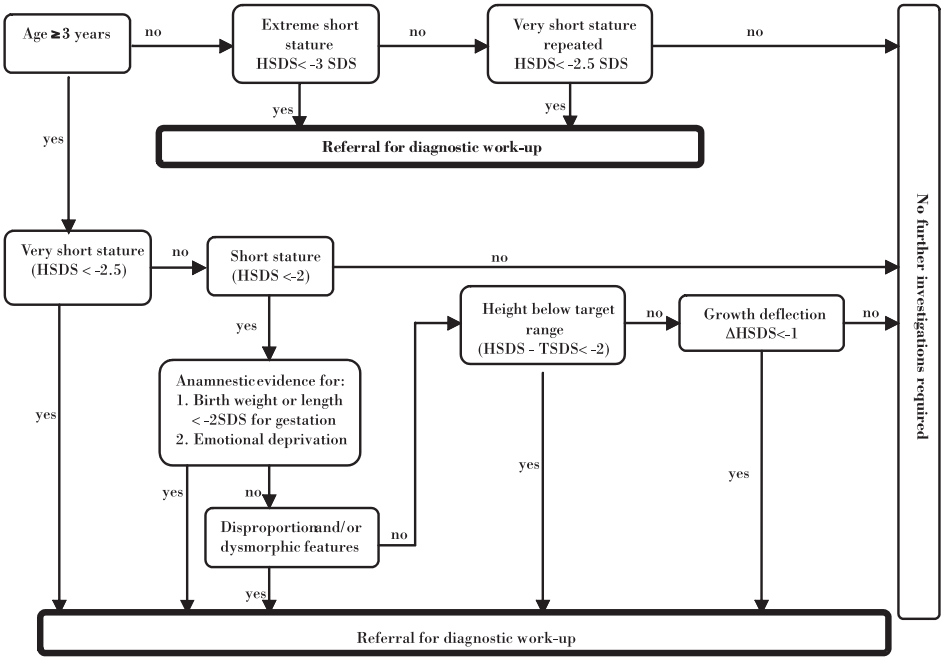


Fig 1. Flowdiagram of proposed criteria for referral of children with growth disorders.
HSDS= Height Standard Deviation Score
THSDS= Target Height Standard Deviation ScoreFig 1. Flowdiagram of new guideline

Table 2. Updated recommendations for laboratory investigations in the diagnostic work up for children with short stature.

Laboratory investigations	In order to diagnose
Blood	
Hb, Ht, Leukocytes, Cell indices, leukocyte differentiation, ESR	Anemia / infections
Creatinine, Sodium, Potassium, Calcium, Phosphate, Alkaline phosphatase, Albumin	Renal diseases, Calcium/ Phosphate disorders, Malabsorption
Acid-base equilibrium	Renal tubular acidosis
IgA-anti endomysium*, anti-tissue glutaminase*, total IgA	Celiac disease
TSH, FT4	Hypothyroidism
IGF-I	Growth hormone deficiency
FSH**	Turner syndrome
Urine	
pH, glucose, protein, blood and sedimentation	Renal diseases

* If one of these parameters is positive a **biopsy** is necessary to confirm celiac disease.
** Only in girls <2 years and > 9 years. If no cause for short stature has been found in girls of all ages, a **karyotype** has to be performed even if FSH is normal.

References

1. Ahmed ML, Allen AD, Sharma A, Macfarlane JA, Dunger DB: Evaluation of a district growth screening programme: the Oxford Growth Study. Arch Dis Child 1993, 69:361-365.
2. Frindik JP, Kemp SF, Kearns FS, Hale B: Growth screening. A positive medical experience. Clin Pediatr (Phila) 1992, 31:497-500.
3. Voss LD, Mulligan J, Betts PR, Wilkin TJ: Poor growth in school entrants as an index of organic disease: the Wessex growth study. BMJ 1992, 305:1400-1402.
4. Hall DM: Growth monitoring. Arch Dis Child 2000, 82:10-15.
5. de Muinck Keizer-Schrama SM: [Consensus 'diagnosis of short stature in children.' National Organization for Quality Assurance in Hospitals]. Ned Tijdschr Geneeskd 1998, 142:2519-2525.
6. Van Buuren, S, Bonnemaijer-Kerckhoffs DJ, Grote FK, Wit JM, Verkerk PH: Many referrals under Dutch short stature guidelines. Arch Dis Child 2004, 89:351-352.
7. Consensus Diagnostiek kleine lichaamslengte bij kinderen. Centraal Begeleidingsorgaan voor de Intercollegiale Toetsing (CBO); 1996.
8. Voss LD, Wilkin TJ, Bailey BJ, Betts PR: The reliability of height and height velocity in the assessment of growth (the Wessex Growth Study). Arch Dis Child 1991, 66:833-837.
9. Fredriks AM, van Buuren S, Jeurissen SE, Dekker FW, Verloove-Vanhorick SP, Wit JM: Height, weight, body mass index and pubertal development reference values for children of Turkish origin in the Netherlands. Eur J Pediatr 2003, 162:788-793.
10. Fredriks AM, van Buuren S, Jeurissen SE, Dekker FW, Verloove-Vanhorick SP, Wit JM: Height, weight, body mass index and pubertal development references for children of Moroccan origin in The Netherlands. Acta Paediatr 2004, 93:817-824.
11. Gibson AT, Carney S, Cavazzoni E, Wales JK: Neonatal and post-natal growth. Horm Res 2000, 53 Suppl 1:42-49.
12. Pinto G, Adan L, Souberbielle JC, Thalassinos C, Brunelle F, Brauner R: Idiopathic growth hormone deficiency: presentation, diagnostic and treatment during childhood. Ann Endocrinol (Paris) 1999, 60:224-231.
13. Lai HJ, Cheng Y, Farrell PM: The survival advantage of patients with cystic fibrosis diagnosed through neonatal screening: evidence from the United States Cystic Fibrosis Foundation registry data. J Pediatr 2005, 147:S57-S63.
14. Sims EJ, McCormick J, Mehta G, Mehta A: Neonatal screening for cystic fibrosis is beneficial even in the context of modern treatment. J Pediatr 2005, 147:S42-S46.
15. Dankert-Roelse JE, Merelle ME: Review of outcomes of neonatal screening for cystic fibrosis versus non-screening in Europe. J Pediatr 2005, 147:S15-S20.
16. Grote F.K., Oostdijk W, de Muinck Keizer-Schrama SMPF, Dekker FW, Verkerk PH, Wit JM: Growth monitoring and diagnostic work-up of short stature: an international inventorisation. J Pediatr Endocrinol Metab 2005, 18:1031-1038.
17. Hokken-Koelega AC, De Ridder MA, Lemmen RJ, Den Hartog H, de Muinck Keizer-Schrama SM, Drop SL: Children born small for gestational age: do they catch up? Pediatr Res 1995, 38:267-271.
18. Doeker B, Simic S, Hauffa BP, Andler W: [Psychosocially stunted growth masked as growth hormone deficiency]. Klin Padiatr 1999, 211:394-398.
19. Gohlke BC, Khadilkar VV, Skuse D, Stanhope R: Recognition of children with psychosocial short stature: a spectrum of presentation. J Pediatr Endocrinol Metab 1998, 11:509-517.
20. Gohlke BC, Frazer FL, Stanhope R: Growth hormone secretion and long-term growth data in children with psychosocial short stature treated by different changes in environment. J Pediatr Endocrinol Metab 2004, 17:637-643.

21. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. GH Research Society. J Clin Endocrinol Metab 2000, 85:3990-3993.
22. Butler J: Biochemical tests of growth hormone status in short children. Ann Clin Biochem 2001, 38:1-2.
23. Kaji M., Nishi Y.: Growth and minerals: Zinc. Growth, Genetics & Hormones 2006, 22:1-7.
24. Lindsay R, Feldkamp M, Harris D, Robertson J, Rallison M: Utah Growth Study: growth standards and the prevalence of growth hormone deficiency. J Pediatr 1994, 125:29-35.
25. Grimberg A, Kutikov JK, Cucchiara AJ: Sex differences in patients referred for evaluation of poor growth. J Pediatr 2005, 146:212-216.
26. Green AA, Macfarlane JA: Method for the earlier recognition of abnormal stature. Arch Dis Child 1983, 58:535-537.
27. Karimi M, Karamifar HA: Short stature in beta-thalassemia minor subjects. Med Sci Monit 2004, 10:CR603-CR605.
28. Nunlee-Bland G, Rana SR, Houston-Yu PE, Odonkor W: Growth hormone deficiency in patients with sickle cell disease and growth failure. J Pediatr Endocrinol Metab 2004, 17:601-606.
29. Raiola G, Galati MC, De S, V, Caruso NM, Pintor C, De Simone M, Arcuri VM, Anastasi S: Growth and puberty in thalassemia major. J Pediatr Endocrinol Metab 2003, 16 Suppl 2:259-266.
30. Thomas PW, Singhal A, Hemmings-Kelly M, Serjeant GR: Height and weight reference curves for homozygous sickle cell disease. Arch Dis Child 2000, 82:204-208.
31. Stephensen CB: Burden of infection on growth failure. J Nutr 1999, 129:534S-538S.
32. Sokol RJ, Stall C: Anthropometric evaluation of children with chronic liver disease. Am J Clin Nutr 1990, 52:203-208.
33. Fine RN: Growth retardation in children with chronic renal insufficiency. Nephron 1997, 76:125-129.
34. Friedman J, Lewy JE: Failure to thrive associated with renal disease. Pediatr Ann 1978, 7:767-773.
35. Rizzoni G, Broyer M, Guest G, Fine R, Holliday MA: Growth retardation in children with chronic renal disease: scope of the problem. Am J Kidney Dis 1986, 7:256-261.
36. Bajpai A, Bagga A, Hari P, Bardia A, Mantan M: Long-term Outcome in Children with Primary Distal Renal Tubular Acidosis. Indian Pediatr 2005, 42:321-328.
37. Caldas A, Broyer M, Dechaux M, Kleinknecht C: Primary distal tubular acidosis in childhood: clinical study and long-term follow-up of 28 patients. J Pediatr 1992, 121:233-241.
38. Caruana RJ, Buckalew VM, Jr.: The syndrome of distal (type 1) renal tubular acidosis. Clinical and laboratory findings in 58 cases. Medicine (Baltimore) 1988, 67:84-99.
39. McSherry E, Morris RC, Jr.: Attainment and maintenance of normal stature with alkali therapy in infants and children with classic renal tubular acidosis. J Clin Invest 1978, 61:509-527.
40. Santos F, Chan JC: Renal tubular acidosis in children. Diagnosis, treatment and prognosis. Am J Nephrol 1986, 6:289-295.
41. Schweizer J.: Coeliac Disease and Malignancy. PhD Thesis. 2004.
42. Abdulkarim AS, Murray JA: Review article: The diagnosis of coeliac disease. Aliment Pharmacol Ther 2003, 17:987-995.
43. Casado dF, Ruibal JL, Reverte F, Bueno G: Evolution of height and bone age in primary congenital hypothyroidism. Clin Pediatr (Phila) 1993, 32:426-432.
44. Davenport ML, Punyasavatsut N, Stewart PW, Gunther DF, Savendahl L, Sybert VP: Growth failure in early life: an important manifestation of Turner syndrome. Horm Res 2002, 57:157-164.
45. Moreno-Garcia M, Fernandez-Martinez FJ, Barreiro ME: Chromosomal anomalies in patients with short stature. Pediatr Int 2005, 47:546-549.

46. King JC: Assessment of zinc status. J Nutr 1990, 120 Suppl 11:1474-1479.
47. Wood RJ: Assessment of marginal zinc status in humans. J Nutr 2000, 130:1350S-1354S.
48. Kant SG, Wit JM, Breuning MH: Genetic analysis of short stature. Horm Res 2003, 60:157-165.
49. Walenkamp MJ, Wit JM: Genetic Disorders in the Growth Hormone - Insulin-Like Growth Factor-I Axis. Horm Res 2006, 66:221-230.
50. Christakis DA, Rivara FP: Pediatricians' awareness of and attitudes about four clinical practice guidelines. Pediatrics 1998, 101:825-830.
51. Coleman P, Nicholl J: Influence of evidence-based guidance on health policy and clinical practice in England. Qual Health Care 2001, 10:229-237.
52. McManus IC, Winder BC, Gordon D: UK doctors' attitudes to the General Medical Council's Performance Procedures, 1997-99. Med Educ 2001, 35 Suppl 1:60-69.
53. Fleuren M, Wiefferink K, Paulussen T: Determinants of innovation within health care organizations: literature review and Delphi study. Int J Qual Health Care 2004, 16:107-123.
54. Cole TJ: Conditional reference charts to assess weight gain in British infants. Arch Dis Child 1995, 73:8-16.
55. Wright CM, Waterston A, Aynsley-Green A: Effect of deprivation on weight gain in infancy. Acta Paediatr 1994, 83:357-359.
56. Wright CM, Matthews JN, Waterston A, Aynsley-Green A: What is a normal rate of weight gain in infancy? Acta Paediatr 1994, 83:351-356.

Summary & Samenvatting

Summary

Growth impairment is considered a relatively early sign of poor health in children. Depending on its setting and the age of the child the impairment is expressed in several ways. In industrialized countries, where malnutrition is rare, the major purpose of growth monitoring, implying regular measurements of weight and length, is early detection of growth disorders, such as Turner's syndrome (TS), Growth Hormone deficiency (GHD) and celiac disease (CD). For an early identification of children with abnormal growth it is important to have correct and well-defined referral criteria as well as a good growth monitoring system, with accurate growth charts and a well defined diagnostic work-up. In this thesis an effort is made to collect evidence on referral criteria and diagnostic procedures for the assessment of short stature in children, leading to a presentation of new guidelines.

In the ***first chapter*** we show that although growth monitoring is widely accepted nowadays, this has not always been the case. It took until the 20th century before child health care became an important issue. We demonstrate that so far mainly arbitrary referral criteria have been used for growth monitoring. Only few guidelines have been published on referral criteria for children with impaired growth and little experimental evidence can be found on the diagnostic work-up in secondary health care, although well-defined referral criteria and a well defined diagnostic work-up are important for an early identification of children with abnormal growth. Besides some general principles of auxological screening and diagnostic work-up in the assessment of short stature, we present the details of the Dutch consensus guideline, the only guideline so far that addresses both the referral and the diagnostic work-up of children with short stature.

Part A (Chapters 2 and 3) reviews the importance of testing for two growth related diseases (celiac disease or cystic fibrosis (CF)) in the routine diagnostic work-up for short stature. We searched the literature for evidence that screening for these diseases would be useful in infants and children with short stature. In ***chapter two*** we conclude that children with short stature should be evaluated for celiac disease. We base our conclusion on the fact that in 2% to 8% of the children with short stature and no gastrointestinal symptoms, celiac disease may be the underlying cause and that this risk increases by 19% to 59% after exclusion of other causes of short stature. In ***chapter 3*** we describe the prior-probability of CF in infants and children with short stature and/or poor weight gain. As only one study could be found on the prior-probability of CF in infants and children with short stature, we searched for scientific reports on length and weight in groups of patients with CF and derived the prior-probability of CF in children with a low length or weight for age from these studies. We conclude that in an infant with a low length or weight for age the prior probability of CF is less than 1%, so that we can assume that in an asymptomatic infant the probability will be even lower. This would argue against performing a sweat test in the early diagnostic work-up of an asymptomatic infant with growth failure. If clinical symptoms or signs suggestive for CF are found in combination with growth faltering, the prior probability is expected to be higher, so that obviously further diagnostic steps like a sweat test are warranted.

In ***Part B*** (Chapters 4 and 5) the current methods of growth monitoring and diagnostic work-up of short stature in practice are described. ***Chapter 4*** describes the results of an inquiry among pediatric endocrinologists in Europe and most industrialized countries around the world about the referral criteria advised for growth monitoring in primary care, and about diagnostic procedures for short stature in secondary care. A response was received from 36 countries. In 27 countries (75 %) a child health care program exists and in 14 (39%) there is a protocol for referral of growth-retarded children. Height for age is mostly used as a referral criterion. Sixteen countries (45%) reported having a guideline in secondary health care for the diagnostic work-up. Although in all countries there is agreement that biochemical, radiological and/or genetic tests are needed for a proper diagnostic work-up, there is a wide variety in recommended tests. We conclude that there is little consensus on referral criteria and diagnostic work-up of children with short stature among industrialized countries.
Chapter 5 aims at getting more information on the current policy of growth monitoring, the definition of failure to thrive and the use of guidelines (especially the DCG) among well-baby-clinic doctors and school doctors (doctors of Primary Health Care 0-19 years) and general practioners in the Netherlands. Therefore questionnaires were sent to 365 general practioners from the region South-Holland North and to 460 Primary Health Care physicians from the whole country in 2002. Analysable questionnaires were returned by 207 general practioners (57%) and 152 Primary Health Care physicians (33%). This inquiry demonstrates that the DCG is unknown to most general practitioners, but is used by approximately 50% of the primary health care physicians, although many of them think that strict application of the referral criteria would lead to too many referrals.

Part C (Chapters 6 and 7) is concerned with an evaluation of existing guidelines.
Chapter 6 is an evaluation of the referral pattern of short stature in primary health care using the Dutch Consensus guideline and the consensus guidelines from the UK, comparing it with cut-off values mentioned in the WHO Global Database on Child growth and Malnutrition. Three sets of referral rules were tested on the growth data of a random sample (n=400) of all children born between 01-01-1985 and 31-12-1988, attending school doctors between 1998 and 2000 in Leiden and Alphen aan den Rijn (the Netherlands). Application of the current Dutch consensus guideline would lead to too many referrals, mainly due to the deflection of length during the first 3 years of life, but also in the pubertal age range. The UKCG leads to far less referrals (0.3%), but may be relatively insensitive to detect clinically relevant growth disorders like Turner syndrome. The WHO-criteria lead to approximate 10% of referrals. New guidelines for growth monitoring are needed, which combine a low percentage of false positive results with a good sensitivity.
Chapter 7 contains the results of a study in two hospitals (Erasmus MC - Sophia Children's Hospital, Rotterdam and Spaarne Hospital, Haarlem), in which we 1) investigated how many children are correctly referred to secondary health care according to existing consensus guidelines; 2) evaluated the diagnostic work-up in secondary health care; and 3) assessed the frequency of underlying medical disorders. Data on growth and additional diagnostic procedures were collected from medical records of new patients referred for short stature to the outpatient clinics in whom the cause of growth

retardation was not yet known (n=542). As the Dutch Consensus Guideline (DCG) is the only guideline addressing referral criteria as well as diagnostic work-up, the analyses are based on its seven auxological referral criteria to determine whether children are correctly referred or not and on all elements of the diagnostic work-up. Of children older than 3 years 76% was correctly referred. . 74-88% of these children were short corrected for parental height, 40-61% had a height SDS <-2.5 and 21% showed height deflection (Δ HSDS < -0.25/ yr or Δ HSDS < -1). In none of the children a complete detailed routine diagnostic work-up was performed and in more than 30% no routine laboratory examination was done at all. Pathologic causes of short stature were found in 27 children (5%). A large share of these were due to GHD (n=7), celiac disease (n=7) and Turner syndrome (n=3). Other pathological causes were: syndromes (n=2: Noonan syndrome, Leri Weill syndrome), anemia (n=3), skeletal diseases (n=4) and emotional deprivation (n=1). Eighty children (14.8%) were classified as persistent short stature after born SGA.

Part D (Chapters 8 till 10) contains biometrical studies to determine cut-off points of auxological criteria to be used in the decision whether growth-retarded children should be referred for further investigations.

First, we describe the diagnostic performance of a broad set of referral criteria for auxological screening for Turner syndrome in the open population in ***chapter 8***. Three archetypal screening rules were applied to longitudinal growth data comparing a group with TS versus a reference group from birth to the age of 10 years. Clear differences in performance of the rules were found. The best rule takes parental height into account. Combining rules can improve diagnostic accuracy. A combined rule that takes absolute height SDS, parental height and growth deflection into account is the best way to screen for TS.

Thereafter optimal auxological referral criteria for detecting celiac disease were determined in ***chapter 9***. For this purpose longitudinal length and weight measurements up to 2.5 years of age from 3 groups of CD patients (two groups with clinical manifestations, one group diagnosed by screening) (n=134) and a reference group obtained from the Social Medical Survey of Children Attending Child Health Clinics (SMOCC) cohort (n=2,151) in The Netherlands were used. We found that testing for CD deserves a place in the diagnostic work-up in young children with failure to thrive, although the efficacy of growth monitoring for the detection of CD is modest. The auxological criteria hardly discriminate between the screened CD group and the reference group. Criteria based on a decrease of body mass index (BMI) or weight standard deviation score (SDS) performed best for the groups with clinical manifestations. Thirty-four percent of the CD children and 2% of the reference children had a deflection in BMI SDS of at least -2.5 per year and a BMI SDS below -1.3 from the age of 0.5 year.

Thirdly, we studied the performance of various criteria concerning length, weight and body mass index (BMI), using longitudinal length and weight measurements up to 2.5 years of age from CF patients visiting three major CF clinics (n=216) and a reference group obtained from the Social Medical Survey of Children Attending Child Health Clinics (SMOCC) cohort (n=2,151) in The Netherlands (***chapter 10)***. We conclude that a weight SDS deflection of -0.2 to -0.5 per year combined with weight SDS below -2.5 has the

highest PPV for infants and BMI SDS decrease of -1 for older children, in the absence of a newborn screening program for CF.

Part E consists of ***chapter 11*** and contains a literature review on the radiographic evaluation of children with growth problems. Short stature as well as tall stature has a wide variety of causes. Tall stature is usually experienced as a less important problem than short stature, but for both clinical presentations it is important to make a correct diagnosis. The identification of the diagnosis frequently relies on radiological criteria. However, no international uniformity exists with respect to the radiographic evaluation of children with growth problems. We recommend that in patients with a possible diagnosis of a skeletal dysplasia a skeletal survey must be performed. In patients with a proportionate stature radiographic analysis of the hand en wrist will be sufficient in most cases. However, whenever there are clinical abnormalities with a possible underlying bone anomaly, a modified skeletal survey is appropriate. The combination of clinical and biochemical features and an appropriate skeletal survey can guide the subsequent molecular analysis.

New evidence-based guidelines for growth monitoring on a population basis are presented in ***Part F (chapter 12)***. By combining evidence found in previous studies, several auxological referral criteria are formulated and applied to longitudinal growth data of four different patient groups, as well as three samples from the general population. The proposed guidelines for growth monitoring show a good sensitivity at an acceptably low false-positive rate in 3-10 year old children. Below the age of 3 years the sensitivity is considerably lower. Almost 30 % of pathology can be detected by a height standard deviation score (HSDS) below -3 or at least two observations of HSDS below -2.5 at a low false-positive rate (<1%) in 0-3 year old infants. These criteria are the proposed auxological screening rules for children in this age group.
For 3-10 year olds, a rule concerning distance to target height of >2 SD in combination with HSDS < -2.0 has the best predictive value. In combination with a rule concerning severe short stature (<-2.5 SDS) and a minor contribution of a rule concerning height deflection, 85.7% of children with Turner's syndrome and 76.5% of short children due to various disorders are detected at a false-positive rate of 1.5-2%.
In the age category 3-10 years height-SDS below –2.5 or height-SDS below –2.0 in combination with various features (small for gestational age, emotional deprivation, dysmorphic features and/or disproportion, >2 SD below target height or >1 SD deflection) are proposed as auxological screening rules.

Finally in ***chapter 13***, the evidence collected for the algorithm for referral of children with short stature and the collected evidence for the diagnostic work-up, are discussed. Recommendations for the diagnostic work-up after referral are being made, the implementation process of the new guideline in the Netherlands is discussed, and some proposals for future research are being offered. We conclude that there is little international consensus on the referral and diagnostic work-up of children with short stature. Our literature studies, evaluation studies and biometrical studies have resulted in an algorithm for the referral of children with short stature and recommendations

for the diagnostic work-up after referral. However, no algorithm can fully replace the clinical judgment of the physicians, and in case of an unusual growth pattern, certainly if associated with clinical symptoms or signs, even if it would not comply with the rules for referral or the recommendations, physicians should still be free to follow their clinical judgment.

Samenvatting

Groeiachterstand wordt gezien als een relatief vroeg signaal voor slechte gezondheid bij kinderen. Afhankelijk van de setting en de leeftijd van het kind wordt de achterstand op verschillende wijzen omschreven. In geïndustrialiseerde landen, waar ondervoeding zeldzaam is, is de voornaamste reden van het vervolgen van de groei van kinderen (verder aangeduid als groeimonitoring), bestaande uit regelmatige metingen van lengte en gewicht, het vroegtijdig herkennen van groeistoornissen, zoals Turner syndroom (TS), groeihormoondeficiëntie (GHD) and coeliakie (CD). Voor een vroege identificatie van een kind met een afwijkende groei is het belangrijk om zowel correcte en goed omschreven verwijscriteria te hebben als een goed groeimonitoring systeem met accurate groeicurven en een goed gedefinieerd diagnostisch werkplan. In dit proefschrift zijn wetenschappelijke gegevens ('evidence') verzameld voor verwijscriteria en diagnostische procedures met betrekking tot de evaluatie van kleine lengte bij kinderen, op basis waarvan een nieuwe richtlijn is opgesteld.

In het ***eerste hoofdstuk*** laten we zien dat groeimonitoring, hoewel heden ten dage wereldwijd geaccepteerd en bij bijna ieder kind tijdens zijn of haar jeugd regelmatig uitgevoerd, niet altijd van belang is geweest. Pas in de twintigste eeuw werd het belang ervan onderkend. Verder laten we zien dat in de literatuur tot op heden voornamelijk arbitraire verwijscriteria zijn gebruikt voor groeimonitoring. Slechts enkele richtlijnen zijn gepubliceerd over verwijscriteria voor kinderen met achterlopende groei en er is weinig experimenteel bewijs over het diagnostisch werkplan in de tweedelijnsgeneeskunde, hoewel goed gedefinieerde verwijscriteria en een goed gedefinieerd diagnostisch werkplan van belang zijn voor een vroege opsporing van kinderen met abnormale groei. Naast enkele algemene principes van auxologische screening en diagnostiek in de evaluatie van kleine lengte, presenteren we de details van de Nederlandse Consensus Richtlijn, de enige richtlijn tot dusver die zowel aandacht besteedt aan de verwijscriteria als aan de laboratoriumdiagnostiek van kleine lengte.

Deel A (Hoofdstuk 2 en 3) bespreekt het belang van testen op bepaalde groei gerelateerde aandoeningen (coeliakie of cystic fibrosis (CF)) tijdens het routine diagnostische werkplan voor kleine lengte. We hebben in de literatuur gezocht naar bewijs voor het nut van het screenen op deze aandoeningen bij kinderen met kleine lengte. In ***hoofdstuk twee*** concluderen we dat kinderen met kleine lengte altijd gescreend moeten worden op coeliakie. Wij baseren onze conclusies op het feit dat coeliakie in 2 tot 8% van de kinderen met kleine lengte zonder gastro-intestinale symptomen de onderliggende oorzaak is. Na uitsluiten van andere oorzaken van kleine lengte neemt dit risico zelfs toe tot 19% tot 59%. In ***hoofdstuk 3*** beschrijven we de vooraf-kans van CF bij kinderen met kleine lengte of slechte gewichtstoename. Aangezien we slechts één studie konden vinden over de vooraf-kans van CF bij kinderen met kleine lengte, hebben we de literatuur gescreened op wetenschappelijke studies over lengte en gewicht bij patiënten met CF en hebben we hieruit de vooraf-kans van CF bij kinderen met kleine lengte of laag gewicht voor leeftijd berekend. We concluderen dat de vooraf-kans van CF bij jonge kinderen met een kleine lengte of laag gewicht voor de leeftijd kleiner is dan 1%, zodat we kunnen aannemen dat

dit nog lager zal zijn bij asymptomatische kinderen. Dit zou tegen een zweettest pleiten als onderdeel van het vroege diagnostische werkplan van asymptomatische jonge kinderen met kleine lengte. Als er klinische symptomen of tekenen suggestief voor CF gevonden worden in combinatie met afwijkende groei, zal de vooraf-kans waarschijnlijk hoger liggen, waardoor verdere diagnostiek zoals een zweettest wenselijk wordt.

In ***Deel B*** (hoofdstuk 4 en 5) worden de huidige methodes van groeimonitoring en diagnostische werkplannen voor kleine lengte in de praktijk beschreven. ***Hoofdstuk 4*** beschrijft de resultaten van een inventarisatie onder kinderendocrinologen uit Europa en de meeste geïndustrialiseerde landen in de wereld over de geadviseerde verwijscriteria voor groeimonitoring in de eerstelijnsgeneeskunde, en over de diagnostische procedures voor kleine lengte in de tweedelijnszorg. Van 36 landen werd een antwoord verkregen. In 27 (75 %) landen bestaat er een "child health care program" en in 14 (39%) landen is er een protocol voor verwijzing van kinderen met een groeiachterstand. Lengte voor leeftijd is het meest gebruikte criterium. Zestien landen (45%) vermeldden dat zij beschikten over een richtlijn voor een diagnostisch werkplan in de tweede lijn. Ondanks dat alle landen het erover eens waren dat biochemische, radiologische en/of genetische tests een noodzakelijk onderdeel zijn van de diagnostiek van groeistoornissen, is er een wijde variatie aan aanbevolen tests. We concluderen dat er onder geïndustrialiseerde landen weinig consensus is over de verwijscriteria en het diagnostisch werkplan voor kinderen met kleine lengte.
Hoofdstuk 5 probeert meer informatie te verschaffen over de huidige uitvoeringspraktijk met betrekking tot groeimonitoring, de definitie van 'failure to thrive' en het gebruik van richtlijnen (specifiek de Nederlandse Consensus Richtlijn) onder jeugdartsen en huisartsen in Nederland. Daarvoor werden er in 2002, 365 enquêtes verstuurd naar huisartsen in de regio Zuid Holland Noord en 460 enquêtes naar jeugdartsen door het gehele land. Door 207 huisartsen (57%) en 152 jeugdartsen (33%) werden analyseerbare vragenlijsten teruggestuurd. Deze inventarisatie laat zien dat de Nederlandse Consensus Richtlijn onder huisartsen bijna niet bekend is, maar dat deze door bijna 50% van de jeugdartsen wordt gebruikt, ondanks dat velen van hen denken dat strikte navolging van de verwijscriteria tot te veel verwijzingen zou leiden.

Deel C (Hoofdstuk 6 en 7) bestaat uit evaluaties van bestaande richtlijnen. ***Hoofdstuk 6*** is een evaluatie van het verwijspatroon van kleine lengte in de eerstelijnsgeneeskunde gebruik makend van de Nederlandse consensus richtlijn en de consensus richtlijn uit Engeland, vergeleken met de afkapgrenzen die in de WHO Global Database on Child Growth and Malnutrition worden vermeld. Drie groepen van verwijscriteria werden getest op groeigegevens van een willekeurige steekproef (n=400) van alle kinderen geboren tussen 01-01-1985 and 31-12-1988, die tussen 1998 and 2000 bekend waren bij de jeugdartsen in Leiden en Alphen aan den Rijn. Toepassing van de Nederlandse Consensus Richtlijn uit 1996 zou tot te veel verwijzingen leiden, voornamelijk door de regel "afbuiging van lengte" gedurende de eerste 3 levensjaren, maar ook in de puberteitsleeftijd. Toepassing van de Engelse consensus richtlijn zou tot veel minder verwijzingen leiden (0.3%), maar deze is relatief ongevoelig zijn voor de detectie van klinisch relevante groeiafwijkingen zoals Turner syndroom. Toepassing van de WHO-

criteria zou aanleiding geven tot ongeveer 10% verwijzingen. Nieuwe richtlijnen voor groeimonitoring die een laag percentage fout-positieven combineren met een goede sensitiviteit, zijn noodzakelijk.
Hoofdstuk 7 bevat de resultaten van een studie uitgevoerd in twee ziekenhuizen (het Erasmus Medisch Centrum - Sophia Kinderziekenhuis in Rotterdam en het Spaarne Ziekenhuis in Haarlem), waarbij wij ten eerste onderzochten hoeveel kinderen volgens de bestaande consensus richtlijn correct verwezen waren naar de tweedelijnsgeneeskunde. Ten tweede evalueerden wij het diagnostisch werkplan in de tweedelijnszorg en als laatste hebben wij de frequentie vastgesteld van de medische stoornissen die werden opgespoord door het toepassen van bovengenoemd onderzoek. Gegevens omtrent groei en aanvullende diagnostische procedures werden verzameld van patienten die verwezen werden naar de polikliniek en waarvan de oorzaak van de groeistoornis nog niet bekend was ten tijde van verwijzing (n=542). Aangezien de Nederlandse Consensus Richtlijn de enige is die zowel verwijscriteria als een diagnostisch werkplan omvat, is de analyse gebaseerd op de zeven auxologische verwijscriteria die aangeven of kinderen juist verwezen werden en verder op alle onderdelen van het diagnostisch werkplan. Van alle kinderen ouder dan drie jaar bleek 76% juist verwezen. Van deze kinderen waren 74 tot 88% verwezen volgens de regel "klein t.o.v target height", 40 tot 61% hadden een lengte standaard deviatie score (SDS) van <-2,5 en 21% vertoonden een lengte afbuiging (Δ SDS <-0,25/jaar of Δ SDS <-1). Bij geen van deze kinderen bleek een volledig gedetailleerd routine diagnostisch werkplan te zijn gevolgd en bij meer dan 30% van de kinderen ontbrak enig gebruikelijk laboratorium onderzoek. Pathologische oorzaken voor kleine lengte werden bij 27 kinderen aangetroffen (5%). Een aanzienlijk deel hiervan was toe te wijzen aan groeihormoondeficiëntie (n=7), coeliakie (n=7) en Turner syndroom (n=3). Andere pathologische oorzaken waren: overige syndromen (n=2; het Noonan en het Leri-Weill syndroom), anemie (n=3), botziekten (n=4) en emotionele deprivatie (n=1). Bij 80 kinderen (14,8%) werd de kleine lengte geclassificeerd als blijvende kleine lengte na SGA (small for gestational age) bij geboorte.

Deel D (hoofdstukken 8 t/m 10) omvat biometrische studies om te bepalen welke afkapgrenzen voor auxologische kernmerken er gebruikt kunnen worden bij de beslissing of kinderen met een achterblijvende groei voor verder onderzoek verwezen moeten worden.

Als eerste wordt de diagnostische doelmatigheid van een breed samengesteld pakket van verwijscriteria beschreven voor een auxologische screening naar het Turner syndroom (TS) binnen een niet geselecteerde populatie (***hoofdstuk 8***). Drie archetypische screening regels zijn toegepast op lengtegroeigegevens vanaf de geboorte tot 10 jaar waarbij de groep met TS werd vergeleken met een referentiegroep. Er werden duidelijke verschillen tussen de doelmatigheid van de diverse regels vastgesteld. De beste regel is die waarbij de lichaamslengte van de ouders wordt meegenomen. De nauwkeurigheid van de diagnose kan verbeterd worden door enkele regels te combineren. Een combinatie van regels die de lengte SDS, de lengte van de ouders en de afbuiging van de groei bevat is de beste manier om TS te onderkennen.

Vervolgens zijn in ***hoofdstuk 9*** de auxologische verwijsregels voor de opsporing van coeliakie vastgesteld. Hiervoor werden lengte- en gewichtsmetingen gebruikt van drie groepen coeliakie patiënten (twee met klinische verschijnselen en één groep ontdekt middels screening) in de leeftijdscategorie tot 2,5 jaar en daarnaast een referentiegroep uit het cohort van de Social Medical Survey of Children Attending Child Health Clinics (SMOCC) in Nederland (n=2151). Wij hebben aangetoond dat testen op coeliakie een plaats verdient in de diagnostiek bij jonge kinderen met groeistoornissen, alhoewel de effectiviteit van groeimonitoring voor het aantonen van coeliakie bescheiden is. De auxologische criteria laten weinig verschil zien tussen de coeliakie groep en de referentiegroep. Criteria gebaseerd op een afname van de body mass index (BMI) SDS of van het gewicht SDS kwamen als beste uit de bus voor groepen met klinische verschijnselen. Vanaf een leeftijd van 6 maanden hadden 34% van de kinderen met coeliakie en 2% van de kinderen uit de referentiegroep een afwijking van de BMI SDS van ten minste -2,5 per jaar en een BMI SDS beneden -1,3.

Ten derde hebben wij de test-eigenschappen van diverse criteria inzake lichaamslengte, gewicht en BMI bestudeerd waarbij gebruik gemaakt is van lengte- en gewicht metingen van cystic fibrosis (CF) patiëntjes tot twee en een half jaar in drie grote CF klinieken (n=216) en daarnaast de gegevens van een referentiegroep verkregen uit het Nederlandse SMOCC cohort (***hoofdstuk 10***). We hebben hieruit berekend dat bij afwezigheid van een CF screening programma bij pasgeborenen een gewicht SDS afwijking beneden -0,2 tot -0,5 per jaar samengaand met een gewicht SDS onder -2.5 de hoogste positieve voorspellende waarde voor peuters vertoont en een BMI SDS afname van -1,0 voor oudere kinderen.

Deel E bestaat uit ***hoofdstuk 11*** en bevat een literatuuroverzicht omtrent radiologische evaluatie van kinderen met groeistoornissen. Kleine lengte zowel als grote lengte hebben een reeks van verschillende oorzaken. Grote lengte wordt gewoonlijk als een minder groot probleem gezien dan kleine lengte, echter voor beide klinische presentaties is het belangrijk om de juiste diagnose te stellen. Het herkennen van de diagnose hangt vaak af van radiologische criteria. Voor de radiologische evaluatie van kinderen met groeistoornissen bestaan geen internationaal aanvaarde normen. Wij bevelen aan dat bij patiënten met een mogelijke diagnose van botdysplasie er een skelet-status wordt uitgevoerd. Bij patiënten met een afwijkende lichaamslengte, gepaardgaande met normale lichaamsproporties zal een analyse van hand- en polsfoto in de meeste gevallen voldoende zijn. Indien er echter klinische kenmerken zijn die passen bij afwijkingen van het skelet is een uitgebreider skelet-onderzoek aangewezen. De combinatie van klinische en biochemische kenmerken en een gericht skelet onderzoek kan een leidraad zijn voor de daaropvolgende moleculaire analyse.

Nieuwe evidence-based richtlijnen voor groeimonitoring worden gepresenteerd in **Deel F** (***hoofdstuk 12***). Door experimentele gegevens uit voorgaande studies te combineren, zijn verschillende auxologische verwijscriteria opgesteld en vervolgens toegepast op lengtegroeigegevens van vier verschillende patiëntengroepen alsmede drie steekproeven uit de normale populatie. De voorgestelde richtlijnen voor groeimonitoring vertonen een

goede sensitiviteit bij een aanvaardbaar lage fout-positieve ratio in de leeftijdscategorie van drie tot tien jaar. Bij kinderen jonger dan drie jaar is de sensitiviteit aanzienlijk lager. Bijna 30% pathologie wordt aangetroffen bij een lengte SDS beneden -3 of bij tenminste twee waarnemingen van lengte SDS beneden -2,5 bij een lage fout-positieve ratio (<1%) bij peuters jonger dan drie jaar, dus deze criteria vormen de voorgestelde auxologische screening regels voor kinderen in deze leeftijdsgroep. Voor drie- tot tienjarigen heeft een regel betreffende een lengte beneden de target height van >-2 SD gecombineerd met een lengte SDS <-2,0 de beste voorspellende waarde. Samen met de regels betreffende zeer kleine lengte (<-2,5 SDS) en in mindere mate de regel betreffende lengtegroeiafbuiging kunnen 85.7% van de kinderen met Turner syndroom en 76.5% van kinderen met kleine lengte als gevolg van andere pathologische oorzaken gevonden worden bij een fout-positieve ratio van 1,5 tot 2,0 %. In de leeftijdscategorie van drie tot tien jaar wordt voorgesteld om een lengte SDS beneden -2,5 of een lengte SDS beneden -2,0 in combinatie met diverse verschijnselen (klein voor de zwangerschapsduur, emotionele deprivatie, dysmorfische afwijkingen en/of disproportie, meer dan 2 SD beneden de target height of meer dan 1 SD afbuiging) te gebruiken als auxologische regels.

Tenslotte wordt in hoofdstuk 13 het algoritme voor de verwijscriteria besproken evenals het verzamelde bewijsmateriaal voor de diagnostiek. Er worden aanbevelingen gedaan voor het diagnostisch werkplan na de verwijzing, het implementatie-proces wordt besproken en ideeën voor verder onderzoek worden aangereikt. Er wordt vastgesteld dat er weinig internationale overeenstemming is omtrent het verwijzingsproces én het diagnostisch werkplan voor kinderen met een kleine lengte. Ons literatuuronderzoek, de evaluaties en de biomedische studies hebben geleid tot een algoritme voor de verwijzing van kinderen met een kleine lengte en aanbevelingen voor de diagnostiek na verwijzing. Echter, geen enkel algoritme kan het klinisch oordeel van een arts volledig vervangen en in het geval van een ongewoon groeipatroon (zeker indien samenvallend met klinische symptomen) moeten artsen de vrijheid hebben om op hun klinisch oordeel af te gaan, zelfs als dit niet mocht sporen met de regels voor verwijzing of de hierboven gedane aanbevelingen.

Appendices

Appendix I

Definitions of several parameters:

1. Standard deviation scores:

SDS is the deviation of the individual height, expressed in standard deviations from the mean height of the population for the same age and sex.

$$\frac{\text{Height – mean height for the same age and sex}}{\text{SD for the same age and sex}}$$

Using SDS instead of percentiles gives more precision in interpretation, especially when concerning decline in growth rate, because of the equidistance between the SDS lines. All height SDS and weight SDS will be calculated using the data from the growth references for height and weight collected in 1997 (8)

2. Percentiles:

Historically percentiles have been used to define height, although the standard deviation scores are more precise. Percentiles can easily be transformed into SD scores and the other way around, if the measurements have a Gaussian distribution.

P0.4 = -2.67 SDS
P3 = -1.88 SDS
P10 = -1.28 SDS
P25 = -0.67 SDS
P50 = 0 SDS

3. Target range:

Target range is the area around the target height, in which healthy children reach their final height. Target height is the mathematical approach of the estimated final height of a boy or a girl on the basis of their genetic potential.

$$TH_{son} = \frac{\text{height of father} + (\text{height of mother} + 13)}{2} + 4.5$$

$$\text{TH-SDS}_{son} = (TH - 184.0) / 7.1$$

$$TH_{duaghter} = \frac{\text{height of mother} (+\text{height of father} - 13)}{2} + 4.5$$

$$\text{TH-SDS}_{daughter} = (TH - 170.6) / 6.5$$

4. Deflection or change in height SDS:

The Change in height SDS is the difference in height SDS between two measurements. In this case the threshold is a change in height SDS of - 0.25 SDS a year, in at least three measurements, with an interval of 6 months each time.

5. Disproportion:

Children with abnormal growth, who have a body proportion outside the normal range, are prone to have a primary growth disorder and should be referred to a specialist. The most suitable parameter for body proportions is the sitting height/ height ratio.

Since the exact description is missing in the DCG we will use in this protocol the following definition:
Disproportion = sitting height/height ratio SDS < -1.88 or > + 1.88

6. Dysmorphology:

A large number of syndromes associated with short stature are also associated with dysmorphology. Because the dysmorphology may be the first sign of the primary growth disorder it is important to refer these children to a specialist. For a list of dysmorphic features associated with small stature see appendix IV.

7. IUGR without catch-up growth:

Most of the children who are small for gestational age show a catch-up growth in the first 2 years after birth. Approximately 15 % do not show catch-up growth and still have a height < -1.88 SDS after two years of age.

Appendix II.

In chapter 3 we report on the results of our analysis of the available literature on growth data in CF aiming at assessing the prior-probability of CF in infants and children with short stature and/or poor weight (taken from a general population). In our literature search we encountered the following difficulties:

1. There is much controversy on the definition of failure to thrive in the literature, and to a lesser extent also on the definition of short length (height) and weight for age.
2. There are no published studies with longitudinal growth data before diagnosis of CF.
3. Except for one single publication in Portuguese (Oliveira et al. J Pediatr (Rio J) 1998;74:213-6), we found no publications that showed data on the prevalence of CF in growth retarded children.

To overcome these difficulties and answer our initial question we had to use an indirect approach based on the following definitions/ assumptions:

1. Short stature is defined as poor length for age (with -1.5 SDS, -2.0 SDS and -2.5 SDS as cutt-offs).
2. We used a low length for age or weight for age (with -1.5 SDS, -2.0 SDS and -2.5 SDS as cutt-offs) as a proxy parameter for failure to thrive (in the absence of longitudinal data)
3. The average incidence of CF in the general Caucasian population is 1:3000 (Bobadilla JL et al. Hum Mutat 2002;19:575-606)

We hope to clarify the indirect approach implying statistical procedures that are difficult to explain in a short report like the CAT in chapter 3, with the following "two-by-two table":

	CF +	CF-
Short stature +	a	b
Short stature -	c	d

1. To answer our question we wish to estimate the percentage of CF in children with short stature (taken from a general population): (a/a+b) *100 (= positive predictive value as a percentage)
2. Based on the assumption on the incidence of CF: a+c= 1 and b+d= 3000.
3. b = (percentage of children with short stature in a population given a certain cut-off) * 3000/100.
   Length, height and weight for age have a Gaussian distribution in this age range, so that standard deviation scores are easily converted into percentiles. The percentages of children with short stature in a population are calculated from the different cut-offs.
4. "a" is the average percentage of short stature in the CF-populations mentioned in the articles: To be able to calculate this percentage we had to follow several steps:

a. The mean length and weight at diagnosis expressed as standard deviations scores (SDS) were either directly derived from the data or by converting percentile positions to SD-scores.

b. From the available studies it became clear that the SD of the length, height and weight for age distributions differed considerably from 1. We therefore calculated the weighted average SD for length (1.41) and weight (1.28) from the data given in three articles (Farrell PM et al. Pediatrics 2001;107:1-13, Ranganathan SC et al. Am J Respir Crit Care Med 2004;169:928-33, and Waters DL et al. Arch Dis Child Fetal Neonatal Ed 1999;80:F1-F7.)
c. For each paper the mean SD-scores for length and weight were then subtracted from the different cut-off points for low weight and short stature and divided by the weighted average SD, in order to derive the SD scores corresponding with the different cut-off points for low weight and short stature.
d. The results of these subtractions were converted into percentiles and the percentages of children with low weight and short stature were calculated.
e. Finally the weighted average from the estimated percentages of step d was calculated.

Acknowledgements

This thesis would not have been accomplished without the help and contribution of other people. First of all I would like to thank all co-authors for their helpful discussions and comments and in particular Paula van Dommelen for her help in the various longitudinal multivariate analyses. I would not have been able to provide the amount of data without the help of several students (J.C.W. van Rijn, J. Goudriaan, H.W. Wiersma, M. Spaans, C.H. Neuteboom, N. Bootsma, L.Y. Man, T. Zwaan, H. Trip, W. Planten). I thank them for this. I acknowledge Dr.J. Bouquet (the Dept. of Paediatrics, ErasmusMC - Sophia Children's Hospital, Rotterdam), A.M. Lodder- van der Kooij (Dept. Child Health Care, Regional Public Health Service Hollands Midden, Leiden), Dr. A. Ketel (Dept. of Paediatrics, Spaarne Hospital, Haarlem), Dr. J.J.E. Hendriks (Dept. of Paediatrics, University Hospital Maastricht, Maastricht) and Dr. J.M. Kouwenberg (Juliana Children's Hospital, The Hague) for their coordinating role in the provision of the medical records used in the different studies. I would also like to express my gratitude to Bernadette Verbeek for her contribution to the study in primary health care and I am grateful for the supervision-committee, who helped me with the outline of this thesis and gave their helpful remarks to the different protocols. This publication was supported by an educational grant from Pfizer. I thank them for giving me the opportunity and freedom to complete this thesis. I am indebted to Frans Willemse, who designed the cover page. I further thank all my fellow researchers in Rotterdam and Leiden for their valuable tips and welcome relaxations. Last but not least I am grateful for the support and help of my family.

Curriculum vitae

The author of this thesis was born on 21st of March, 1972 in Bemmel (Gelderland) and spent most of her childhood in Zoeterwoude, the Netherlands. She attended secondary school in Leiden, Stedelijk Gymnasium, where she passed her exam in 1990. After a year of language courses in Chambery (France) and Beaconsfield (England) she started her study of Medicine at the Catholic University of Leuven (Belgium). She stayed in Leuven to conclude her master's degree and returned to Leiden, the Netherlands, in 1997 to finish her medical degree at the University of Leiden on 20th of August 1999. From August 1999 till May 2001 she worked as a resident at the departments of paediatrics of the Bronovo Hospital and the Juliana Children's Hospital, the Hague and the ErasmusMC-Sophia Children's Hospital in Rotterdam. In May 2001 she started her research-fellowship at the department of paediatrics at the Leiden University Medical Centre (supervisor Prof. Dr. J.M. Wit), working most of her time on the research presented in this thesis. At the same time she performed a randomised controlled trial at the Sophia Children's Hospital, in which she studied growth hormone treatment in children with rheumatic disease, corticoid induced growth retardation and osteopenia. During her fellowship she obtained a Master of Science degree in Epidemiology at the Netherlands Institute for Health Sciences (NIHES), Erasmus University, Rotterdam. In September 2006 she started her training as a general practitioner at the Leiden University. Floor is married to Menno Landsmeer and together they have one son (Michiel) and are expecting their second child in May 2007.

List of publications

Peer-reviewed publications:

S. Van Buuren, P. van Dommelen, G.R. Zandwijken, F.K. Grote, J.M. Wit, PH.Verkerk. Towards evidence based referral criteria for growth monitoring. Arch.Dis.Child 2004;89(4):336-41.

S. van Buuren, D.J.A. Bonnemaijer-Kerckhoffs, F.K. Grote, J.M. Wit, P.H.Verkerk. Many referrals under dutch short stature guidelines. Arch.Dis.Child 2004;89(4):351-352.

J.C. van Rijn, F.K. Grote, W. Oostdijk, J.M.Wit. Short stature and the probability of coeliac disease, in the absence of gastrointestinal symptoms. Arch.Dis.Child 2004;89(9):882-3.

F.K. Grote, W. Oostdijk, S.M.P. F. de Muinck Keizer-Schrama, F.W. Dekker, P.H. Verkerk, J.M. Wit. Growth monitoring and diagnostic work-up of short stature: an international inventorisation. J Pediatr Endocrinol Metab 2005; 18(11): 1031-38

F.K.Grote, L.W.A. Van Suijlekom-Smit., D. Mul, W.C.J. Hop, R.Ten Cate, W. Oostdijk, W. Van Luijk, C.J.A. Jansen-van Wijngaarden, S.M.P.F. de Muinck Keizer-Schrama. Growth hormone treatment in children with rheumatic disease, corticoid induced growth retardation and osteopenia. Arch Dis Child. 2006 Jan;91(1):56-60.

Other publications and abstracts:

J.M.Wit, W.Oostdijk, F.K. Grote [Diagnostiek van kleine lichaamslengte “revisited”] Boerhaave Commissie voor Post-academisch Onderwijs in de Geneeskunde. Nascholingsweek Kindergeneeskunde Leiden 2002: 129-136.

F.K.Grote; L.W.A. Van Suijlekom-Smit.; D. Mul ; R.Ten Cate; W. Oostdijk; W. Van Luijk; W.C.J. Hop; S.M.P.F. de Muinck Keizer-Schrama. Growth Hormone Treatment in Children with Rheumatic Diseases. Horm res 2002; 58(suppl2):109

FK Grote; W Oostdijk; SMPF de Muinck Keizer-Schrama; FW Dekker; JM Wit. International inventarisation of growth monitoring and diagnostic work-up of short stature. Horm Res 2003;60(suppl 2):32

Buuren, S., van, Dommelen, P., van, Zandwijken, G.R.J., Grote, F.K., Wit, J.M., Verkerk, P.H. Diagnostic performance of growth monitoring for screening on Turner syndrome. Horm Res 2003;60(suppl 2):34-35.

FK Grote, W Oostdijk, SMPF de Muinck Keizer-Schrama, P van Dommelen, FW Dekker, HA Moll , JM Wit. Diagnostic Workup of Short Children. Horm Res ;62 (suppl 2): 159-160.