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Assessment of Nutritional Status in the Diagnostic Evaluation of the Child with Growth Failure

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Abstract
Current clinical guidelines provide information about the diagnostic workup of children with growth failure. This mini-review focuses on the nutritional assessment, which has received relatively little attention in such guidelines. The past medical history, in particular a low birth size and early feeding problems, can provide information that can increase the likelihood of nutritional deficits or several genetic causes. The current medical history should include a dietary history and can thereby reveal a poorly planned or severely restricted diet, which can be associated with nutritional deficiencies. Children on a vegan diet should receive various nutritional supplements, but insufficient compliance has been reported in one-third of cases. While proper use of nutritional supplements in children consuming a vegan diet appears to be associated with normal growth and development, insufficient intake of supplements may impede growth and bone formation. Physical examination and analysis of height and weight over time can help differentiating between endocrine causes, gastrointestinal disorders, psychosocial problems, or underlying genetic conditions that prevent adequate nutritional intake. Laboratory screening should be part of the workup in every child with short stature, and further laboratory tests can be indicated if warranted by the dietary history, especially in children on a poorly planned vegan diet.

Introduction

When a child with short stature and/or growth faltering, further abbreviated as growth failure (GF), is referred to a general practitioner or a paediatrician, the clinician is expected to carry out a proper diagnostic evaluation. A previous paper on the Dutch guideline for general paediatricians described the diagnostic workup of children with GF as a stepwise process [1].

To ensure a targeted approach, the first step is that the clinician should remember the three main categories of frequent and/or clinically relevant causes of GF: (1) primary growth disorders (intrinsic to the epiphyseal

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Table 1. Information to be collected from the past medical history of a child with GF

Clinical feature	Phenotype	Consequences
Birth length and weight[1]	Born SGA (birth length and/or weight <−2 SDS)	No catch-up growth in 10%. SGA associated with increased likelihood of primary growth disorder
OFC at birth[1]	Microcephaly at birth	Increased likelihood of primary growth disorder, a.o. microcephalic primordial dwarfism, *IGF1* or *IGF1R* mutations, multiple syndromes
	Relative macrocephaly at birth	Increased likelihood of primary growth disorder, a.o. SRS, 3M syndrome, neurofibromatosis 1, and Turner syndrome
Early feeding problems	Low BMI SDS in infancy and as toddler	• Environmental enteropathy (frequent in low-middle income countries) • Increased likelihood of gastrointestinal disorders (e.g., coeliac disease) • Increased likelihood of *IGF1R* haploinsufficiency, SRS, PWS, Noonan syndrome, multiple other syndromes

BMI, body mass index; OFC, occipitofrontal circumference; PWS, Prader-Willi syndrome; SDS, standard deviation score; SGA, small for gestational age; SRS, Silver-Russell syndrome. [1]If no information length or OFC at birth is available, it is advised to try and obtain information on measurements in early infancy and calculate SDS, which can be used as proxy for birth length and OFC SDS.

growth plate); (2) secondary growth disorders (extrinsic to growth plate); and (3) idiopathic. In the ESPE and International Classifications of Paediatric Endocrine Diagnoses [2, 3], as well as in the Dutch guideline [1], the last category only included "Idiopathic Short Stature." We later considered it better to include short children born small-for-gestational age ("short SGA") (if the cause is unknown) into this category as well [4].

The second step is a careful clinical assessment consisting of a detailed medical history (including past history, current history, and family history), thorough physical examination, and growth curve analysis. The most relevant questions that the clinician should ask while taking the medical history and the most important elements of the physical examination and growth curve analysis that could serve as diagnostic clues for certain disorders were reviewed previously [1].

The third step is a screening procedure consisting of an X-ray of the left hand/wrist and laboratory investigations. We previously emphasized that the X-ray should be investigated not only for skeletal age (bone age) but also for anatomical abnormalities suggestive of a form of skeletal dysplasia [1]. Regarding the components of laboratory screening in children with GF, the authors of the guideline tried to collect all available evidence before deciding to include or exclude laboratory tests in the screening panel, in some cases limited to certain age ranges [1].

The fourth step consists of collecting all diagnostic clues for primary or secondary growth disorders, assessing their probability, and deciding on further testing. The current mini-review is focused on an element that received relatively little attention in the guideline: the nutritional assessment of the child with GF. We divide this topic into six parts: (1) past medical history; (2) current medical history; (3) physical examination; (4) growth curve analysis; (5) laboratory screening; and (6) conclusions.

Past Medical History

It is self-evident that a full past medical history is needed for any patient seen by a paediatrician [1]. Regarding the nutritional assessment, we now expand on two issues: (1) assessment of prenatal growth and nutrition and (2) feeding problems in infancy and young childhood. The consequences of such information on the differential diagnosis are summarized in Table 1.

Assessment of Prenatal Growth and Nutrition

Prenatal growth is assessed during pregnancy using serial ultrasound measurements of the foetus, and postnatally by measurement of birth weight, length, and head circumference (occipitofrontal circumference, OFC). Obstetricians and neonatologists define growth restriction in the newborn as either a birth weight below the third percentile or at least three of the following five criteria: either birth weight, birth length, or OFC below the tenth percentile, prenatal diagnosis of foetal growth restriction, or maternal risk factors [5]. Maternal risk factors include young maternal age, gestational hypertension or preeclampsia, smoking, maternal short stature, as well as

maternal underweight or inadequate weight gain during pregnancy [6].

Maternal deficiencies of macro- and micronutrients may lead to a decreased nutrient source for foetal growth, changes in placental function, and epigenetic modifications of the foetal genome [7]. Several studies have reported positive correlations between birth weight and maternal intake of milk, fruits, and green leafy vegetables [8–11]. Pregnant women on a plant-based diet may be at risk for a deficient intake of protein, vitamin D, vitamin B12, zinc, and iron [12–15]. A vegetarian or vegan diet has been associated in some, but not all, studies with lower birth weight [16–21], although reported effect sizes vary greatly.

When taking a medical history, most paediatric endocrinologists are more focused on birth size (a cross-sectional indicator) than on longitudinal indicators of intrauterine growth restriction, and it is important to note that these terms are not synonymous. In paediatric endocrine consensus meetings, small for gestational age (SGA) was defined by paediatric endocrinologists as a birth weight and/or length below −2 standard deviation score (SDS) for gestational age and sex [22, 23]. SGA can be caused by maternal health and obstetric factors, placental insufficiency, and foetal (epi)genetic factors [23, 24]. Approximately 90% of children born SGA show catch-up growth in the first 2–3 years [25] and are usually not referred to a paediatrician for GF. In contrast, those who remain short in childhood should be referred to a paediatrician or paediatric endocrinologist, because this group requires proper diagnostic workup, suffers more often from a primary growth disorder [26], and may be eligible for recombinant human growth hormone (GH) treatment [23, 24].

While the paediatric endocrine definition of SGA has been useful in clinical practice, we believe that there are also disadvantages. The main disadvantage is that in many newborns birth length is either not measured at all or with poor accuracy. Therefore, the label SGA is often only based on a low birth weight, which is usually the result of limited placental function in the last trimester of pregnancy when foetal weight velocity peaks [24]. This is unfortunate, because birth length appears to be a better predictor of adult height than birth weight [27], and is also a better diagnostic clue for the recently uncovered primary growth disorders [24]. For example, mean birth length of children born with haploinsufficiency of *ACAN, IHH, NPR2*, or *SHOX* ranges from −2.4 to −1.1 SDS, while their mean birth weight SDS ranges from −1.1 to −0.7 SDS [24, 28].

In the Netherlands, we have tried to obviate this problem by explaining (para)medical health workers that birth length can be measured accurately and safely [29] and by expressing the first length measurement in the child health clinic (usually at 4–6 weeks of age) as SDS for age and use this as a proxy parameter for birth length SDS, if length at birth was not measured.

A third anthropometric indicator of prenatal growth, OFC at birth, has received relatively little attention from paediatricians and paediatric endocrinologists. We believe that the clinical evaluation of the short child should include an inquiry about the OFC at birth or, if unavailable, the first OFC measurement after birth. Microcephaly at birth, and also in childhood, is an important clinical marker of several causes of GF. The likelihood of a genetic cause of short stature is increased considerably if the child is microcephalic [26], e.g., various forms of microcephalic primordial dwarfism [30], genetic defects of *IGF1* or *IGF1R* [31], and many other syndromes.

Besides microcephaly, also relative macrocephaly at birth is an important indicator of several primary growth disorders. In the Netchine-Harbison clinical scoring system for Silver-Russell syndrome (SRS), relative macrocephaly at birth (defined as an OFC at birth at least 1.5 SDS above birth weight and/or length SDS) is one of the six clinical criteria [32]. Relative macrocephaly is also associated with 3M syndrome, neurofibromatosis 1, and Turner syndrome (reviewed in [1]).

Early Feeding Problems

In low- or mid-income countries, early feeding problems are often encountered in children with environmental enteropathy, associated with chronic infections and infestations by poor sanitary conditions. There is a vast literature about this condition (for a recent review, see [33]). Under better socioeconomic conditions, poor feeding in infancy and/or young childhood has been noticed in several primary and secondary growth disorders. However, also parents of children with Idiopathic Short Stature often mention that their child has a poor appetite, and in fact, their body mass index (BMI) and serum IGF-I are usually in the low-normal range [34].

Primary Growth Disorders Associated with Early Feeding Problems

A vast number of rare genetic disorders are related to early life feeding difficulties and short stature. Most are syndromic causes of short stature, such as Williams-Beuren syndrome (OMIM #194050), Coffin-Siris syndrome (OMIM #135900), KBG syndrome (OMIM

#148050), Kabuki syndrome (OMIM #147920), Cornelia de Lange syndrome (OMIM #300590), and DiGeorge syndrome (OMIM #188400). The three relatively frequent syndromes in which feeding problems are prominent are described in more detail below.

In Noonan syndrome, feeding problems are not included into the formal clinical criteria [35], but a recent study showed that feeding problems occur frequently in children with Noonan syndrome [36]. Out of 108 patients with Noonan syndrome, 71 had feeding problems, 52 of whom of early onset. A total of 40 patients (and 33 with early-onset feeding problems) required tube feeding. Children with a genetic mutation other than in *PTPN11* or *SOS1* had significantly more feeding problems in the first year than carriers of other mutations. A strong decrease in the prevalence of feeding problems was found after the first year of life and only 15 children developed feeding problems later in life, of which 7 required tube feeding [36].

Out of the many major, minor, and supportive clinical diagnostic criteria of Prader-Willi syndrome (PWS) proposed by a consensus meeting before the time that genetic testing was easily available [37], infantile feeding problems or failure to thrive was one of the eight major criteria. In a report on a retrospective review of patients with PWS confirmed by genetic testing [38], the validity and sensitivity of clinical diagnostic criteria published before the widespread availability of testing were assessed for all affected patients. Feeding problems in infancy, excessive weight gain after 1 year, hypogonadism, and hyperphagia were all present in ≥93% of patients. For children between 2 and 6 years of age, hypotonia with history of poor suck associated with global developmental delay was considered as sufficient criteria to prompt genetic testing [38].

In the Netchine-Harbison clinical scoring system for SRS, feeding difficulties and/or low BMI are listed as one of the six components [32]. Its definition reads "BMI ≤−2 SDS at 24 months or current use of a feeding tube or cyproheptadine for appetite stimulation". Feeding difficulties are present in approximately 70% of patients with SRS versus 25% in non-SRS SGA [32].

Secondary Growth Disorders Associated with Early Feeding Problems

Early feeding problems are also encountered in several disorders of the gastrointestinal tract that can cause short stature, e.g., coeliac disease. A recent study on the effects of screening for coeliac disease in the general Dutch paediatric population showed that the clinical presentation has shifted towards less severe and extra-intestinal symptoms. In 24% of cases, anorexia and lassitude were reported [39]. There are also several feeding and eating disorders in the psychosocial field, e.g., "Avoidant Restrictive Food Intake Disorder" (ARFID) [40]. Regarding endocrine causes, the parents of many children with *IGF1R* haploinsufficiency reported feeding difficulties [41–43].

Current Medical History

A detailed medical history enables an estimate of the likelihood of an iatrogenic cause (e.g., methylphenidate treatment), psychosocial short stature, or eating disorders such as anorexia nervosa. In this mini-review, we emphasize that the current medical history should also include a dietary history and thereby potentially uncover a poorly planned or severely restricted diet resulting in nutritional deficiencies. We specially wish to focus on children on a vegetarian-type diet. In Europe, like many other parts of the world, the prevalence of vegetarianism is increasing, rising to around 10% [44, 45]. To our knowledge, figures about the percentages of children consuming a vegetarian-type diet are lacking.

Vegetarian-type diets, i.e., diets avoiding meat and fish, can be categorized by the food of animal origin that is still accepted into either vegetarian (lacto-ovo-vegetarian, lactovegetarian, and ovo-vegetarian) or vegan diets (in which also dairy products and eggs are excluded [46]). Another sort of diet is called "raw food diet," based on non-cooked plant foods, using grounding and fermentation for enhancing digestibility. A raw food diet is thought unsuitable for children, because of the risk of vitamin B12 deficiency [47] and acute small bowel obstruction due to a phytobezoar containing undigested vegetable materials [48]. Further, macrobiotic diets are being used, favouring locally produced foods with minimal processing, including fowl or fish once or twice weekly but excluding dairy products. Finally, "fruitarians" consume a diet limited to fruits and nuts [49].

In two review papers [46, 50], the authors concluded that, in general, vegan children show normal growth and are less often obese than non-vegan children. However, growth and body weight were generally found within the lower reference range, with a small percentage of short outliers [46]. A similar tendency was noted in the German VeChi study [51], where in 430 children aged 1–3 years, height <−2 SDS occurred only in children on a vegan (3.6%) or vegetarian (2.4% children) diet [51]. For children consuming a macrobiotic diet, slow growth has been

Table 2. Summary of the recommendations for nutritional supplements for infants, children, and adolescents on a vegan diet according to the French-speaking Paediatric Hepatology, Gastroenterology, and Nutrition Group [45]

Food component	Recommendation
General	A vegan diet is not recommended for infants, children, and adolescents due to the risk of nutritional deficiencies that are inevitable in the absence of supplements
Protein	Protein intakes are in line with requirements, provided that the sources between cereals and legumes are sufficiently varied to ensure the essential amino acid requirements. The only exception are infants fed with an inadequate vegetable beverage
Vitamin B12	In children who no longer consume rice- or soy-based infant formula, vitamin B12 supplementation is systematic; the dose depends on the child's age
Calcium	Calcium supplementation is necessary as soon as the consumption of rice- or soy-based infant formula decreases and in a routine manner in adolescents. The prescribed dose depends on other calcium intakes (mineral water, calcium-rich plants)
Vitamin D	Vitamin D supplementation should be systematic, as in all children, but the doses should be those recommended for children at risk
Iron	Iron supplementation will only be prescribed after confirmation of a deficiency by serum ferritin testing, which should be regularly monitored. The consumption of rice- or soy-based infant formula should be encouraged to last as long as possible, ideally up to at least 6 years of age
Zinc	Regular plasma zinc concentration dosing and monitoring will allow a decision to be made on possible zinc supplementation
Iodine	Regular consumption of iodized salts dispenses with iodine supplementation
Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)	In infants, the consumption of an infant formula not enriched in DHA justifies favouring oils rich in ALA (rapeseed, walnut, soybean). In older children, systematic supplementation with EPA and DHA in the form of algae is necessary. Otherwise, the diet should favour foods rich in omega-3

documented in a prospective study, followed by catch-up growth in the subgroup of children who had increased the consumption of fatty fish and/or dairy products [52, 53].

Limited evidence was found that children on a vegan diet can consume all the necessary nutrients [46, 50], and this can become even more challenging if vegan diets and food allergy co-occur [54]. However, there is no doubt that a poorly planned vegan diet can increase the risk of micronutrient deficiencies, mainly iodine, iron, zinc, calcium, vitamins A, B2, B12, and D, and long-chain polyunsaturated *n*-3 fatty acids. Deficiencies of these micronutrients can lead to various health conditions, such as anaemia, developmental delay, fatigue, and irritability [50, 54–56].

The effect of micronutrient deficiency on growth is less clear and sometimes even conflicting [57–59]. However, stunting was described in several case studies. For example, in an infant weaned to soy milk not fortified with calcium and vitamin D and a vegan diet, growth arrest of both weight and height was described, with catch-up growth after supplementation with vitamin D and calcium [60]. Weaning an infant to a vegetarian or vegan diet is challenging with a high risk of dietary insufficiencies and requires guidance by a dietician [61, 62]. Besides an effect on linear growth, there are also reports that a vegetarian or vegan diet diminishes bone mineral content. In a study in Polish children, bone mineral content (adjusted for body size) was decreased by 3.7–5.6% in children consuming a vegan diet [63].

Several international scientific societies have issued recommendations concerning veganism in children. While the American Academy of Pediatrics and the German Nutrition Society advised against a vegan diet in children, the Nutrition Committee of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), Italian Nutrition Society, and the French French-speaking Pediatric Hepatology, Gastroenterology, and Nutrition Group stated that, if the family so wishes, a dietary and

medical framework with regular monitoring should be provided (reviewed in [45]). Recommendations of the French group [45] are summarized in Table 2.

As applies to all medical recommendations, compliance in real life is never 100%. It is assumed that today, 1/3 to 1/2 of all adults on a vegan diet use supplements (reviewed in [50]). Typically, these numbers do not incorporate the use of fortified foods or drinks. In a study on Polish children on a vegetarian or vegan diet, nearly a third of children on either vegetarian or vegan diets were not given any B12 supplements or B12-fortified foods [63].

Many parents and children question if supplements or specific food products can increase height gain. So far, studies have not demonstrated a clinically relevant effect of nutritional therapy or supplements on height gain in children with a varied intake without deficiencies [64]. A prospective, randomized, double-blinded, placebo-controlled trial of nutritional supplementation in 3- to 9-year-old prepubertal children did show a statistically significant effect on linear growth after 1 year, but the change in height SDS was very low (0.00 ± 0.14 in "poor" responders and 0.12 ± 0.12 in "good" responders, respectively, over 6 months) [65]. Similar results were obtained in the open-labelled extension-phase study [66].

Some studies have suggested that a lack of dairy milk consumption is related to less linear growth, which is in line with observations that milk stimulates the GH-IGF-1 axis [67–69]. There is some indirect evidence that adult height is associated with dairy protein intake across countries in Europe and beyond [70, 71]. Another argument in favour of a positive effect of ingestion of dairy products, coinciding with an increasing prevalence of persistent lactase expression, is the finding of increased body stature after *Homo sapiens* started cattle-breeding in regions such as Northern Europe [72]. Obviously, these observations do not prove a causal role. In order to elucidate the effect of dairy products on height gain, well-controlled long-term follow-up studies are needed of children on a vegan diet from birth till adult height.

Parents, children, and/or adolescents can have various reasons to exclude food products or to adhere to a special diet, such as food allergies or sensitivities, behavioural conditions (such as ARFID [40]), perceived health benefits, religious practices, and ideological or ethical reasons. A restricted diet can be caused by financial reasons but may also be the (first) indication of the development of an eating disorder [73].

A proper dietary history should uncover a poorly planned or severely restricted diet (associated with potential nutritional deficiencies). When taking a dietary history, it is important to use a supportive, non-judgemental approach. Insight in the motivation and reasons for a (restricted) diet is a prerequisite for giving effective education and support to parents. Suggestions for issues to discuss in the dietary history are presented in Table 3. In cases of low weight-for-height, restricted diets, or doubts about the nutritional quality or quantity, a patient can be referred to a dietician.

Physical Examination

Each child with GF should undergo a full physical examination, including anthropometry (height, weight, OFC). BMI (kg/m^2) should be calculated. In special cases, the measurement of skinfold thickness may be indicated. These measurements and BMI should be compared with the respective growth charts and preferably expressed as SDS. It is also important to obtain information about all previous height and weight measurements. For practical purposes, children with short stature can be divided into three nutritional categories to help navigate the differential diagnosis.

Relatively High BMI SDS

If children have progressive short stature (ongoing loss of height SDS compared to peers) while their BMI SDS is relatively high or continues to rise over time, there is a fair chance that an endocrinopathy may be the cause. The well-known "endocrine cross" of slowing linear growth with a concomitant rise in BMI is typical for endocrine conditions such as GH deficiency, hypothyroidism, hypercortisolism, and craniopharyngioma with hypothalamic involvement and/or secondary pituitary dysfunction. In this category of children, the physical exam should focus on typical features of GH deficiency (a.o., mid face hypoplasia, frontal bossing, thin hair, excess abdominal fat with characteristic fat layering, and micropenis in affected boys), hypothyroidism (a.o., coarse and dry hair, goitre, pale skin, relative bradycardia), and Cushing syndrome (a.o., moon facies with facial redness, truncal obesity, muscle atrophy of arms and legs, although symptoms in children can often be limited).

Craniopharyngioma is notoriously difficult to diagnose on physical exam since headaches or visual disturbances may be a very late sign. Endocrine deficiencies, and particularly GF, usually precede the neurological symptoms. Any new-onset pituitary deficiencies that have been confirmed by laboratory testing including provocative GH testing should be further evaluated by cranial MRI [74].

Low BMI SDS

Referrals to paediatric endocrinologists for short stature or poor linear growth can also be part of a larger clinical

Table 3. Examples of questions to clarify dietary habits and potential nutritional deficiencies

Suggested questions	Elaboration or advice
How many meals and snacks does your child eat in an ordinary day?	
Are there any food products that your child does not eat (e.g., gluten-containing products)?	
Does your child eat meat or meat products?	If yes, how often (daily, ... times a week)? All types of meat or only meat of certain animal species? If no, reason?
Does your child eat fish, shellfish, or crustaceans?	If yes, how often (... times a week)?
Does your child eat or drink dairy products?	If yes, how often (daily ... portions, weekly ... portions) If no, does your child use plant-based dairy alternatives? Are these fortified with calcium and vitamin D, and do they have a protein content comparable to the dairy product?
Does your child eat eggs?	
On average, how many pieces of fruit does your child eat each day?	
On average, how many servings of vegetables does your child eat each day?	
If your child follows a vegetarian or vegan diet, does he/she regularly eat protein-rich products (such as soy-based products, plant-based meat substitutes, or legumes)?	
If your child follows a vegan diet, do you give vitamin D and/or calcium supplementation?	
If your child follows a vegan diet, do you consult a dietician and do you give a vitamin B12 and other supplements?	If no, strongly advise to consult a dietician. Vitamin B12 supplementation is crucial to prevent deficiencies in a vegan diet
Do you prepare food for your child according to a special diet, such as raw food diet?	
Does your child skips meals or is he/she a picky eater?	If yes, specify
Does it occur that you cannot supply a meal or certain food (products) to your child due to financial or other reasons?	If yes, you might elaborate this further or refer to a social worker to assist the family

picture associated with poor weight gain and other symptoms, often referred to as "failure to thrive" (FTT). The exact definition of FTT is not universally agreed upon, but the term is typically used for young children (<3 years) with abnormal growth parameters (both length and weight) and may be associated with non-specific symptoms of the gastrointestinal tract, irritability, decreased sleep quality, low energy levels, or poor overall development. This separates FTT from children with isolated or idiopathic (non-syndromic) short stature, who generally thrive well and have very few medical complaints other than their short stature. The workup of a child with failure to thrive is therefore noticeably different from children with isolated short stature and tends to be more comprehensive, especially if there are no dietary or environmental causes identified that may explain poor weight gain in the patient. A thorough FTT workup may therefore include screening for occult gastrointestinal disease (e.g., food allergies, coeliac disease), detailed urine and stool analysis, or specific screening for metabolic or genetic disorders depending on the clinical presentation [75].

Also in older children with short stature with clear signs of long-standing malnourishment, low BMI, and/or other signs of caloric deficit, the aetiology should primarily be sought in gastrointestinal factors (such as environmental enteropathy, Crohn's disease, or coeliac disease), psychosocial deprivation, or anorexia nervosa. Coeliac disease may present with typical abdominal bloating and wasting of the gluteus muscles, but can also present with isolated GF in the absence of any phenotypical abnormalities [76]. In teenagers, undiagnosed inflammatory bowel disease can be a cause of unexplained GF, produced by a combination of chronic inflammation, interleukin production, and a wide range of nutritional deficiencies [77]. Physical exam in short underweight children should also be directed at subtle signs of chronic stress, psychosocial deprivation, and/or eating disorders in every age range, e.g., ARFID [40]. Besides these gastrointestinal and psychosocial disorders, there are also genetic conditions that cause GF in combination with a low BMI, such as *IGF1R* haploinsufficiency and SRS.

Normal BMI SDS

Finally, there is the group of short children with a completely normal BMI development over time, in whom linear GF appears to be fully independent of nutritional status and who appear healthy other than their short stature. In practice, this is the largest group of short children as it also includes children with benign conditions such as constitutional delay of growth and puberty and the polygenic form of familial short stature. In addition, there is a wide range of skeletal dysplasias that lead to disproportionate short stature and an otherwise normal BMI and nutritional state. It should be noted in this respect that many skeletal dysplasia syndromes are actually associated with relatively high age-adjusted BMI values in the absence of elevated fat mass and do not require additional screening for obesity-associated comorbidities.

Growth Curve Analysis

When evaluating longitudinal growth, it is imperative to take nutritional status and BMI into account in a time-dependent manner. As stated previously, hormonal deficiencies typically produce visible slowing of linear growth velocity, while BMI simultaneously increases in the opposite direction. This is in contrast with short stature due to nutritional deficiencies that often shows two phases [78]. In the first phase, the nutritional status gradually worsens with a decrease in BMI, while linear growth remains relatively unaffected. However, if the nutritional deficiency persists and/or BMI further decreases, longitudinal growth will start to slow down (second phase). The duration of the first phase is variable, but typically spans several months or more, depending on age and the severity of the caloric or nutritional deficit. The bottom line is that the majority of children will need to experience a prolonged phase (months) of nutritional deficiencies before the resilient process of linear growth starts to falter. Therefore, it is crucial to obtain accurate growth parameters (including weight and BMI) throughout entire childhood but especially in the year directly preceding the change in growth rate that prompted presentation to clinic.

Laboratory Screening

In the guideline for the diagnosis of GF, we proposed that for each referred child, laboratory screening should be performed, independent of the severity of short stature or growth faltering [1]. The literature search for the present mini-review has not led to a revision of the list of laboratory investigations. If at this general screening anaemia is documented, further investigations are warranted to check for deficiencies of cobalamin, iron, or vitamin D. Depending on the dietary history, laboratory screening can be further extended. For example, iron status (complete blood count, serum ferritin) should be checked in all children with little or no consumption of meat and fish. Vitamin D can be measured in children in whom the estimated vitamin D intake via the diet or supplementation is low. Vitamin B12 should only be measured in children with a vegan diet if concerns about insufficiency exist, e.g., if supplementation is not administered or in case of macrocytic anaemia. Since clear evidence on the relation between micronutrient deficiency and growth is lacking, screening of these parameters (e.g., iodine, iron, zinc, selenium) is currently not recommended, except if the dietary history warrants this [55, 56, 79].

Conclusion

In the clinical assessment of a child with GF, nutritional assessment is an important component. When taking the past medical history, the clinician should enquire about birth weight, length, and OFC and any feeding problems in the first years of life. The current medical history should include a dietary history and thereby uncover a poorly planned or severely restricted diet, which can be associated with potential nutritional deficiencies.

As part of a full physical examination, the clinician should compare the course of height SDS of the child with that of BMI SDS. If short stature is combined with a BMI SDS in the upper half of the reference range or above, or if analysis of the growth curve shows growth faltering concomitant with increasing BMI SDS, the clinician should be alert to diagnose endocrine causes, such as hypothyroidism, Cushing syndrome, and GH deficiency (idiopathic or caused by an intracranial tumour). If children have short stature with clear signs of long-standing malnourishment, low BMI, and/or other signs of caloric deficit, the aetiology should primarily be sought in gastrointestinal factors, psychosocial deprivation, various feeding and eating disorders (e.g., anorexia nervosa or ARFID), or underlying genetic conditions (e.g., *IGF1R* haploinsufficiency and SRS). Laboratory and radiology screening are needed for each child with poor growth, and depending on the dietary history, laboratory screening can be extended. In particular, this applies to children on a poorly planned vegan diet.

Conflict of Interest Statement

H.V., S.D.J., W.O., and C.B. have no conflicts of interest to declare. J.M.W. is a member of the Editorial Board of Hormone Research in Paediatrics and has served as a consultant for Merck, LUMOS, AGIOS, and B2Pharm and received speaker's fees from Merck, Pfizer, Novo Nordisk, and Sandoz.

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Each of the authors was responsible for the first draft of the various sections. H.V. drafted the paragraph on current medical history, Tables 1 and 3, and laboratory testing. S.D.J. and J.M.W. drafted the paragraph on past medical history and Table 2. W.O. and H.V. drafted the paragraph on the effect of vegan diet on growth. C.B. drafted the paragraphs on failure to thrive, physical examination, and growth analysis. J.M.W. took the initiative for the mini-review, designed the format, and coordinated the subsequent versions of the manuscript that were commented upon by all authors. All authors approved of the manuscript prior to submission.

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