Genetic syndromes in the family : child characteristics and parenting stress in Angelman, CHARGE, Cornelia de Lange, Prader-Willi, and Rett syndrome

Wulffaert, J.

1 Introduction

INTRODUCTION

There is increasing scientific interest in genetic syndromes in the field of intellectual disabilities (ID). Initially, syndromes were detected on the basis of resemblance of physical characteristics (e.g. Cornelia de Lange syndrome, Prader-Willi syndrome). The advances made in genetics have opened the road to the identification of syndromes based on genotype instead of phenotype. This does not mean that the phenotype approach is no longer relevant. Not only do parents understand the diagnosis of a genetic syndrome better when they can see what the physical and behavioural consequences are, but also research into these characteristics is needed for the development of treatment strategies.

In general, studies of genetic syndromes associated with ID will have one of two different targets. The first is to unravel the pathways between genes, brain, and behaviour. The second is to generate syndrome-specific knowledge, valuable for clinical practice (Dykens, 2001; Dykens & Hodapp, 2001; Oliver & Hagerman, 2007). This study belongs in the second category.

Currently, around one-third of ID cases is estimated to be caused by a genetic disorder (Heikura et al., 2005) and around 1500 syndromes associated with ID have been genetically identified (Oliver & Hagerman, 2007). Some of these genetic syndromes have gained much attention in the field of behavioural sciences, such as Down syndrome, Fragile X syndrome, Prader-Willi syndrome, and Rett syndrome, but most syndromes have barely been investigated (Hodapp & Dykens, 2001, 2004, 2009). Even less is known about the families in which individuals with a genetic syndrome and ID grow up. In the present contribution the focus will be on the behavioural phenotype of individuals with five different genetic syndromes, (Rett syndrome, CHARGE syndrome, Cornelia de Lange syndrome, Angelman syndrome, and Prader-Willi syndrome), and on the relationship between the behavioural phenotypes and the parental perception of the child-rearing situation. Although there are various ways to define the concept ‘behavioural phenotype’, in this study the widespread definition introduced by Dykens (1995, p. 523) is used: the behavioural phenotype is “the heightened probability or likelihood that people with a given syndrome will exhibit certain behavioural or developmental sequelae relative to those without the syndrome”.

Aims of the study

There is much to learn about the behaviour of individuals with a rare genetic syndrome and how having a child with a genetic syndrome affects the family. For most syndromes knowledge of the behavioural phenotype is still developing, calling for more studies with valid and reliable instruments to further determine the behavioural phenotype. Moreover, extensive knowledge of syndrome-specific behaviour is a first prerequisite for the development of interventions. Furthermore, there are hardly any studies on the perception of the child-rearing situation for the five syndromes.

In this regard, parenting stress in particular is a relevant objective, because it can severely hinder positive outcomes for both the child and the family. Distressed parents are less likely to promote the child's development optimally and, for instance, can become depressed and may have poorer physical health (Deater-Deckard, 2004; Oelofsen & Richardson, 2006; Singer, 2006). In addition, children with ID appear particularly sensitive to the influence of a less than optimal family environment (Pazcowski & Baker, 2007).

The aim of the present study is therefore to expand knowledge of the child and family characteristics associated with specific genetic syndromes in order to be able to formulate recommendations for clinical practice. To this end, we investigated 1) the behavioural phenotype of five genetic syndromes (i.e. Rett, CHARGE, Cornelia de Lange, Angelman, and Prader-Willi syndrome), 2) the child-rearing experiences of the parents, more specifically the perception of stress as related to the upbringing, and 3) the relationship between child characteristics and perceived parenting stress.

This study was carried out in co-operation with several Dutch Parent Support Groups. The support groups for these five syndromes were highly interested in the research project. They recognized the clinical relevance and decided to support the study. All members of the support groups with a child with one of the five aforementioned syndromes received a request to participate in the research project. For CHARGE syndrome additional families were approached through co-operation with an outpatient CHARGE clinic at the University of Groningen. Parents who agreed to participate received several questionnaires to fill out concerning their child's behaviour and their perception of the child-rearing situation. Furthermore, an extensive interview was carried out with parents on the development of their child. The remainder of this chapter provides

a description of the five genetic syndromes and introduces the central concepts of this dissertation. An overview of the dissertation is provided at the end of this chapter.

Five genetic syndromes associated with intellectual disabilities

In the following paragraphs the syndromes under study are described briefly with regard to the classification, prevalence, level of functioning and behavioural characteristics.

Rett syndrome is caused by mutations of the X-linked *MECP2* gene. Mutations of the *CDKL5* (X-chromosome) and *NTNG1* (chromosome 1) gene are described as more rare causes. *MECP2* mutations are found in approximately 85% of the cases (Matijevic, Knezevic, Slavica, & Pavelic, 2009; Percy, 2008). The gene mutations are also associated with other phenotypes, thus clinical criteria are needed for diagnosis (Hagberg, Hanefeld, & Skjeldal, 2002; Percy, 2008), see Appendix A, Box A.1 for the criteria for classical Rett syndrome. In addition, diagnostic criteria exist for atypical variants, e.g. the preserved speech variant (see Hagberg et al., 2002). The development of classical Rett syndrome follows four stages; stagnation, regression, a pseudostationary period, followed by motor deterioration (Hagberg, 2002). Rett syndrome almost exclusively affects females (Percy, 2008). Prevalence rates for classical and atypical variants range from 0.88:10,000 to 2.2:10,000 (Laurvick, De Klerk, et al., 2006; Skjeldal, Von Tetzchner, Aspelund, Herder, & Lofterød, 1997).

Cognitive and adaptive skills in Rett syndrome are in the severe to profound ID range, occasionally with higher abilities in the atypical variants (Dahlgren Sandberg, Ehlers, Hagberg, & Gillberg, 2000; Demeter, 2000; Mount, Charman, Hastings, Reilly, & Cass, 2003). Behaviours associated with the syndrome according to the diagnostic criteria are the loss of purposeful hand skills between 6 and 30 months, stereotypic hand movements (e.g. hand wringing), emerging social withdrawal, communication dysfunction, a loss of learned words, disturbed breathing (e.g. hyperventilation), bruxism, and an impaired sleep pattern (Hagberg et al., 2002). Other characteristic behaviours are facial grimacing, repetitive mouth/tongue movements, screaming/crying/laughing during the night, and signs of fear and anxiety (Mount, Charman, Hastings, Reilly, & Cass, 2002). Findings are contradictory about whether clear associations exist between the *type* of gene defect and the physical and behavioural phenotype (Matijevic et al., 2009). Rett

syndrome is the only syndrome in this dissertation that is described as a separate category in the major classification systems for mental and health disorders and is placed under the pervasive developmental disorder section (American Psychiatric Association [APA], 2000; World Health Organization [WHO], 1993).

CHARGE syndrome is caused by defects of the *CHD7* gene on chromosome 8 (Vissers et al., 2004). A diagnosis can be based on the presence of a gene mutation, but also on the clinical criteria of Blake et al. (1998) and Verloes (2005), see Appendix A, Box A.2. Among those with typical CHARGE syndrome, *CHD7* mutations are found in over 90% of cases (Bergman et al., 2008). Multiple anomalies occur in the syndrome and some are included in the acronym: **C**oloboma of the eyes, **H**eart defects, **A**tresia of the choanae, **R**etardation of growth and/or development and/or central nervous system anomalies, **G**enital hypoplasia, **E**ar anomalies and/or deafness (Pagon, Graham, Zonana, & Yong, 1981). The incidence of CHARGE syndrome lies between 1:8,5000 and 1:12,5000 (Sanlaville & Verloes, 2007).

CHARGE syndrome has a very heterogeneous physical and behavioural appearance (Blake, Salem-Hartshorne, Abi Daoud, & Gradstein, 2005; Vervloed, Hoevenaars-Van den Boom, Knoors, Van Ravenswaaij, & Admiraal, 2006). The level of functioning covers the whole spectrum; normal intelligence quotients (IQ) and adaptive functioning to profound deficits in both respects can be present. A substantial proportion of individuals with CHARGE syndrome functions in the lower range (Harvey, Leaper, & Bankier, 1991; Johansson et al., 2006; Salem-Hartshorne & Jacob, 2005; Smith, Nichols, Issekutz, & Blake, 2005). Behavioural problems often reported are adherence to routines, attention problems, hyperactivity, irritability, self-injurious behaviour, sleep problems, stereotypical behaviour and tactile defensiveness. Findings are inconclusive with regard to aggression (Blake et al., 2005; Graham, Rosner, Dykens, & Visootsak, 2005; Johansson et al., 2006). There is a heightened risk for attention-deficit/hyperactivity disorder, autism spectrum disorders, anxiety disorders (especially obsessive-compulsive disorder), and Tourette syndrome. However, the classification of co-morbid psychiatric disorders in this multi-sensory impaired population is controversial (Blake et al., 2005; Hartshorne & Cypher, 2004; Johansson et al., 2006; Vervloed et al., 2006; Wachtel, Hartshorne, & Dailor, 2007). Currently no genotype-phenotype associations are known. Even in family members with the same gene mutation, including monozygotic twins, a different

phenotype was found. Differences have been reported between persons with and without gene mutations (Jongmans et al., 2006; Lalani et al., 2006; Wincent et al., 2008). Thus far, possible gene relationships were only tested for physical characteristics.

Cornelia de Lange syndrome is caused by mutations of one of at least three genes: *NIPBL* (chromosome 5), *SMC3* (chromosome 10), and *SMC1A* (X-chromosome). *NIPBL* mutations are detected in 44% to 56% of the cases, *SMC3* and *SMC1A* mutations in approximately 5% (Bhuiyan et al., 2006; Deardorff et al., 2007; Gillis et al., 2004; Krantz et al., 2004; Musio et al., 2006; Selicorni et al., 2007; Tonkin, Wang, Lisgo, Bamshad, & Strchan, 2004; Yan et al., 2006). A diagnosis can also be based on clinical criteria (see Appendix A, Box A.3; Kline et al., 2007). A classical and a mild type are distinguished, with less severe developmental and physical problems in the mild variant (Ireland, Donnai, & Burn, 1993; Van Allen et al., 1993). The prevalence of the classical and mild types combined is estimated to be between 1:10,000 and 1:62,000 (Barisic et al., 2008; Opitz, 1985).

Cognitive skills in Cornelia de Lange syndrome range from profound deficits to normal IQ. The same pattern is present for adaptive skills. Overall, most individuals have a moderate to profound ID (Basile, Villa, Selicorni, & Molteni, 2007; Beck, 1987; Berney, Ireland, & Burn, 1999; Oliver, Arron, Sloneem, & Hall, 2008). Behavioural problems often reported are anxiety, compulsive behaviour, emotional instability, excessive screaming, feeding problems, hyperactivity and attention problems, irritability, oppositional behaviour, self-injurious behaviour, and stereotyped behaviour. Results are mixed concerning the frequency of aggression and sleep disturbances (Basile et al., 2007; Berney et al., 1999; Hawley, Jackson, & Kurnit, 1985; Hyman, Oliver, & Hall, 2002; Sarimski, 1997b). Autism spectrum disorders are frequently present although discussion is ongoing whether there is an autistic-like behavioural profile or a truly co-morbid disorder. The high prevalence seems syndrome-specific and not only related to the low levels of functioning (Basile et al., 2007; Berney et al., 1999; Moss et al., 2008; Oliver et al., 2008). Individuals with *NIPBL* mutations seem more severely affected, physically as well as behaviourally, compared to those without this mutation. Individuals with a truncating *NIPBL* mutation are more severely affected than those with a missense *NIPBL* mutation (Gillis et al., 2004; Selicorni et al., 2007; Yan et al., 2006). However, this pattern was not significant in all studies (Bhuiyan et al., 2006).

Angelman syndrome is caused by defects on chromosome 15 from the maternal side and gene mutations are detected in approximately 90% of cases. Four different genetic mechanisms are known nowadays, i.e. a deletion of maternal origin (70%-75%), mutations of the *UBE3A* gene (5%-10%), an imprinting defect (3%-5%), and a paternal uniparental disomy (UPD) (2%-3%) (Clayton-Smith & Laan, 2003). When no defects are recognized in genetic tests, the syndrome is diagnosed when the person fits the clinical criteria (see Appendix A, Box A.4; Williams et al., 2006). Birth prevalence is estimated at 1:40,000, but population prevalence rates as high as 1:10,000 have also been reported (Petersen, Brøndum-Nielsen, Kjærsgård-Hansen, & Wulff, 1995; Thomson, Glasson, & Bittles, 2006).

Cognitive skills in Angelman syndrome are mainly in the severe to profound disability range. A proportion may function at a moderate ID level and mild delays are occasionally reported (Peters et al., 2004; Thomson et al., 2006). Adaptive skills range from moderate to severe/profound deficits with a strong positive association between cognitive and adaptive abilities (Duker, Van Driel, & Van de Bercken, 2002; Peters et al., 2004). Characteristic behaviours described in the clinical features are frequent laughter/smiling, apparently happy demeanour, easily excitable with often uplifted hand-flapping or waving, hypermotoric behaviour, none or minimal use of words, feeding problems, sleep problems, fascination with water, and abnormal food-related behaviour (Williams et al., 2006). Debate is on-going whether there is a heightened prevalence of autism spectrum disorders or whether certain behaviours should be seen as autistic traits characteristic for Angelman syndrome (Pelc, Cheron, & Dan, 2008). There is a strong focus on unravelling connections between specific gene defects within the syndrome and physical and behavioural characteristics. Individuals with deletions are generally more severely affected in the physical and developmental domains compared to those with an UPD or imprinting defect. Individuals with an *UBE3A* mutation fall grossly between the deletion and UPD group (Clayton-Smith & Laan, 2003; Williams et al., 2006).

Prader-Willi syndrome is caused by the same gene defects on chromosome 15 as seen in Angelman syndrome, but in Angelman syndrome the inherited information from the *maternal* chromosome 15 is missing or not functioning, while in Prader-Willi syndrome it is the *paternal* gene that shows a defect. Gene defects are a paternal deletion (70%-75%), maternal UPD (20%-30%), imprinting defect (1%-5%) or paternal

chromosomal translocation (<1%). In 99% of the cases a gene mutation is detected (Cassidy & Driscoll, 2009; Goldstone, Holland, Hauffa, Hokken-Koelega, & Tauber, 2008). An initial diagnosis is made using clinical criteria (see Appendix A, Box A.5; Holm et al., 1993). The development takes place in two stages; the first phase is characterised by hypotonia and failure to thrive. In the second phase, starting at the age of one to six years, problems with weight gain turn into life-long problems with overeating. This hyperphagia is due to insufficient functioning of the hypothalamus and, without dietary interventions, can lead to life-threatening obesity (Dykens, Hodapp, & Finucane, 2000; Goldstone et al., 2008). The population prevalence is estimated to be between 1:8,000 and 1:52,000 (Åkefeldt, Gillberg, & Larsson, 1991; Whittington et al., 2001).

The IQ of people with Prader-Willi syndrome is mostly in the borderline to moderate delayed range; a near normal distribution of IQ with a downward shift of 40 points is found (Curfs, 1992 as cited in Dykens et al., 2000; Whittington et al., 2004). Adaptive functioning is very often weaker than what is expected on the basis of IQ, caused by behavioural problems including food-related issues such as hoarding food (Dykens et al., 2000). Characteristic behavioural problems given in the diagnostic criteria are temper tantrums, violent outbursts, perseverance, stealing, lying, skin picking, and a tendency to be argumentative, oppositional, rigid, manipulative, possessive, and stubborn (Holm et al., 1993). Symptoms of affective disorders, obsessive-compulsive disorder, and psychosis are highly prevalent and full-blown co-morbid disorders are also present. It is still unclear whether there is a heightened risk for attention-deficit/hyperactivity disorder and autism spectrum disorders (Cassidy & Driscoll, 2009; Dykens et al., 2000; Dykens & Shah, 2003; Goldstone et al., 2008; Hiraiwa, Maegaki, Oka, & Ohno, 2007). Those with UPD and deletions are most often compared; individuals with UPD are less likely to have the typical facial characteristics and hypopigmentation. They exhibit fewer behavioural problems and have a higher verbal IQ, but psychosis and autism spectrum disorders are more frequent. *Within* the group with a deletion, people with a larger deletion seem to have lower levels of functioning and more compulsions compared to those with a smaller deletion (Cassidy & Driscoll, 2009; Dykens & Shah, 2003; Goldstone et al., 2008).

The above descriptions of the five syndromes evoke the question whether there are any syndrome-specific characteristics present that can be stressful for parents with a child with such a syndrome. To study this, a general framework for parenting stress is needed,

which will be provided in the next paragraph. After that, the association between child characteristics and parenting stress in genetic syndromes will be discussed.

Parenting stress

Raising a child with ID can be a stressful experience for parents, although at the same time positive effects can exist, such as experiencing personal growth or a closer marital bond (Hassall & Rose, 2005; Hastings & Beck, 2004; Hatton & Emerson, 2003; Head & Abbeduto, 2007; Olsson, 2008). Different theories on stress exist. One of the most influential is the theory on coping and appraisal by Lazarus and Folkman (1984). According to this theory, psychological stress is the result of the judgment of a person that a certain event endangers his well-being. By means of coping processes, cognitive and behavioural efforts to deal with these events, a person tries to manage these demands. Other theories, for example the one on *family* stress as outlined by McCubbin, Cauble, and Patterson (1982), place more emphasis on the sociological view. Its central focus is on how families make use of support from other family members and the community in the process of coping and adaptation. It is emphasized that in all families certain events occur during a lifetime; either expected such as the transition from childhood to adolescence or sudden, more unexpected events such as serious illness of a family member. Whether these changes are successfully managed depends on the resources of the family as a whole and its individual members. In addition to several stress theories, different models exist that were specifically designed to define the factors which influence *parenting* stress and coping. Parenting stress is distress related to the child-rearing situation and the demands that come with the parenting role (Deater-Deckard, 1998). There is considerable overlap between these models. The common features within them are child characteristics, environmental characteristics and the parent's cognitive style (Hassall & Rose, 2005).

A useful model to depict the process of parenting stress in families with a child with ID was designed by Perry (2004). This model is chosen because it is clear and practical enough to generate syndrome-specific knowledge by applied research and at the same time integrates the different theoretical angles. These theories include the aforementioned theory on coping and stress and sociological family stress theories, but also family systems theory applied to children with ID (Turnbull, Summers, & Brotherson, 1986 as cited in Perry, 2004), ecological theory (Bronfenbrenner, 1979), social support

theory (Cohen & Syme, 1985), and developmental psychopathology (Cicchetti & Lynch, 1993).

The combination of these theories led to the model depicted in Figure 1.1. Parenting stress there is the negative outcome after the impact of the stressors is mediated and/or moderated by resources and supports. S*tressors* are divided into child characteristics (e.g. age, developmental level) and other life stressors (e.g. illness of family members, unemployment). *Resources* are divided into the parent's individual personal resources (e.g. cognitive coping strategies, personality characteristics such as optimism) and the family system resources (e.g. marital satisfaction, socio-economic status). *Support systems* are divided into informal social support (concrete help and emotional support received from e.g. neighbours) and formal support and services (professional interventions e.g. individual treatment). In this project the focus lies on the *negative outcome*, i.e. feelings of parenting stress, although in the model positive outcomes (e.g. personal growth) are also mentioned. Furthermore, the child's characteristics are incorporated in the model and are related to the outcome of parenting stress.

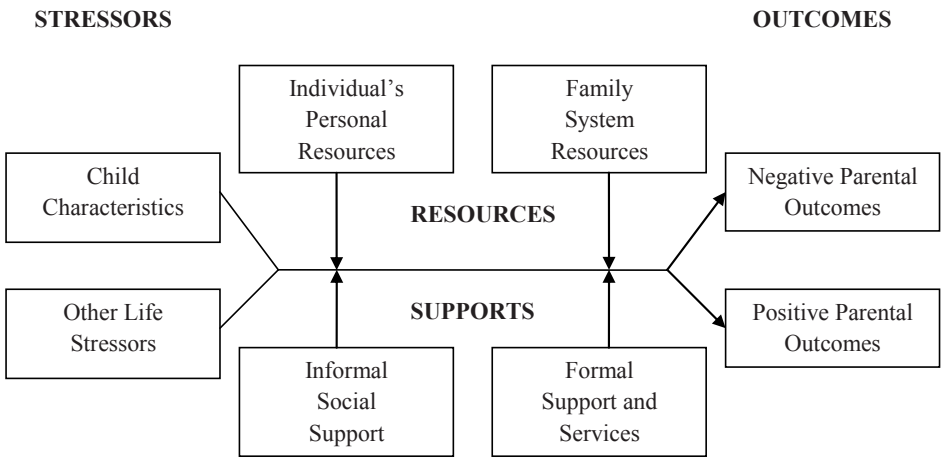

Figure 1.1 A model of stress in families of children with developmental disabilities by A. Perry, 2004, *Journal on Developmental Disabilities, 11*, p. 5. Copyright 2004 by the Ontario Association on Developmental Disabilities. Depicted with permission of the author.

Parenting stress and child characteristics in genetic syndromes

Parenting stress can severely hinder positive outcomes for both the child and the parent. It is thus an important domain of clinical practice, e.g. as a target for prevention.

However, research into the upbringing situation of families with a child with a rare genetic syndrome is scarce. Given this lack of knowledge, the focus of this project is on perceived parenting stress. We decided to investigate the relationship between parenting stress and the most obvious stressor within such families, i.e. the characteristics of the child. Previous studies have shown relationships between the child's behavioural characteristics and parenting stress, but the type of syndrome determined which child characteristics were relevant for parental perception (e.g. Farmer, Deidrick, Gitten, Fennell, & Maria, 2006; Fidler, Hodapp, & Dykens, 2000).

The decision which child characteristics to include in the present study was partly based on practical grounds. First, the required amount of time of the participants had to be reasonable, especially since some of these parents already do not have sufficient time for their regular family tasks. Second, because of limited financial resources, it was not possible to see the participating children and their parents individually. Therefore questionnaires filled out by the parents were used as the main source of information. The child characteristics measured are adaptive functioning, the presence of the autistic disorder, behavioural problems, and the child's age and gender. The considerations that led to the choice of these child characteristics, besides the abovementioned practical grounds, are presented in the following paragraphs.

Adaptive behaviour includes the abilities of a person in the conceptual, social and practical domains through which people can function in everyday life (American Association on Intellectual and Developmental Disabilities, 2009; Hodapp & Dykens, 2004). The presence of impairments in adaptive functioning is one of the criteria of ID, in addition to subaverage cognitive functioning and onset during childhood (APA, 2000). In some studies on ID, relationships between the level of adaptive and cognitive functioning are found, but in people with mild ID in particular they may be unrelated (Hodapp & Dykens, 2004).

In the field of genetic syndromes far fewer studies have been carried out into the level of adaptive functioning than into cognitive skills. The child's adaptive skills might however be even more relevant in relation to parenting stress; the level of adaptive functioning has a large impact on the amount of support a child needs with basic activities in everyday life. Studies on parenting stress and adaptive behaviour have been carried out for several genetic syndromes. Adaptive behaviour played a significant role in parenting stress among mothers of children with Joubert syndrome but not the fathers (Farmer et al.,

2006). For mothers with a child with Fragile X syndrome the level of adaptive functioning was not related to parenting stress (Bailey, Sideris, Roberts, & Hatton, 2008). This suggests that the impact of the level of adaptive functioning on parenting stress is syndrome-specific. Therefore, and because of it's high relevance for daily family life, adaptive behaviour is a relevant child characteristic for the current study to determine the relationship with parenting stress in the five syndromes.

Autistic disorder is present in a large proportion of the individuals with ID, although a wide range in prevalence estimates exists because of different sample selections, instruments, and level of functioning of participants. In a recent study, using the latest classification criteria, 8.8% of those with mild to profound ID also had the autistic disorder. The highest prevalence rates are found at the lower end of the ID spectrum (De Bildt, Sytema, Kraijer, & Minderaa, 2005). The combination of ID and the autistic disorder is highly disabling for the child (Van Berckelaer-Onnes, 1996). For parents this combination is stressful; it is more distressing than having a child with only ID (Blacher & McIntyre, 2006; Hastings, Daley, Burns, & Beck, 2006).

There are indications that the autistic disorder, or the more broadly defined autism spectrum disorders, are associated with some genetic syndromes found in people with ID. The five syndromes in this dissertation have been mentioned in this context as well. Debate is still on-going about whether there are mainly specific 'autistic' profiles in different genetic syndromes or whether there truly are valid co-morbid cases. Furthermore the link between ID, genetic syndromes, and prevalence of autism spectrum disorders is still speculative (Cohen et al., 2005; Gillberg, 1992; Moss & Howlin, 2009; Zafeiriou, Ververi, & Vargiami, 2007). In this study the focus is on the impact of autistic disorder symptoms on the parental perception of stress. As far as we know, the relationship between parenting stress associated with genetic syndromes and symptoms of the autistic disorder has not been investigated before. Given the high prevalence of the autistic disorder and its impact on parents, this is seen as a highly relevant child characteristic in the current study.

Behavioural problems occur at a higher rate in those with ID compared to those without ID (Dekker, Koot, Van der Ende, & Verhulst, 2002; Došen, 2005). The subject of behavioural problems in individuals with ID falls in a complex field of research (see e.g. Allen & Davies, 2007). One of the difficulties in this field is the use of different terms (e.g. behavioural problems, challenging behaviour, psychopathology) and uncertainties

about the definitions of these terms. As a consequence prevalence rates vary widely, also because of differences in sample selection, informants, instruments, age and level of ID of the participants (Dekker, 2003; Dykens, 2000). Dekker (2003) compared prevalence studies of behavioural problems/psychopathology in children with ID and reported a rate between 4% and 65% of the participants. Again, in the present study the focus is on the impact of the child's behavioural problems on parenting stress.

Studies on parent's experiences and the child's behavioural problems have been carried out for several genetic syndromes. Hodapp (1999) concludes that the child's behavioural problems are the best predictor of parenting stress compared with other child characteristics, i.e. age, gender, and IQ. This is based upon research into Prader-Willi syndrome, Smith-Magenis syndrome, and 5p- syndrome. In contrast, in another study the strongest predictor for family stress was younger age of the child with Down syndrome, behavioural problems in Smith-Magenis syndrome, and both age and behavioural problems in Williams syndrome (Fidler et al., 2000). Since the presence of behavioural problems has proven to be a strong predictor of parenting stress in many developmental studies, this characteristic could not be left out of this study of the five syndromes.

Chronological age of the child has proven to be related to parenting stress in some genetic syndromes but with different directions. For example, higher levels of parenting stress were related to younger age of children with Down syndrome and Williams syndrome, but with higher age of children with Joubert syndrome (Farmer et al., 2006; Fidler et al., 2000). This child characteristic is therefore also taken into account in the present study.

Gender has not often been found to be related to parenting stress in specific genetic syndromes, but in some cases it was. For example, fathers with a daughter with Joubert syndrome reported more stress than fathers with a son, but gender was not related to parenting stress in mothers of the same group of children (Farmer et al., 2006). Since gender thus also seems to vary as a risk factor of parenting stress in specific syndromes, this child characteristic was also included in the current study.

Overview of the dissertation

This dissertation contains five articles which are all based upon the same behavioural assessment instruments in a similar research format. In each of the articles, thus for the separate syndromes, somewhat different aspects are highlighted. To give a

comprehensive description of the same characteristics for all syndromes, an overview is provided in the general discussion (chapter 7). The articles stand alone and can be read separately. Consequently, some overlap between the chapters is inevitable. The articles have been published and/or submitted to journals in American English and British English, therefore, different spelling is used in the different articles.

In chapter 2 screening for autistic disorder symptoms in females with Rett syndrome is described. In the major classification systems for mental and health disorders Rett syndrome is placed under the pervasive developmental disorders and a diagnosis of Rett syndrome precludes a diagnosis of the autistic disorder. However, given the low level of functioning of these females, a co-morbid autistic disorder is expected in a substantial proportion. In this article the controversial issue of whether placement of Rett syndrome under the pervasive developmental disorders is appropriate is considered.

In chapter 3 parenting stress in mothers with a child with Rett syndrome is reported. This study builds upon, replicates and expands current knowledge on families with a child with Rett syndrome. The relationships between parenting stress and behavioural problems, and parenting stress and the presence of the autistic disorder are explored for the first time. Implications for clinical practice are given.

In chapter 4 the perception of parenting stress by mothers and fathers of children with CHARGE syndrome is discussed. In this heterogeneous syndrome a lot of different physical and behavioural problems can be present. Several of the important problems were measured and the relationship of these child characteristics with the perceived parenting stress is investigated. Suggestions for clinical practice and future studies into this complex syndrome are given.

In chapter 5 a comprehensive overview of characteristics of individuals with Cornelia de Lange syndrome and the parenting stress of their mothers and fathers is presented. With a scarcely used statistical technique in the ID field (i.e. categorical principal component analysis) it became possible to generate a detailed description of this syndrome. Further recommendations for future research and clinical practice are based upon this successful technique for research into rare genetic syndromes.

In chapter 6 parenting stress of mothers with a child with either Angelman syndrome or Prader-Willi syndrome is compared. Both syndromes are caused by changes in the genetic information of the same small area of chromosome 15, and may therefore be called related, but in Angelman syndrome the gene defect is on

the maternal chromosome whereas in Prader-Willi syndrome it is on the paternal side. First, parenting stress and the relationship with child characteristics *within* both syndromes is investigated. Then, the levels of parenting stress *between* the syndrome are compared. Recommendations for support for these families are given.

In chapter 7 an overview and comparison of child and parenting characteristics is given for all five syndromes. This overview leads to general and syndrome-specific recommendations for clinical practice. Finally, limitations of the present study and directions for future research are discussed.

APPENDIX A

Box A.1 *Diagnostic criteria for classical Rett syndrome (Hagberg et al., 2002)*

Necessary criteria

- Apparently normal prenatal and perinatal history
- Psychomotor development largely normal through the first 6 months or may be delayed from birth
- Normal head circumference at birth
- Postnatal deceleration of head growth in the majority
- Loss of achieved purposeful hand skill between ages ½ - 2½ years
- Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms
- Emerging social withdrawal, communication dysfunction, loss of learned words, and cognitive impairment
- Impaired (dyspraxic) or failing locomotion

Supportive criteria

- Awake disturbances of breathing (hyperventilation, breath-holding, forced expulsion of air and saliva, air swallowing)
- Bruxism
- Impaired sleep pattern from early infancy
- Abnormal muscle tone successively associated with muscle wasting and dystonia
- Peripheral vasomotor disturbances
- Scoliosis/kyphosis progressing through childhood
- Growth retardation
- Hypotrophic small and cold feet; small, thin hands

Exclusion criteria

- Organomegaly or other signs of storage disease
- Retinopathy, optic atrophy, or cataract
- Evidence of perinatal or postnatal brain damage
- Existence of identifiable metabolic or other progressive neurological disorder
- Acquired neurological disorders resulting from severe infections or head trauma

Box A.2 *Diagnostic criteria for CHARGE syndrome (Blake et al., 1998; Verloes, 2005)*

Blake et al. (1998):	**Verloes (2005):**
Major criterion ▪ Coloboma - coloboma of iris, retina, choroid, disc; microphthalmia ▪ Choanal atresia - unilateral/bilateral, membranous/bony, stenosis/atresia ▪ Characteristic ear abnormalities - external ear (lop or cup shaped), middle ear (ossicular malformations, chronic serous otitis), mixed deafness, cochlear defects Cranial nerve dysfunction - I: anosmia, VII: facial palsy (unilateral of bilateral), VIII: sensorineural deafness and vestibular problems, IX and/or X: swallowing problems	**Major signs** ▪ Coloboma (iris or choroid, with or without microphthalmia) ▪ Atresia of choanae ▪ Hypoplastic semi-circular canals
Minor criterion ▪ Gential hypoplasia - males: micropenis, cryptorchidism, females: hypoplastic labia, both: delayed, incomplete pubertal development ▪ Developmental delay - delayed motor milestones, hypotonia, mental retardation ▪ Cardiovascular malformations - all types: especially conotruncal defects (e.g. tetraology of Fallot), arteriovenous canal defects, and aortic arch anomalies ▪ Growth deficiency - short stature ▪ Orofacial cleft - cleft lip and/or palate ▪ Tracheoesophageal-fistula-tracheoesophageal defects of all types ▪ Distinctive face	**Minor signs** ▪ Rhombencephalic dysfunction (brainstem dysfunctions, cranial nerve VII to XII palsies and neurosensory deafness) ▪ Hypothalamo-hypophyseal dysfunction (including GH and gonadotrophin deficiencies) ▪ Abnormal middle or external ear ▪ Malformation of mediastinal organs (heart, esophagus) ▪ Mental retardation
CHARGE classification ▪ All 4 major signs OR 3 major and 3 minor signs	**CHARGE classification** **Typical CHARGE** ▪ 3 major signs OR 2/3 major signs + 2/5 minor signs **Partial/incomplete CHARGE** ▪ 2/3 major + 1/5 minor **Atypical CHARGE** ▪ 2/3 major + 0/5 minor OR 1/3 major + 3/5 minor

Box A.3 *Diagnostic criteria for Cornelia de Lange syndrome (Kline et al., 2007)*

Facial

- Synophrys (arched, fine eyebrows) and ≥ 3 of: long eyelashes; short nose, anteverted nares; long, prominent philtrum; broad or depressed nasal bridge; small or square chin; thin lips, down-turned corners; high palate; widely spaced or absent teeth

Growth

- ≥ 2 of: weight below 5th centile for age; height or weight below 5th centile for age; OFC below 2nd centile for age

Development

- ≥1 of: developmental delays or mental retardation; learning disabilities

Behaviour

- ≥ 2 of: attention deficit disorder ± hyperactivity; obsessive-compulsive characteristics; anxiety; constant roaming; aggression; self-injurious behaviour; extreme shyness or withdrawal; autistic-like features

Musculoskeletal

- Reduction defects with absent forearms

OR

- Small hands and/or feet (below 3rd centile) or oligodactyly and ≥ 2 of: 5th finger clinodactyly; abnormal palmar crease; radial head dislocation/abnormal elbow extension; short 1st metacarpal/proximally placed thumb; bunion; partial 2,3 syndactyly toes; scoliosis; pectus excavatum; hip dislocation or dysplasia

OR

- ≥ 3 of: 5th finger clinodactyly; abnormal palmar crease; radial head dislocation/abnormal elbow extension; short 1st metacarpal/proximally placed thumb; bunion; partial 2,3 syndactyly toes; scoliosis; pectus excavatum; hip dislocation or dysplasia

Neurosensory/skin

- ≥ 3 of: ptosis; tear duct malformation of blepharitis; myopia ≥ -6.00 D; major eye malformation or peripapillary pigmentation; deafness or hearing loss; seizures; cutis marmarata; hirsutism, generalised; small nipples and/or umbilicus

Other major systems

- ≥ 3 of: gastrointestinal malformation/malrotation; diaphragmatic hernia; gastroesophageal reflux disease; cleft palate or submucous cleft palate; congenital heart defect; micropenis; hypospadias; cryptorchidism; renal or urinary tract malformation

Cornelia de Lange diagnosis

- Positive mutation on Cornelia de Lange testing

OR

- Facial findings and meet criteria from two of the growth, development or behaviour categories

OR

- Facial findings and meet criteria for three other categories, including one from growth, development or behaviour, and two from other categories

Box A.4 *Clinical features of Angelman syndrome (Williams et al., 2006)*

Consistent (100%)

- Developmental delay, functionally severe
- Movement or balance disorder, usually ataxia of gait, and/or tremulous movements of limbs. Movement disorder can be mild. May not appear as frank ataxia but can be forward lurching, unsteadiness, clumsiness, or quick, jerky motions
- Behavioural uniqueness: any combination of frequent laughter/smiling; apparent happy demeanour; easily excitable personality, often with uplifted hand-flapping, or waving movements; hypermotoric behaviour
- Speech impairment, none or minimal use of words; receptive and non-verbal communication skills higher than verbal ones

Frequent (more than 80%)

- Delayed, disproportionate growth of head circumference, usually resulting in microcephaly by age 2 years. Microcephaly is more pronounced in those with 15q11.2-q13 deletions
- Seizures, onset usually < 3 years of age. Seizure severity usually decreases with age but the seizure disorder lasts throughout adulthood
- Abnormal EEG, with a characteristic pattern. The EEG abnormalities can occur in the first 2 years of life and can precede clinical features, and are often not correlated to clinical seizure events

Associated (20% - 80%)

- Flat occiput
- Occipital groove
- Protruding tongue
- Tongue thrusting; suck/swallowing disorders
- Feeding problems and/or truncal hypotonia during infancy
- Prognathia
- Wide mouth, wide-spaced teeth
- Frequent drooling
- Excessive chewing/mouthing behaviours
- Strabismus
- Hypopigmented skin, light hair, and eye colour compared to family, seen only in deletion cases
- Hyperactive lower extremity deep tendon reflexes
- Uplifted, flexed arm position especially during ambulation
- Wide-based gait with pronated or valgus-positioned ankles
- Increased sensitivity to heat
- Abnormal sleep-wake cycles and diminished need for sleep
- Attraction to/fascination with water; fascination with crinkly items such as certain papers and plastics
- Abnormal food related behaviours
- Obesity (in the older child)
- Scoliosis
- Constipation

Box A.5 *Diagnostic criteria for Prader-Willi syndrome (Holm et al., 1993)*

Major criteria

- Neonatal and infantile central hypotonia with poor suck, gradually improving with age
- Feeding problems in infancy with need for special feeding techniques and poor weight gain/failure to thrive
- Excessive or rapid weight gain on weight-for-length chart (excessive is defined as crossing two centile channels) after 12 months but before 6 years of age; central obesity in the absence of intervention
- Characteristic facial features with dolichocephaly in infancy, narrow face or bifrontal diameter, almond-shaped eyes, small-appearing mouth with thin upper lip, down-turned corners of the mouth (3 or more required)
- Hypogonadism – with any of the following, depending on age:
  a) genital hypoplasia, male: scrotal hypoplasia, cryptochidism, small penis and/or testes for age (<5th percentile); female: absence or severe hypoplasia of labia minora and/or clitoris
  b) delayed or incomplete gonadal maturation with delayed pubertal sings in the absence of intervention after 16 years of age (male: small gonads, decreased facial and body hair, lack of voice change; female: amenorrhea/oligomenorrhea after age 16)
- Global developmental delay in a child younger than 6 years of age; mild to moderate mental retardation or learning problems in older children
- Hyperphagia/food foraging/obsession with food
- Deletion 5q11-13 on high resolution (>650 bands) or other cytogenetic/molecular abnormality of the Prader-Willi chromosome region, including maternal disomy

Minor criteria

- Decreased fetal movement or infantile lethargy or weak cry in infancy, improving with age
- Characteristic behaviour problems – temper tantrums, violent outbursts and obsessive/ compulsive behaviour; tendency to be argumentative, oppositional, rigid, manipulative, possessive, and stubborn; perseverating, stealing, and lying (5 or more of these symptoms required)
- Sleep disturbance or sleep apnea
- Short stature for genetic background by age 15 (in the absence of growth hormone intervention)
- Hypopigmentation – fair skin and hair compared to family
- Small hands (<25th percentile) and/or feet (<10th percentile) for height age
- Narrow hands with straight ulnar border
- Eye abnormalities (esotropia, myopia)
- Thick viscous saliva with crusting at corners of the mouth
- Speech articulation defects
- Skin picking

Supportive findings

- High pain threshold
- Decreased vomiting
- Temperature instability in infancy or altered temperature sensitivity in older children and adults
- Scoliosis and/or kyphosis
- Early adrenarche
- Osteoporosis
- Unusual skill with jigsaw puzzles
- Normal neuromuscular studies

Prader-Willi diagnosis

- Major criteria are weighted at one point each; minor criteria are weighted at one half point
- Children three years of age or younger: five points are required for diagnosis, four of which should come from the major group
- Children three years of age to adulthood: total score of eight is necessary for the diagnosis. Major criteria must comprise five or more points of the total score