Genetic Syndromes in the Family

Child Characteristics and Parenting Stress in Angelman, CHARGE, Cornelia de Lange, Prader-Willi, and Rett Syndrome

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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.

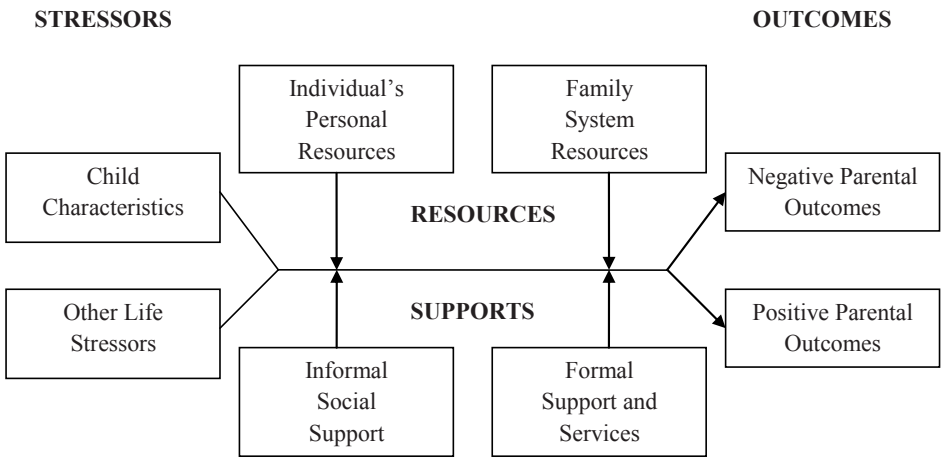

Figure 1.1 A model of stress in families of children with developmental disabilities by A. Perry, 2004, *Journal on Developmental Disabilities, 11*, p. 5. Copyright 2004 by the Ontario Association on Developmental Disabilities. Depicted with permission of the author.

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

2 Autistic disorder symptoms in Rett syndrome

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ABSTRACT

According to the major classification systems it is not possible to diagnose a comorbid autistic disorder in persons with Rett syndrome. However, this is a controversial issue, and given the level of functioning of persons with Rett syndrome, the autistic disorder is expected to be present in a comparable proportion as in people with the same level of functioning. To investigate, parents of 52 females with classical and atypical Rett syndrome (2.4 – 49.3 years) completed the Developmental Behavior Checklist (DBC), the Diagnostic Interview for Social and Communication Disorders (DISCO) and the Dutch Vineland Screener 0-6 (VS 0-6). All participants had a severe to profound intellectual disability according to the VS 0-6. Behavior indicated an autistic disorder in 42% (DBC) to 58% (DISCO) of the Rett cases. Autistic behavior had decreased in 19% such that they no longer met the criteria for autistic disorder. Some participants were suspected of having a comorbid autistic disorder, though not more often than can be expected at their level of functioning. Clinicians should be aware of the possibility of a comorbid autistic disorder as much as they should be in other people with this level of functioning.

INTRODUCTION

Rett syndrome (RS) is a neurodevelopmental disorder with a particular course: a seemingly normal early development is disturbed by a loss of acquired developmental skills, but is followed afterwards by a so-called 'wake up period'. The RS phenotype consists of a classical and certain atypical variants. In classical RS the physical and developmental characteristics fall in four stages, i.e. stagnation (I), regression (II), a pseudostationary period (III) followed by late motor deterioration (IV). The course and features differ for the atypical variants (Hagberg, 2002). According to an overview study, people with RS have a severe but mostly profound intellectual disability (ID), with occasionally higher abilities in the atypical variants (Demeter, 2000). Although RS almost exclusively affects females, some cases of males with RS are known. Mutations in the *MECP2* gene were identified as a cause of RS and now can be detected in most individuals with RS (Percy, 2008). Our knowledge of the genetics and medical aspects of RS has increased dramatically over the last couple of years and was recently reviewed by Percy (2008). The behavior of people with RS however, has received far less attention in

recent years. In this study we focus on the behaviors in relation to the classification of the autistic disorder (AD).

Soon after Rett syndrome became internationally known, one of the diagnostic pitfalls mentioned was to diagnose infantile autism in persons with RS by overestimating the autistic behaviors seen in stages I and II (Hagberg & Witt-Engerström, 1986). It has been observed that the autistic behaviors usually improve or become less prominent when the persons grow older (Gillberg, 1986; Hagberg & Witt-Engerström, 1986). Research into the features of AD, qualitative impairments in social interaction and communication, and restricted, stereotyped patterns of behavior, interests and activities (American Psychiatric Association [APA], 2000), has been carried out in RS. Qualitative differences between people with RS and those with AD with regard to social interaction have been stressed by various authors. In several studies, some to all of the participants with RS were socially orientated and enjoyed social interaction (Dahlgren Sandberg, Ehlers, Hagberg, & Gillberg, 2000; Kerr, Archer, Evans, Prescott, Gibbon, 2006; Olsson & Rett, 1987). Not all authors found this social orientation, but they still clearly distinguished the behavior of people with RS from that of people with AD. In contrast to people with AD, people with RS did not exhibit resistance or a defense reaction when approached (Gillberg, 1987; Olsson & Rett, 1990). On the other hand, Woodyatt and Ozanne (1992) concluded that the six girls in their study made poor eye contact and showed almost no awareness of the people around them.

Research into the other two domains which are impaired in people with AD, namely qualitative impairments in communication and stereotyped patterns of behavior, has shown mixed results for people with RS. Most of them function at the pre-intentional level of communication (Dahlgren Sandberg et al., 2000; Woodyatt & Ozanne, 1992); according to Woodyatt and Ozanne (1997), communicative functions were impaired in persons with RS, even compared to persons with profound ID. Hagberg (2002) however, stressed the importance of intense eye communication as an alternative mode to interact for these severely disabled persons. In a study with 30 participants with the preserved speech variant of the syndrome, all showed echolalia (Zapella, Gillberg, & Ehlers, 1998). Stereotypic hand movements like washing and wringing have been mentioned as the core feature of RS (Hagberg, 2002) and these could be clearly differentiated from the stereotypic behavior seen in AD (Olsson & Rett, 1987).

In two more recent studies with standardized instruments, autism symptoms have been compared between children with RS and children with comparable levels of ID (Mount, Charman, Hastings, Reilly, & Cass, 2003; Mount, Hastings, Reilly, Cass, & Charman, 2003). Mount, Hastings et al. (2003) found that children with RS (all were under 18 years) showed more autistic behavior than children with severe to profound ID. However, compared to the behavior of children with the same level and comorbid AD, girls with RS showed a different behavioral profile. The AD group displayed more 'truly autistic' behavior (e.g. avoiding eye contact, not responding to others' feelings), whereas girls with RS showed more related symptoms (e.g. underactive, unhappy). In a different study, girls with classical RS (aged 11 to 18 years) were compared with children with severe and profound ID whereby the authors controlled for differences in developmental level and motor skills. Participants with RS scored in the range people with AD obtain, but with a slightly different pattern. The children with classical RS may show some but not the full range of autistic behavior (Mount, Charman, et al., 2003).

Although differences in behavior between people with RS and those with AD have been reported, the behavior of some people with RS fulfilled all criteria for AD. Two out of eight participants with RS (11 to 36 years) met the criteria for AD of the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV: APA, 1994) (Dahlgren Sandberg et al., 2000). Eight out of 12 females (3 to 24 years) met DSM-III-R criteria (APA, 1987) for AD (Mazzocco et al., 1998). Of 30 persons with the RS preserved speech variant (5 to 28 years) 97% met DSM-IV criteria for AD (Zapella et al., 1998). People with ID have a higher risk of a comorbid diagnosis of AD. Exact prevalence rates are difficult to compare between publications, for instance because of different levels of functioning in the sample, and the definitions and instruments used. In a sample of children with severe to profound ID, at which level almost all persons with RS function, 37% also had AD (Deb & Prasad, 1994). Keeping this high prevalence of AD in people with severe to profound ID in mind, it is expected that a substantial percentage of people with RS have a comorbid AD, whereas others have not.

However, this is a highly controversial point in relation to the major classification systems, i.e. the DSM-IV-TR and the International Statistical Classification of Diseases 10 (ICD-10). There, RS is classified under the pervasive developmental disorders (PDDs) and a diagnosis of RS excludes a diagnosis of autistic disorder or childhood autism (CA) (APA, 2000; World Health Organization [WHO], 1993). Debate about this topic is

ongoing. Opponents of this view wondered why RS was placed in the PDD section when not all RS girls show autistic symptoms. The fact that other genetic syndromes with as high or even higher risk for autistic symptoms were not included in this particular section seemed to argue against this decision as well (Gillberg & Billstedt, 2000; Wing, 2005). Others stated that the clinical picture of RS is different from AD and therefore a subcategory in the PDD section is justified (Rutter, 1994) or placement in that section seemed most relevant at that time (Tsai, 1992). Gillberg (1992) strongly underlined the possibility of diagnosing both RS and AD in an individual.

In this study, in addition to Gillberg's opinion, we want to test the hypothesis that AD symptoms will be present in people with RS in proportions comparable to those in the population of people with a severe to profound ID. We therefore investigated the presence of AD symptoms in children and adults with classical or atypical RS in the Netherlands. We decided to take a broad age range to explore whether autistic symptoms are similar in different age groups, since such a comparison is currently lacking. Apart from this we also want to determine whether autistic symptoms change in some individuals, as this has not been investigated with a semi-structured instrument before. We expect AD symptoms in some individuals to become less prominent as they grow older, as suggested in earlier research.

METHOD

Participants

Participants were 52 families with a daughter with RS; the youngest person was 2.4 years old, the oldest participant 49.3 years. Mean age was 16.5 years (*SD* = 11.8 years). Children (0 to 18 years) accounted for 63% of the sample. Of the 52 participants, 41 had classical RS and 10 atypical RS. For one person the RS type was unknown; this person had an *MECP2* mutation. Of the 41 participants with classical RS, 35 appeared to have *MECP2* mutations; only two females did not have an *MECP2* mutation. For four persons the presence or absence of *MECP2* mutations was unknown, either because genetic screening had not been carried out, or because genetic screening was carried out before the discovery of the *MECP2* gene as a cause of RS. Of the 10 participants with atypical RS, 8 had *MECP2* mutations and 2 did not.

Procedure

The participating families were members of the Dutch Rett Parent Support Group. By letter from the parent support group, all 190 families were asked to take part in the current study. Initially parents of 52 daughters with RS joined the project, but for 3 females it was unclear whether they really had RS; for 1 female no questionnaire was returned. These four persons were excluded from further analyses. After preliminary results were presented at the national family day 2007 of the Dutch Rett Parent Support Group, six other parents expressed willingness to participate. For two of these six children it was unclear whether they really had RS. Data on these two females were also excluded, which left data on 52 persons available for analyses. The participating parents were asked whether their child had classical or atypical RS and whether an *MECP2* mutation was present. Some parents did not know the answers to these questions. In that case written permission to contact the relevant medical specialist was obtained from all but one parent and all specialists approached provided genetic records.

After giving written consent to participate, parents were contacted by phone to schedule an interview with the research assistants. Subsequently the questionnaires were sent out. Parents were asked to send them back in the return envelope before the interview, but the option existed to discuss uncertainties with the interviewers and return the questionnaires afterwards. Parents who did not return the questionnaires were called and encouraged to send it back. If items of the questionnaires were unanswered, the research assistants tried to contact parents by phone and then asked them to complete the blank items verbally. There was limited time to call the parents afterwards as the interval between the original completion of the questionnaires and the completion of items by phone was set to a month. There remained 21 participants for whom one or more items of the questionnaires were unanswered.

Research instruments

The *Developmental Behavior Checklist–Primary Carer* (DBC-P) assesses the emotional and behavioral problems of children with ID over the past six months (Einfeld & Tonge, 2002; Dutch version: Koot & Dekker, 2001). Parents rate 95 items on a three-point scale: score 0 if the item is ‘not true as far as you know’, score 1 if ‘somewhat or sometimes true’, and score 2 if ‘very true or often true’. A total behavior problem score and five subscale scores can be computed. Inter-rater and retest reliability, internal

consistency, and construct and criterion validity are all satisfactory (Koot & Dekker, 2001). The DBC-P has an autism screening algorithm (DBC-ASA), consisting of 29 items of the questionnaire, which screens for autistic disorder as defined by DSM-IV (APA, 1994). The DBC-ASA has good validity to detect children with AD. A cutoff score of 17 had a sensitivity of .86 and specificity of .69. Internal consistency is .94 (Brereton, Tonge, Mackinnon, & Einfeld, 2002).

The *Diagnostic Interview for Social and Communication Disorder–10th revision* (DISCO-10) is a semi-structured interview to support clinicians in diagnosing autism and related disorders in people of all ages and levels of functioning for past and present behavior (Wing, 1999). For research purposes, different algorithms exist (Wing, Leekam, Libby, Gould, & Larcombe, 2002). In DISCO-10 there are, among others, algorithms based on the PDD classifications in ICD-10 and DSM-III-R. We decided to take the ICD-10 criteria for CA as the DSM-III-R criteria are outdated. Good inter-rater reliability has been obtained with the Swedish DISCO-10 translation (Nygren et al., 2009). Good correspondence between a clinical diagnosis of autistic disorder or childhood autism and DISCO-10 CA classification is demonstrated in several studies (Billstedt, 2007; Hoekstra, 2007). In our study the research assistants who took the interview always worked in pairs and received DISCO-10 training by officially registered instructors.

The *Vineland Screener 0-6* (VS 0-6: Scholte, Van Duijn, Dijkxhoorn, Noens, & Van Berckelaer-Onnes, 2008) is a Dutch screening instrument adapted from the Vineland Screener as developed by Sparrow, Carter, and Cicchetti (1993). The VS 0-6 measures the level of adaptive functioning by 72 items on the domains of communication, daily living skills, socialization, and motor skills. Parents indicate on a four-point scale whether the person exhibits the behavior in daily life: score 0 for ‘no, never’, score 1 for ‘sometimes or partly’, and score 2 for ‘yes, usually’. A fourth possible score is ‘unknown’ if the parent is unsure. The VS 0-6 is developed to measure the adaptive developmental level of children up to age six or older people with comparable levels of functioning. It shows good reliability and validity. Inter-rater reliability (intra-class correlation .90 - .97), test-retest reliability (intra-class correlation .97 - .99), and internal consistency (Cronbach’s alpha .95 - .99) have coefficients of .90 or higher for the total score and the four domains. The content validity, construct validity, and criterion validity have all proven to be sufficiently adequate (Scholte et al., 2008).

The first 20 participating parents did not fill out the VS 0-6, but were interviewed with the expanded form of the Vineland Adaptive Behavior Scales (VABS; Sparrow, Balla, & Cicchetti, 1984). The research assistants received the official training for this interview. As the combination of the DISCO-10 and VABS interview appeared to be time-consuming for the parents, it was decided to replace the VABS with the VS 0-6 questionnaire. The relevant items from the VABS interview were used to complete the VS 0-6 for the first 20 participants.

Statistics

The DBC-P and VS 0-6 manuals give rules for the maximum number of missing items per individual to keep the measurement reliable. For the DBC-P no more than 10% of the items per subscale or total scale can be missed; in the VS 0-6 a maximum of three missing items or scores 'unknown' is allowed. Inspection of data revealed this limit was not exceeded for any individual on the instruments and that there were no patterns of missing data. For the DBC-P, mean values for the relevant item were computed and rounded off to 0, 1 or 2. For the VS 0-6, in accordance with the manual, missing items were replaced with a score of 1. If the data showed no serious deviations from a normal distribution, *t*-tests were used. For DBC-P item analysis we wanted to determine which behaviors were present in persons with RS. Therefore we added scores 1 and 2 since both indicate behavior exhibited by a person, as opposed to score 0 when the behavior is not present. To study differences in items between groups, chi-square tests for association were used because after the aforementioned transformation the DBC-P items were dichotomous. If the expected count in one or more of the cells was less than 5, Fisher's exact test was used for that item. For the DISCO-10 the specifically designed computer program was used to calculate the current and past classifications of CA.

RESULTS

Level of functioning

The level of adaptive functioning of the 52 participants was measured with the VS 0-6. Transformation of the raw scores with the Dutch norms yielded a mean age of adaptive functioning of 7.6 months (*SD* = 4.4 months). Only four persons (8%) had a level higher than 12 months (13, 16, 18 and 28 months). Although the course of development

for the younger participants is not totally clear yet, it can be concluded that in line with most other research all participating persons with RS have a profound to severe ID.

Autistic symptoms in Rett syndrome

The DBC-ASA shows whether further assessment of the presence of AD is indicated. The DBC-ASA score was above the cutoff for 22 persons (42%), which means they exhibited behavior which is related to AD; 30 persons (58%) had a score below the cutoff point. The algorithm yielded a higher percentage of persons with RS who did not score in the AD range compared to those who did. The items forming the DBC-ASA were selected based on their discriminative power between persons with AD and without AD and were not selected on their relationship with DSM-IV criteria for AD (only three items were added to the DBC-ASA because of the relationship with DSM-IV AD criteria). Thus, this implies that the screening algorithm describes behavior which can be categorized under the criteria of the classification systems, and as such can be regarded as 'truly autistic', and behavior which statistically turned out to predict whether a person has the autistic disorder but does not fall under the classification system criteria for AD. To acquire further insight into the presumably autistic behavior of the participants with RS, item analysis of the DBC-ASA was used. Table 2.1 shows how many females with RS obtained a score 1 or 2, which implies the behavior described is exhibited by the person, for all DBC-ASA items. This results in a percentage per item which indicates how often the item is true, listed in descending order, of 'truly autistic' behavior separated into three domains and more general or associated behavior.

The prevalence of behaviors rated on the DBC-ASA varied widely. Unfortunately no published research on DBC-ASA item analysis in persons with AD is present and as such a comparison of the symptom profile of the RS participants with other groups is not possible. Most types of 'truly autistic' behavior, as listed in Table 2.1, appeared in less than 50% of the persons. The participants showed more associated behaviors, which can be seen in both people with AD and people with ID. Some of the items had a low score because of the nature of development in RS: only six participants were able to speak some words, so the item about repeating words over and over was not likely to get a high score. This behavior, however, was present in four of the six verbal participants. Low scores on items such as lighting fires or running away should be seen in the light of the physical disabilities of the participants; most of them simply did not have enough motor skills to

Table 2.1 *Item analysis of the DBC-ASA for persons with Rett syndrome*

DBC-ASA item	**Rett syndrome (%)** (N=52)
Abnormalities in social interaction	
Aloof, in her own world	73
Doesn't respond to others' feelings	52
Avoids eye contact	50
Resists being cuddled, touched or held	27
Prefers to do things on her own	25
Abnormalities in communication	
Repeats the same word or phrase over and over	8
Restricted, repetitive and stereotyped behavior/interests/activities	
Repeated movements of hands, body, head or face	92
Stares at lights or spinning objects	52
Preoccupied with only one or two particular interests	29
Likes holding or playing with unusual object	29
Smells, tastes, or licks objects	29
Upset over small changes in routine/environment	27
Flicks, taps, twirls objects repeatedly	25
Arranges objects or routine in strict order	17
Gets obsessed with idea or activity	12
Associated behavior	
Poor attention span	87
Laughs or giggles for no obvious reason	81
Makes non-speech noises	79
Mood changes rapidly for no apparent reason	62
Screams a lot	50
Unrealistically happy	50
Poor sense of danger	42
Impatient	39
Overactive, restless, unable to sit still	27
Throws or breaks objects	19
Wanders aimlessly	14
Has temper tantrums	14
Deliberately runs away	6
Lights fires	0

Note. DBC-ASA = Developmental Behavior Checklist-Autism Screening Algorithm.

perform these actions. On the other hand, 92% of the females scored on the item 'repeated movements of hands, body, head or face', which was not unexpected as repeated hand movements are the hallmark of RS (Hagberg, 2002).

Autistic symptoms compared between younger and older persons with Rett syndrome

To study possible differences between people with RS of different ages, the sample was divided into children up to 10 years of age (n = 24) and older individuals (n = 28). Participants older than 10 years are all post-regression, so if autistic behavior decreases with age it is expected that a lower percentage of these individuals will score above the DBC-ASA cutoff. Nine (37.5%) of the girls younger than 11 years scored below the cutoff, 15 girls (62.5%) scored above. Of the persons aged 11 years or older, 21 (75%) scored below the cutoff, 7 (25%) scored above. The older participants were less likely to need screening for AD. For the total DBC-ASA, younger persons scored significantly higher (M = 18.8, SD = 9.3) compared to older persons (M = 13.7, SD = 6.4) as shown by a t-test for unequal variances, $t(40) = 2.3$, $p = .03$.

Item analysis with chi-square tests showed that differences in the percentage of items being 'true' were significant at the .01 level for only one item. The item 'smells, tastes, or licks objects' occurred more often in younger persons. Four other items were more prevalent for younger participants at the .05 level, namely preoccupied with only one or two particular interests, impatient, overactive/restless/unable to sit still, and wanders aimlessly. Older participants scored less often above the cutoff; most of them showed some autistic behavior but not the whole range of behavior.

The course of autistic behavior in people with Rett syndrome

In addition to the DBC-ASA percentage of participants who were suspected of AD, the DISCO-10 was also used. According to the DISCO interview, 30 persons (58%) currently have a classification of CA, whereas 22 persons (42%) do not have this classification. The DISCO algorithm gave an identical classification for 77% of the participants with RS as the DBC-ASA. The DISCO can be used to determine whether the CA classification changed with age in some individuals. Of the 40 participants who received a CA classification in the past, 10 (25%) no longer met criteria for the

classification for their present behavior (Table 2.2). Eight of these participants were older than 10 years, which means post-regression.

Thus, the behavior of some persons with RS (19%) changed in such a way that they first could be classified as having childhood autism, whereas currently they no longer meet criteria for this classification.

Table 2.2 *DISCO current and past classification of CA*

	DISCO 'current'		**Total**
	No CA	CA	
DISCO behavior 'ever'			
No CA	12	-[a]	12
CA	10	30	40
Total	22	30	52

Note. DISCO = Diagnostic Interview for Social and Communication Disorders; CA = Childhood Autism.
[a] DISCO behavior 'ever' includes 'current' behavior. Therefore it is not possible to get a CA classification on 'current behavior' and not on 'behavior ever'.

DISCUSSION

The current study is the first to describe autistic disorder symptoms in a sample of females with RS with a broad age range and to track changes in autistic behavior in individuals with (semi)standardized instruments. In line with our hypothesis, further assessment of the presence of AD is necessary in a substantial, but still minor, part of the sample according to the DBC-ASA. The percentage for this (42%) is in agreement with percentages found for people with profound and severe ID (Deb & Prasad, 1994), the level at which almost all persons with RS, and also in this sample, function. On the DISCO-10 interview a somewhat higher percentage of CA is found (58%).

The decrease in autistic behavior in some persons, as observed in earlier research (Gillberg, 1986; Hagberg & Witt-Engerström, 1986), is supported by the results of the DBC-ASA and the DISCO-10. According to the DBC-ASA autistic behavior is present in both younger and older participants, but the younger persons fall within the AD range more often. These girls show more symptoms, whereas most older, post-regression persons display some autistic characteristics but not enough to indicate AD. In one-quarter of the persons with RS with a CA classification in the past, based on the DISCO-10,

autistic symptoms decreased in such a way that they do not fulfill ICD-10 CA criteria anymore. Most of these participants are post-regression.

Our findings support the view of Gillberg (1992) that a diagnosis of comorbid AD in RS, if applicable, should be possible since this will be the case for some persons with RS. The need to keep individual differences between persons with RS in mind had already been stressed by Rett (1986) and turns out to be true for the presence of AD in females with RS. Thus, it is important to make a clear distinction between persons with RS and persons with RS *and* AD in the classification process. The presence of a comorbid AD will have implications for the approach and care of a person with RS, as it has in people without RS. Clinicians should be aware of the heightened possibility of AD as much as they should be in people with a severe to profound ID without RS. The diagnostic process, which is already difficult in people functioning at these low levels, can take several years in RS because of the need to follow the development of the child due to possible changes over time in RS.

However, another important issue concerning RS in the DSM-IV-TR and ICD-10 is the placement of RS under the PDD section. According to our data there are many persons with RS who are not suspected of AD because of a lack of AD symptoms. In the current project no measure of the category pervasive developmental disorder not otherwise specified (PDD-NOS) or atypical autism was used. This classification is, however, not strongly validated in people with severe and profound ID. The boundaries of the PDD-NOS or atypical autism classification, which are already unclear in the general population, become even more unstable at the lowest levels of functioning (Mahoney et al., 1998; Njardvik, Matson, & Cherry, 1999; Towbin, 2005). Keeping these considerations in mind, we hold the view that our data might be supportive of the opinion of Gillberg and Billstedt (2000) and Wing (2005) that it is inappropriate to classify RS under the section for PDD. AD/CA in RS does not seem to be present more often (DBC-ASA), or is present only slightly more often (DISCO-10), than in people without the syndrome but with the same level of functioning (Deb & Prasad, 1994). In addition, other genetically identified syndromes associated with autism (e.g. Zafeiriou, Ververi, & Vargiami, 2007) are also not included in this section. Therefore, a reconsideration of the placement of RS under the PDD section might be needed.

A limitation in the current study is the lack of observational data in addition to the use of a questionnaire and semi-structured interview to establish a diagnosis of AD/CA. It

would be an important step in RS research to use clinical diagnoses of AD in future studies with large samples. Furthermore, the decrease in AD symptoms in a substantial proportion of the participants is measured in retrospect by the DISCO-10 interview. This will have a negative effect on the reliability of the information. The best direction in research seems to be to follow the persons with RS from the moment the syndrome is identified to get more objective measures of behavior over the lifespan.

The autism screening instruments obtained a 77% agreement on AD/CA classification for our sample, which may be seen as a satisfactory amount in the population of people with a severe to profound ID. However, it would be interesting to compare these often used instruments in depth to gain more insight into the usefulness of these instruments and their similarities and differences in people with ID. For this particular purpose a much larger sample, not restricted only to RS, should be used.

The use of standardized instruments is a strength but at the same time can be a limitation. The DBC-ASA was developed for a diverse population, namely people with different levels of ID. It is likely that very few people with RS were included in the standardization sample, given the relatively low incidence of the syndrome. Unique behavior in RS will therefore probably not be accounted for in the instrument. On the other hand, some DBC-ASA items are almost always present in the RS group, such as repeated hand movements. A few other types of behavior presumably cannot be performed by most persons with RS because of their limited physical abilities, like running away. The question arises of whether cutoff scores developed for the general ID population should be the same for such a specific population. To answer this requires an extensive study. To date, using standardized instruments with well-known psychometric properties seems the best option we have to obtain objective and reliable information. The Rett Syndrome Behavior Questionnaire is a useful instrument for obtaining specific RS information (Mount, Charman, Hastings, Reilly, & Cass, 2002), but seemed less suitable for our focus on autism in RS.

A last limitation is the composition of the sample. By gathering data via the Dutch Rett Parent Support Group, and it is possible the parents concerned had certain characteristics, such as relatively high socio-economic status, which could influence the results. In addition, not all members of the parent support group participated in our study. Apart from that, obtaining a well-balanced sample with respect to age also turned out to be difficult. These limitations may have put constraints on the generalization of our results.

An interesting next step in research would be the worldwide linking of the genetic information to the behavioral phenotype. Several projects have already shown the influence of the type of *MECP2* mutations for the phenotype including some behavioral aspects (Percy, 2008). A much larger sample than ours is needed to search for the possible link between the type of gene mutation and autistic behavior. This may be done in an international database with much used standardized and translated behavioral instruments such as the DBC, VABS and Rett Syndrome Behavior Questionnaire. In this way our knowledge on the link between behavior and genetics in Rett syndrome could be expanded, with new possibilities for diagnostics and treatment.

3 Parenting stress in mothers with a child with Rett syndrome

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ABSTRACT

Parenting stress can have severe negative consequences. This study investigates maternal parenting stress in families with a child with Rett syndrome (RS) and the relationship with child characteristics. Twenty-four mothers of a child (2-17 years) with RS participated. Four questionnaires were used: the Nijmegen Parenting Stress Index-Short, Vineland Screener 0-6, Developmental Behaviour Checklist, and Rett Syndrome Behaviour Questionnaire. Parenting stress was high in 46% of the mothers. Maternal parenting stress was not related to the child's age, adaptive functioning, and presence/absence of the autistic disorder. General behavioural problems correlated positively with parenting stress. Of RS specific behaviours, only general mood problems correlated positively with parenting stress. Having a child with RS is a risk factor for high maternal parenting stress. Especially when children show behavioural problems, support is needed. Future studies should focus on processes that lead to different outcomes in these families, as not all mothers perceive much stress.

INTRODUCTION

Rett syndrome (RS) is a neurodevelopmental disorder whereby *MECP2* gene mutations exist in most persons with the syndrome (Percy, 2008). RS is almost exclusively present in females. A classical variant and certain atypical ones are distinguished. One of the hallmarks of the syndrome is a seemingly normal early development, followed by the loss of acquired developmental skills usually at the age of one to two years. After this regression period, some improvement in later years does occur (Hagberg, 2002). Most females with RS function on the severe to profound level of intellectual disability (Demeter, 2000).

The characteristics of the syndrome make the occurrence of stress in family life imaginable. High levels of parenting stress are an important target for intervention; such distress can lead to withdrawn parenting and distressed parents are less likely to promote the child's development optimally (Deater-Deckard, 2004). It can have negative consequences for parents as well, such as poorer physical health (Oelofsen & Richardson, 2006) and depression (Singer, 2006). In some parents with a child with RS high stress levels were found, although most parents reported stress in the normal range. No relation

between parenting stress and the child's age, adaptive level or cognitive functioning was found (Perry, Sarlo-McGarvey, & Factor, 1992). In contrast, psychosocial stress in mothers was higher when more RS specific behaviour was present, in particular general RS mood problems, behaviours indicative of fear/anxiety, RS specific night-time problems, and total amount of typical RS behaviour (Sarimski, 2003).

The aim of the present study is to expand the knowledge on parenting stress in mothers with a child with RS and to investigate which child characteristics are related to maternal parenting stress. This knowledge may contribute to more specific support for these families. As far as we know, this is the first study to relate maternal parenting stress to general behavioural problems of children with RS. The relation between maternal parenting stress and a co-morbid autistic disorder in RS will also be explored. The combination of a child with ID and autism is more distressing than having a child with ID only (Blacher & McIntyre, 2006). However, it is unclear whether this also applies to mothers with a child with RS.

METHOD

Participants

Participants were 24 families with a daughter with RS. They were part of a larger study on RS. In this paper only children between the age of 2 to 18 years were included for whom the mother filled out the questionnaire on parenting stress to obtain a relatively homogeneous group. They make up 46% of the larger sample, see Wulffaert, Van Berckelaer-Onnes, and Scholte (2009) for more details on the procedure and participants. Mean age was 9.2 years (*SD* = 4.74; range 2.4 – 17.2). The classical variant was present in 18 females of whom 16 had a *MECP2* mutation, 1 did not have a *MECP2* mutation and in 1 female no genetic testing was carried out. In five participants the atypical RS variant was present, all had a *MECP2* mutation. For one female the RS variant was unknown, but a *MECP2* mutation was confirmed.

Research Instruments

The *Nijmegen Parenting Stress Index-Short* (NPSI-S; De Brock, Vermulst, Gerris, & Abidin, 1992) is an official translation and adaptation of the Parenting Stress Index by Abidin (1983, as cited in De Brock et al., 1992). It measures parenting stress in families

with children from approximately 2 to 13 years. Since the level of functioning of the RS females not exceeded this level, the instrument was considered appropriate for the purpose. A total score is computed and classified into seven norm categories, for mothers and fathers separately, defining parenting stress level. Dutch non-clinical and clinical norms are available; the non-clinical norm group, based on families of the normal population, was used. Psychometric properties are reasonable to good (De Brock et al., 1992).

The *Vineland Screener 0-6 years* (VS 0-6; Scholte, Van Duijn, Dijxhoorn, Noens, & Van Berckelaer-Onnes, 2008) is a Dutch screening instrument adapted from the Vineland Screener by Sparrow, Carter, and Cicchetti (1993). The VS 0-6 measures the level of adaptive functioning of children up to the age of six or older people with comparable levels of functioning. An adaptive behaviour composite score is based on the domains communication, daily living skills, socialisation, and motor skills. The instrument has good reliability and validity (Scholte et al., 2008).

The Dutch version (Koot & Dekker, 2001) of the *Developmental Behaviour Checklist-Primary Carer* (DBC-P; Einfeld & Tonge, 2002) assesses emotional and behavioural problems in children with intellectual disabilities. A total behaviour problem score is computed together with five subscale scores (disruptive/antisocial behaviour, self-absorbed behaviour, communication disturbance, anxiety, social relating problems). Psychometric properties are satisfactory to good (Koot & Dekker, 2001). The DBC-P has an additional autism screening algorithm which reliably screens for the autistic disorder (Einfeld & Tonge, 2002).

The *Rett Syndrome Behaviour Questionnaire* (RSBQ; Mount, Charman, Hastings, Reilly, & Cass, 2002) describes behavioural and emotional features typical for RS. A Dutch translation was developed for this study. A total score is computed together with eight subscale scores (general mood, breathing problems, hand behaviours, repetitive face movements, body rocking and expressionless face, night time behaviours, fear/anxiety, walking/standing). Is has good psychometric properties (Mount et al., 2002).

All questionnaires have been processed conform the instructions of the official manuals and for the RSBQ conform the related article by Mount et al. (2002).

Data-analysis

The relationships between maternal parenting stress and child characteristics were determined by correlational analyses in SPSS 16.0. For the child characteristic 'presence of the autistic disorder' a comparative analysis of means was used. An alpha of .05 was chosen for all analyses. In case of non-normality following the Saphiro-Wilks test, non-parametric variants for *t*-tests and Pearson correlations were carried out, i.e. Mann-Whitney tests and Spearman correlations. Univariate outliers were given the next highest score plus or minus one, depending whether the outlier was at the higher or lower end. Effect sizes of $r = .10$ were seen as small, $r = .30$ as medium, and $r = .50$ as large (Field, 2009).

RESULTS

In Table 3.1 the perceived parenting stress in the participating mothers is compared to the non-clinical norm group. Overall, parenting stress was high in mothers with a child with RS. Although some mothers perceived stress levels categorised as very low to below the mean (5; 20%), nearly half of them (11; 46%) experienced high to very high stress.

Table 3.1 *Parenting stress in mothers with a child with Rett syndrome (n = 24)*

Maternal parenting stress NPSI-S norm category non-clinical norm group		**Mothers of a child with Rett syndrome % (*n*)**
Category	Percentiles in norm population	
Very low	0% - ≤ 5% (5%)[a]	4% (1)
Low	5% - ≤ 15% (10%)	4% (1)
Below the mean	15% - ≤ 35% (20%)	12% (3)
Mean	35% - ≤ 65% (30%)	17% (4)
Above the mean	65% - ≤ 85% (20%)	17% (4)
High	85% - ≤ 95% (10%)	**17% (4)**
Very high	95% - ≤ 100% (5%)	**29% (7)**

Note. NPSI-S = Nijmegen Parenting Stress Index-Short.
[a] Percentage of total population between brackets

The adaptive level of functioning was very homogeneous as expected, ranging from 3 to 14 months ($M = 7.9$ months, $SD = 3.19$). For both the DBC-P and RSBQ the number of items per subscale differ; to make mean scale scores comparable within the

instruments, scores were standardised with a possible range between 0 to 2 (see Table 3.2). DBC-P subscales self-absorbed behaviour and the autism screening algorithm received the highest mean scores. The least problems were mentioned on the disruptive/antisocial and communication disturbance subscales. On the RSBQ by far the highest score was measured on the hand behaviours scale, the lowest score on the night-time behaviour scale. According to the DBC-ASA 11 children did not need further screening for the autistic disorder, whereas in 13 children the autistic disorder was suspected to be present and further individual assessment was needed.

Table 3.2 *Standardised mean scores and correlations between raw maternal parenting stress scores and behavioural problems measured with the DBC-P and RSBQ (n = 24)*

	M	***SD***	***r***	***p***
DBC-P				
Self-absorbed	.63	.26	.59	<.01**
Autism screening algorithm	.61	.33	.53	<.01**
Social relating	.51	.31	.42	.04*
Total Problem Behaviour Score	.40	.21	.62	<.01**
Anxiety	.38	.35	.49	.02[a]*
Communication disturbance	.23	.23	.39	.06[a]
Disruptive/antisocial	.21	.20	.49	.02[a]*
RSBQ				
Hand behaviours	1 .51	.37	-.09	.67[a]
Fear/anxiety	.97	.46	.18	.39
RSBQ total	.90	.33	.19	.37
General mood	.87	.49	.48	.02*
Breathing problems	.83	.66	.04	.87[a]
Body rocking and expressionless	.82	.39	-.02	.91
Repetitive face movements	.75	.58	.04	.86[a]
Walking/standing	.63	.59	.09	.70[a]
Night-time behaviours	.47	.40	.14	.51[a]

Note. DBC-P = Developmental Behaviour Checklist; RSBQ = Rett Syndrome Behaviour Questionnaire.
[a] = Spearman correlation.
* $p < .05$, ** $p < .01$

Maternal parenting stress was not significantly nor substantially related to the child's age (r_s = -.19, p = .37), neither was there a significant relation between stress and

adaptive functioning (r = .18, p = .39). All DBC-P (sub)scales, except communication disturbances, related significantly with maternal parenting stress. These were positive correlations and ranged from medium (r^2 = .38) to small effects (r^2 = .18) (see Table 3.2). On the RSBQ only the general mood subscale related significantly and positive to maternal parenting stress with a small effect size (r^2 = .23). Maternal parenting stress was not related to the presence of autistic disorder according to the t-test for unequal variances (t (16) = -1.41, p = .18).

DISCUSSION

Raising a child with RS places mothers at risk for high levels of parenting stress; nearly half of them reported high to very high levels. However, there are also mothers who do not perceive heightened stress levels. The child's age and level of adaptive functioning does not influence the level of maternal parenting stress. These results are in line with the study by Perry et al. (1992). In the current study there appeared strong positive relationships with several specific behavioural problems, with medium sized effects for the total problem behaviour score, self-absorbed behaviour, and autism screening algorithm. Behaviours specific for RS were not related to parenting stress, except a positive relation with more general mood problems. Finally, although a significant correlation was found between maternal parenting stress and the autism screening algorithm, there was no difference for parents with a child scoring above versus below the cut off for autistic disorder. Thus, maternal parenting stress is comparable in children who presumably have a co-morbid autistic disorder versus those who do not.

The absent relationship between stress and adaptive abilities may be caused by the lack of variation in the children's level of functioning; in our sample nearly all had abilities below the developmental age of one year. In studies into other genetic syndromes, behavioural problems in general appeared the strongest predictor for parenting stress (Hodapp, 1999). The current study suggests that this pattern also exists in families with a child with RS. Overall RS specific behaviours were not related to maternal parenting stress. We hypothesize that these characteristic behaviours are nowadays so well known to belong to the syndrome, also for parents, that they might no longer induce much stress. Finally, although maternal parenting stress was related to behaviours indicative of the autistic disorder, there was no difference in stress between mothers with a child without

the autistic disorder and those who needed further individual assessment for it. Thus, for maternal parenting stress the *amount* of autistic behavioural problems seems more distressing. See Wulffaert, Van Berckelaer-Onnes, and Scholte (2009) for a further discussion of the controversial issue of a co-morbid autistic disorder in RS.

The relationship between RS specific behaviour and parental perceptions and well-being remains unclear. In the current study an association was found between RS general mood problems and maternal parenting stress. Other studies reported relationships between specific RS behaviour and more broadly defined psychological stress, and physical and mental health (Laurvick, Msall, et al., 2006; Sarimski, 2003). However, the results differed on which *specific* RS behaviours were relevant for parental perceptions. Future studies are needed to fully understand the impact these RS behaviours have on parents.

One of the limitations of our study is the small sample size which results in problems with statistical power. Also, the current study has a cross-sectional design. For persons with intellectual disabilities, results are mixed whether the child's behavioural problems cause parenting stress or whether there is a bi-directional effect (Hassall & Rose, 2005; Hastings & Beck, 2004; Olsson, 2008). Long-term follow-up studies are thus needed to investigate this pathway in RS. Furthermore, parental and environmental characteristics such as (in)formal support and parental coping strategies are characteristics influencing the outcomes of the stress process (Hassall & Rose, 2005; Perry, 2004). These factors should be incorporated in future studies to give a more coherent description of the families with RS. Finally, we follow Olsson's (2008) view that in future studies it is important to focus on the *processes* that lead to different outcomes in these families. Why do some families with a child with RS adapt well to their specific situation and others do not? There is still a lot to discover on causality and influencing risk and protective factors in research in families with RS.

The finding that parenting stress is high in nearly half of the mothers should raise awareness on the need for support for these families. When the child shows behavioural problems, parents should get additional support to manage them with reduced parenting stress as a consequence (Hastings & Beck, 2004). Laurvick, Msall, et al. (2006) found that in RS lower parental stress levels are associated with better mental health of mothers. Support for the child will thus benefit the health of parents as well. As there is no relation between stress and the child's age, support should be a continuous process and not only

limited to the early years, which can be so devastating in these families. Finally, we want to incorporate the advice by Sarimski (2003) and Laurvick, Msall, et al. (2006) that support in these families should also focus on the challenges caused by physical disabilities in RS (e.g. the feeding and dressing process) and underline the positive impact on the family system when mothers have time for own activities beside caretaking, such as having work outside the house or free time. The challenges these families face are many and deserve professional and specified support.

4 Parenting stress in CHARGE syndrome and the relationship with child characteristics

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ABSTRACT

This study investigates the parental perception of stress related to the upbringing of children with CHARGE syndrome and its association with behavioral and physical child characteristics. Parents of 22 children completed the Nijmegen Parenting Stress Index-Short, Developmental Behavior Checklist, and Dutch Vineland Screener 0-12 and reported their child's problems with hearing, vision and ability to speak. Parenting stress was high in 59% of the subjects. Behavioral problems on the depression, autism, self-absorbed and disruptive behavior scales correlated positively with parenting stress. A non-significant trend was found, namely higher stress among the parents of non-speaking children. No associations were found with other child characteristics, i.e. level of adaptive functioning and intellectual disability, auditory and visual problems, deafblindness, gender, and age. Raising a child with CHARGE syndrome is stressful; professional support is therefore essential for this population. More research into other possible influencing characteristics is needed to improve family-oriented interventions. Since CHARGE is a rare syndrome, closer international collaboration is needed, not only to expand the group of study subjects to increase statistical power, but also to harmonize research designs and measurement methods to improve the validity, the reliability, and the generalization of the findings.

INTRODUCTION

CHARGE syndrome is a genetic disorder in which multiple anomalies are present from birth. The acronym is derived from the combination of the following problems: **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). At present, the criteria of Blake et al. (1998) and Verloes (2005) are usually used to diagnose the syndrome. These sets differ in some aspects, but both make use of rules about the number of 'major' and 'minor' signs needed for a CHARGE diagnosis. In addition to the clinical criteria, presence of a *CHD7* gene mutation on chromosome 8 is another way to establish the diagnosis (Vissers et al., 2004). According to a recent review, physical problems in many persons, besides those mentioned in the acronym, include vestibular problems, gastro-

oesophageal reflux, facial paralysis, and feeding and swallowing problems (Sanlaville & Verloes, 2007). For those suffering from the syndrome, impairments affect all senses and as a result have a severe impact on development (Brown, 2005). Incidence has been estimated to range between 1:8,500 to 1:12,500 live births (Sanlaville & Verloes, 2007).

Persons with CHARGE syndrome vary widely in the combination of physical problems present as well as their level of functioning and behavioral characteristics (Blake, Salem-Hartshorne, Abi Daoud, & Gradstein, 2005; Vervloed, Hoevenaars-Van den Boom, Knoors, Van Ravenswaaij, & Admiraal, 2006). The level of functioning ranges from profound intellectual disability (ID) to normal intelligence, but a substantial proportion seem to function in the lower range (Johansson et al., 2006; Salem-Hartshorne & Jacob, 2005; Smith, Nichols, Issekutz, & Blake, 2005). Behavioral problems are often mentioned but the behavioral phenotype has not yet been completely defined. Self-injurious behavior, sleep problems, hyperactivity, irritability, attention problems, tactile defensiveness, adherence to routines, and stereotypical behaviors have been described (Blake et al., 2005; Graham, Rosner, Dykens, & Visootsak, 2005; Johansson et al., 2006). Results regarding the occurrence of aggression are contradictory (Blake et al., 2005; Graham et al., 2005; Johansson et al., 2006). The behavioral problems seem to be more manifest in older persons (Hartshorne & Cypher, 2004; Vervloed et al., 2006). Some studies, however, report low rates of behavioral problems (Graham et al., 2005; Smith et al., 2005).

Virtually all research has focused only on the child with CHARGE syndrome. Although this is inherent to the issue at stake, children develop in interaction with the environment and as such the parents play a vital role for these vulnerable children. Therefore, the way parents experience the childrearing situation needs to be considered. This may ultimately lead to better support for the family system. One way to describe the perception of parents is to measure level of parenting stress. Perry (2004) designed a model to depict the factors that influence the development of stress in families with a child with a developmental disability. It consists of four components, each divided into two domains. The first component in the stress process is the *stressor*, which can be divided into (1) child characteristics versus (2) other life stressors (e.g. divorce). Secondly, the *resources* of the family are divided into (1) family system resources (e.g. socio-economic status), and (2) personal resources of the parent (e.g. coping style). Thirdly, the *support* a family receives can be from (1) a professional service or (2) an informal system. The

resources and support systems act upon the influence of the stressor on parenting stress. The fourth component is the *outcome* for a parent, either (1) positive or (2) negative. Thus, parents can perceive stress due to their family situation of a child with a developmental disability but can also experience a positive outcome, such as personal growth.

Raising a child with a genetic syndrome is a highly specific child-rearing situation. Research on parenting stress in families with a child with a genetic syndrome has shown that the influence of child characteristics on stress is syndrome-specific (e.g. Fidler, Hodapp, & Dykens, 2000) and that children with different genetic syndromes elicit different reactions from their environment (Dykens, Hodapp, & Finucane, 2000; Hodapp, 1999). Although Hodapp (1999) concludes that for different genetic syndromes behavioral problems are the best predictor of parenting stress, relationships with chronological age have been found for some syndromes as well (Fidler et al., 2000). The only published study of parenting stress in CHARGE syndrome shows that 48% of parents with a child up to 50 months perceive significantly high levels of stress. Parents of children with the syndrome who are also blind report more stress. Neither deafness, nor the number of medical problems has, however, been found to be related to stress. Furthermore high stress levels are related to problems in attachment and parental bonding (Reda & Hartshorne, 2008). So far perceptions of parenting stress are only known for parents with very young children with CHARGE syndrome and the relationship of stress with the behavioral phenotype is as yet unknown. This limited knowledge led to the current project.

The first aim was to test the hypothesis put forward by Reda and Hartshorne (2008) that the upbringing of a child with CHARGE syndrome is related to elevated perceived stress levels. This study tested the hypothesis in subjects with a broader age range. The second aim was to test the hypothesis that child characteristics, both behavioral and physical, are related to parenting stress. We tested the specific influence of CHARGE syndrome on the factors: level of adaptive functioning, level of intellectual disability, behavioral problems, ability to speak, auditory and visual problems, deafblindness, gender, and chronological age. In line with research on CHARGE syndrome and several other genetic syndromes (Fidler et al., 2000; Hodapp, 1999; Reda & Hartshorne, 2008) higher levels of parenting stress were expected to be significantly related to (1) behavioral problems, (2) visual problems, and (3) chronological age. For the other researched factors, this study explored the presence of syndrome-specific relationships with the perceived parenting stress.

Testing these hypotheses is important, since it gives insight into the experience of parents rearing a child with the specific characteristics of CHARGE syndrome. High levels of parenting stress can have severe implications, such as harsh or withdrawn parenting with consequences for child development (Deater-Deckard, 2004). Therefore, professionals will need to inform parents about the impact of this syndrome on the entire family system and provide appropriate support in the relevant domains to improve the well-being of the whole family. We have chosen to focus on one specific component of Perry's model (2004) as a possible stressor, namely child characteristics in CHARGE syndrome.

METHOD

Participants

Twenty-two children with CHARGE syndrome (16 boys and 6 girls) and their parents participated. The age of the children[1] ranged from 1.7 to 22.2 years (M = 11.0, SD = 5.54). Of the 22 children, 21 had a *CHD7* gene mutation. One child met the criteria of both Blake et al. (1998) and Verloes (2005) for CHARGE syndrome, but genetic screening has not been carried out (yet).

Procedure

All 55 members of the Dutch CHARGE Parent Support Group were requested through a letter to participate in the current study, and 15 parents agreed to the request. Through collaboration with a Dutch CHARGE-specific outpatient clinic, parents of 11 additional children agreed to participate. Sadly, one child died shortly after his parents had filled out the questionnaires, but they still consented to the use of the data.

Informed consent was obtained for participation in the project. All participants gave written permission for file analysis at the school or day care centre. Parents received the questionnaires by post and were asked to return them through an included pre-paid envelope. Confirmation of the CHARGE diagnosis was either obtained through file analysis or by contacting the medical specialist involved. One child had to be excluded because the CHARGE diagnosis was not clearly supported by the file analysis and the

[1] Besides younger children and adolescents, adults with CHARGE syndrome were included in the project as well. However, as they remain *children of* their parents the term children will be used throughout this article to describe the participants with CHARGE syndrome.

mother did not give permission to contact their medical specialist. In two cases medical specialists were not definite about the presence of CHARGE syndrome; in both cases other genetic syndromes were suspected also. For one child, no *CHD7* gene mutation was found and the criteria of Blake et al. (1998) and Verloes (2005) were not met; this case was excluded from the data-set. Ultimately, data for 22 children were used in the analysis.

Research instruments

Measurement of parenting stress

The *Nijmegen Parenting Stress Index-Short* (NPSI-S: De Brock, Vermulst, Gerris, & Abidin, 1992) is an officially translated and adapted version of the Parenting Stress Index by Abidin (1983 as cited in De Brock et al., 1992). It measures parenting stress in families with children from approximately 2 to 13 years. Since level of adaptive functioning of the children did not exceed this level, this instrument was considered appropriate for the purpose. Twenty-five items are scored on a six-point scale. Dutch non-clinical and clinical norms are available for mothers and fathers separately. In this study the non-clinical norm group was used. Internal consistency measured with Cronbach's alpha in the non-clinical and clinical population groups is higher than .91. The NPSI-S shows good criterion validity with accurate prediction of membership of the clinical and non-clinical population. Construct validity is only investigated for the extended version of the instrument: concurrent validity ranges from 'satisfactory' to 'good' and discriminant validity is considered reasonable (De Brock et al., 1992).

Measurement of child characteristics

The *Vineland Screener 0-12 years* (VS 0-12: Van Duijn, Dijkxhoorn, Noens, Scholte, & Van Berckelaer-Onnes, 2009) is a Dutch screening instrument adapted from the Vineland Screener by Sparrow, Carter, and Cicchetti (1993). The VS 0-12 measures the level of adaptive functioning of children up to the age of 12 or older people with comparable levels of functioning. An adaptive behavior composite score (90 items) is based on the domains communication, daily living skills, socialization, and motor skills. Parents indicate on a three-point scale whether the child exhibits the particular behavior in everyday life. Good reliability and validity have been established in a normal population. Inter-rater reliability has intra-class correlations for the four domains and adaptive behavior composite between .92 - .98, intra-class correlations for test-retest reliability

range from .90 - .96, and Cronbach's alphas range from .96 - .99 (Van Duijn, Dijkxhoorn, Noens, et al., 2009). The VS 0-12 years is an expansion of the VS 0-6 years which has proven to have adequate content, construct, and criterion validity (Scholte, Van Duijn, Dijkxhoorn, Noens, & Van Berckelaer-Onnes, 2008). A regression formula was developed based upon normal population data to estimate the adaptive level of functioning (Van Duijn, Dijkxhoorn, Van Berckelaer-Onnes, Scholte, & Noens, 2010).

The Dutch version (Koot & Dekker, 2001) of the *Developmental Behavior Checklist-Primary Carer* (DBC-P: Einfeld & Tonge, 2002) assesses emotional and behavioral problems in people with an intellectual disability. Parents rate 95 items on a three-point scale about behavior in the past six months. A total behavior problem score is computed together with five subscale scores (disruptive/antisocial behavior, self-absorbed behavior, communication disturbance, anxiety, social relating problems). Intra-class correlations for inter-rater reliability range from .52 to .67 for the total score and the different subscales. Internal consistency (Cronbach's alphas .66 to .95) and test-retest reliability (intra-class correlations between .76 and .89) are high. Construct and criterion validity are satisfactory (Koot & Dekker, 2001). Besides the five subscales the DBC-P has an additional autism screening algorithm which reliably screens for the autistic disorder. Internal consistency is .94 (Einfeld & Tonge, 2002). Two other scales with face validity concerning psychiatric conditions are the depression scale and hyperactivity scale. For the depression scale inter-rater reliability and concurrent validity for the depressive disorder have been proven (Tonge & Einfeld, 2003). The hyperactivity scale has good construct validity and Cronbach's alpha is .88 (Einfeld & Tonge, 2002).

Information on the expressive communication abilities of the child was gathered through various means. A dichotomous score was coded for speaking/non-speaking. If, according to the parents, the child named or gestured towards some people or things when asked, the child was categorized as 'speaking'. Parents indicated whether their child had problems with hearing (unable to hear or hears very little) and vision (unable to see or sees very little) on the DBC-P. Children were categorized as being deafblind if parents indicated problems with both hearing and seeing. All questionnaires have been processed conform the instructions of the official manuals.

Data analysis

Based on the VS 0-12 data, the level of adaptive functioning can be calculated using a regression formula that was derived from normal population data. In this study we estimated the level of intellectual disability on the basis of the level of adaptive functioning on the VS 0-12. For children up to 9 years of age, we computed a developmental quotient (DQ) [VS 0-12 score / chronological age * 100] and classified the level of intellectual disability based upon Došen (2005), see Table 4.1. Children 10 years and older can no longer obtain a DQ of 100 with the current regression formula. Therefore, we made a classification based upon the developmental level of the older children, see Table 4.1. SPSS 14.0 was used for the analyses. Assumptions for Pearson correlations and *t*-tests were met and an alpha of .05 was chosen for all analyses.

Table 4.1 *Classification of intellectual disability based on Došen (2005)*

Level of intellectual disability	Developmental quotient	Developmental age
Profound	0 - 20	< 2 years
Severe	20 - 35	2 - 4 years
Moderate	35 - 50	4 - 7 years
Mild	50 - 70	7 - 12 years
None	> 70	> 12 years

RESULTS

Parenting stress

The NPSI-S was filled out for 22 children. This was done by 17 mothers and 1 father. In the remaining four cases, two couples filled it out together and for the other two questionnaires the gender of the respondent was unknown. In these last four cases the norm group for mothers was used. On the NPSI-S the mean raw score was 77.1 (*SD* = 30.58), ranging from 25 to 132 (maximum possible score 150).

A large number of parents perceived high levels of stress related to the upbringing of their child. Only 9% scored ‘very low’ compared to the norm, 4% had stress levels below the mean and 14% scored around the mean of the norm group. Another 14% received a score above the mean. Nearly one-third (27%) experienced high levels of stress and

another third (32%) scored within the highest possible category. Compared to the non-clinical norm group, where 10% and 5%, respectively, fell in the high and very high category, this is a very large proportion of the parents.

Child characteristics

The VS 0-12 was filled out reliably for 20 children. The raw total scores ranged from 18 to 163 (maximum possible score 180). The adaptive level of functioning ranged from 0.2 years to 8.6 years (M = 4.5, SD = 3.24). To estimate level of intellectual disability, VS 0-12 scores were transformed as explained in the data analysis section. A wide range of functioning was found. Seven children had a profound ID (32%), one had a severe ID (4%), three had a moderate ID (14%) and four had a mild ID (18%). Five children had no ID (23%). For two children categorizing was not possible (9%), because there were too many missing values on the VS 0-12.

The total problem score on the DBC-P ranged from 3 to 78 (maximum possible score 190). A score above the cut-off point of 46 indicates a substantial number of behavioral problems (Einfeld & Tonge, 2002); this was the case for six children (27%).

In Table 4.2, the findings with regard to the DBC-P subscales are presented. Since the number of items differs between subscales, mean subscale scores were computed to make the scale scores comparable. These scores can range from 0 to 2 and were highest for the hyperactivity subscale followed by the autism screening algorithm (see Table 4.2).

Table 4.2 *Mean subscale scores Developmental Behavior Checklist–Primary Carer (N = 22)*

DBC-P subscale	**Mean subscale score**	**Standard deviation**
Hyperactivity	0.82	0.47
Autism screening algorithm	0.56	0.40
Self-absorbed behavior	0.47	0.36
Disruptive/antisocial behavior	0.46	0.27
Social relating problems	0.41	0.41
Depression	0.39	0.25
Anxiety	0.31	0.26
Communication disturbance	0.30	0.23

Furthermore a considerable variation in the behavior of the participants was found. Only 13% of the items were applicable to more than half of the children (i.e. a score of 1 or 2). Behaviors prevalent in 51% to 60% of the children were: aloof, in his/her own world; makes non-speech noises; overly attention-seeking; sleeps too little, disrupted sleep; stubborn, disobedient or uncooperative; underreacts to pain. Five items were prevalent in 61% to 70% of the children: becomes over-excited; poor attention span; has temper tantrums; irritable; noisy or boisterous. The most prevalent behavior was impatience. This was identified in 86% of the children.

Nearly two-thirds of the children (14; 64%) had means of expressing themselves, and thus could be categorized as speaking children, whereas 8 (36%) were non-speaking. Problems with hearing were prevalent among the majority of the children (17; 77%). A smaller group of children (7; 32%) had problems with seeing. All seven children with visual difficulties also had hearing problems and were placed in the deafblind category (32%). A total of five children had no problems with either hearing or seeing.

Parenting stress in relation to child characteristics

Parenting stress was not significantly associated with the level of adaptive functioning of the child with CHARGE syndrome (r = -.20, p = .41). To relate level of parenting stress to the level of ID, a dichotomy was made based upon the VS 0-12 results. Children with a profound, severe or moderate ID were grouped together (11 lower functioning children; 55%), as were children with a mild or no ID (9 higher functioning children; 45%). The mean raw NPSI-S score for the lower functioning children was 78.2 (SD = 31.84) and for the higher functioning children 75.0 (SD = 34.02). No significant difference between the mean levels of parenting stress was found, $t(18)$ = -.22, p = .83.

Parenting stress appeared to be related to certain behavioral problems. All (sub)scales except that of communication disturbances correlated positively with parenting stress. There were significant correlations with four subscales (see Table 4.3). Higher levels of behavioral problems on the subscales depression (R^2 = .32), disruptive/antisocial behavior (R^2 = .19), self-absorbed behavior (R^2 = .19), and the autism screening algorithm (R^2 = .19) were related to higher levels of parenting stress. The correlation between parenting stress and the total problem behavior score was not significant, but a p-value of .05 can be interpreted as a trend (R^2 = .18). The association between parenting stress and

the depression subscale had a large effect size. The associations with the other three significant subscales had medium-sized effects (Cohen, 1992).

Table 4.3 *Correlation between raw score Nijmegen Parenting Stress Index-Short and Developmental Behavior Checklist–Primary Carer (N = 22)*

DBC-P (sub)scale	**Correlation raw NPSI-S score**	***p* value**
Depression	.57	.01
Disruptive/antisocial behavior	.44	.04
Self-absorbed behavior	.44	.04
Autism screening algorithm	.44	.04
Total behavior problem score	.42	.05
Social relating problems	.25	.26
Anxiety	.20	.37
Hyperactivity	.15	.51
Communication disturbance	- .13	.55

The stress levels of parents with non-speaking children (M = 93.4, SD = 19.18) were higher than for those with speaking children (M = 67.9, SD = 32.52). Although this difference was not significant at an alpha level of .05, it can be considered a trend in the data ($t(20) = 2.02$, $p = .06$). Parents of hearing children (M = 80.2, SD = 24.51) and those with children who had hearing problems (M = 76.2, SD = 32.77) did not differ in their stress levels, $t(20) = .25$, $p = .81$. Neither was there a difference between parents with children who had good vision (M = 76.5, SD = 27.80) and those with children who had problems with seeing (M = 78.4, SD = 38.31), $t(20) = -.13$, $p = .90$. The children who had visual problems, were all considered deafblind, so this factor was not researched further. The gender of the child had no influence on the NPSI-S scores. Parents of boys (M = 75.8, SD = 28.15) experienced similar amounts of stress as parents of girls (M = 80.7, SD = 39.12), $t(20) = -.32$, $p = .75$. The NPSI-S score was also not related to the chronological age of the child ($r = .20$, $p = .36$).

DISCUSSION

In line with the first hypothesis it turned out that the upbringing of a child with CHARGE syndrome is related with the experience of high stress levels in two-thirds of the parents. The percentage found was even higher than that reported by Reda and Hartshorne (2008), who investigated only parents of younger children. However, the second hypothesis was only partly corroborated. Specific behavioral problems were related to higher stress levels (i.e. behavior indicative of depression and autistic disorder, disruptive behavior, and self-absorbed behavior, with a trend for the total behavior problem score). The hypothesis that there is an association between parenting stress and chronological age was based upon research into other genetic syndromes (Fidler et al., 2000) and was not confirmed in this study of CHARGE syndrome. Although it lies beyond the reach of this article and study, because of restrictions in analysis-methods with this small number of participants, we assume that the stress parents experience during the lifespan of their child is related to various factors at different ages. Our presumption, based on clinical experience, is that in young children the medical problems with associated surgeries and hospital stays cause a lot of stress for the parents, whereas later in life parents experience more stress because of behavioral problems or worries concerning the development of the child. Although not tested in this article as we looked only into single relationships because of sample size, in our view this would be an important supplementary consideration for future research. The hypothesis that higher stress levels occur in parents with a visually impaired child was also not corroborated although this hypothesis was based upon CHARGE-specific research (Reda & Hartshorne, 2008). A possible explanation for this contradictory result could be the difference in defining the visual disability. In the current project this was described as any problem with seeing, whereas Reda and Hartshorne identified a visual disability when no better than moderate visual impairment in the best eye was present. These contradictory results need to be harmonized in future projects to understand the actual influence of visual disability on parenting stress. Besides behavioral problems, no association with parenting stress appeared for the level of adaptive functioning, level of ID, problems in hearing and seeing, deafblindness, gender and chronological age of the child. A trend was found of lower stress levels for parents with speaking children versus those with non-speaking children. Overall the notion of Hodapp (1999) that behavioral problems of children with specific genetic syndromes have

the strongest associations with parenting stress was also found to be true for CHARGE syndrome.

As mentioned by Blake et al. (2005) and Vervloed et al. (2006), it is difficult to describe the typical CHARGE person because the characteristics are so highly variable. Our sample was also heterogeneous with regard to physical and behavioral problems, for example only 13% of the measured behavioral problems were exhibited by more than half of the participants. However, medium to large effects found for several specific behavior patterns show that parenting stress and children's behavioral problems are clearly associated. The shared factor in the participating families is the perception of high levels of stress raising a child with CHARGE syndrome, with these levels being even higher when the children also display behavioral problems.

These findings suggest that professional support for families is an essential part of the assistance needed, and even more so if behavioral problems are present. In such case, parents should get additional support to manage the behavioral problems to lower the stress levels. It must also be emphasized that the child rearing support must be a continuous process, since the stress is not only high among parents with younger children but also among those with older children. Support should thus not be restricted to the turbulent early years of the child's life. As we did not find any significant association between parenting stress and the child factors studied except behavioral problems, professionals should investigate each family individually to determine which factors make the upbringing situation stressful in this particular case. In addition, our experience in an outpatient clinic and the results of Blake et al. (2005) reveal the involvement of many different professionals in the care of these children. The appointment of one professional as a key figure in streamlining all information and as provider of support could relieve parents of this task and promote family well-being. In addition to the care and support for the child with CHARGE syndrome itself, it is of the utmost importance to assist the parents in order to promote the well-being of the whole family system.

However, especially the results on to the relationship between parenting stress and the child characteristics need to be interpreted with caution. A serious problem in many studies, and in this project also, with people with CHARGE syndrome is the small number of participants. This has consequences for the ability to detect a significant effect. According to Cohen (1992) with an alpha of .05, preferred power of .8 and 26 to 28 participants, large effect sizes are needed to get statistically significant outcomes with *t*-

tests and Pearson correlations. This poses serious problems for the interpretation and meaning of our and other research results, since it remains unclear whether there truly is no association between the measured child characteristics and parenting stress or whether our sample is simply too small to determine statistically significant effects. Besides this, in the current project participants were distributed unevenly over some categories. For example the number of boys (16) outnumbered the girls (6) and the groups of children with (17) or without (5) hearing problems were also uneven. As it is unclear in which way this may have influenced our results, this is another reason for cautious interpretation.

Another limitation is the use of instruments that are not adapted and normed for this specific population with so many sensory problems. It is possible that the capacities of children with these problems are underestimated by the use of adaptive functioning to categorize the level of ID. However, the use of IQ tests is also problematic, especially for children functioning at the lowest levels with additional disabilities. So far, adaptive functioning may be the best measure we have to give an indication of the abilities of these children. Also, use of the DBC-P could have its limitations. It could be that children without an ID, exhibit behavioral problems which are not included in the DBC-P. Again the heterogeneity of the sample makes the choice of instruments a complicated issue. However, in our sample only five children were categorized as not having an ID, thus the choice of the DBC-P, based on earlier reports about the level of functioning, seems justified.

In this project we only focused on the relationship between certain child characteristics and the perception of parenting stress. For future projects looking further into these child characteristics is essential. We focused on behavioral problems, but it is also known that there is a heightened risk for psychiatric disorders in CHARGE syndrome, such as autism spectrum disorders, obsessive-compulsive disorder, attention deficit/hyperactivity disorder and Tourette syndrome (Blake et al., 2005; Wachtel, Hartshorne, & Dailor, 2007). Although the DBC-P describes behaviors characteristic of depression, autistic disorder and hyperactivity, this is not a substitute for an individual descriptive diagnosis. This issue is however not that straightforward; for example, diagnosing autism spectrum disorders in this multi-sensory impaired group is controversial (Hartshorne & Cypher, 2004; Johansson et al., 2006; Vervloed et al., 2006). In view of the possible impact of a co-morbid psychiatric disorder, this seems to be an important broadening of the child characteristics measured here. However, as Perry (2004) points

out, not only child characteristics influence the perception of parents of the child rearing situation. Focusing more on the differences in the family context, such as differences in resources and support, can give a more comprehensive notion of the complex process that leads to parenting stress in this complex population. In addition, a useful step to include other relevant child and family characteristics would be to first continue with a more qualitative approach by in-depth interviews with parents. In this way specific and new insights can be generated concerning the possible related factors to parenting stress which afterwards can be investigated in a larger CHARGE population with a quantitative approach. Finally, in this study mainly mothers filled out the questionnaires. Studies into parenting stress in both mothers and fathers with a disabled child show contradicting results, but the majority of the studies report comparable stress levels between mothers and fathers (Macias, Saylor, Haire, & Bell, 2007). However, from a clinical perspective, it would be an important additional factor to investigate in this specific population as it can generate valuable knowledge for intervention.

In sum, this study is the first to describe the experience of parents about the upbringing of a child with CHARGE syndrome with a broad age range. The heavy burden of this situation for a substantial part of the parents has become clear, extending Reda and Hartshorne's study (2008). Results regarding the relationship of parental perception and their child's characteristics can be seen as a first exploration of this topic. Perhaps the most important step in research of CHARGE syndrome will be a co-operation between researchers worldwide to be able to collect a large number of children with the syndrome and their families. This will not only resolve the lack of statistical power of studies, but will also help to harmonize measurement methods and research designs, thus raising the validity, reliability, and the generalization of the findings of research with regard to CHARGE syndrome. Although internet surveys among parents in different countries are being carried out already, more active collaboration between researchers in different domains seems necessary.

5 Simultaneous analysis of the behavioural phenotype, physical factors, and parenting stress in people with Cornelia de Lange syndrome

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ABSTRACT

Studies into the phenotype of rare genetic syndromes largely rely on bivariate analysis. The aim of this study was to describe the phenotype of Cornelia de Lange syndrome (CdLS) in depth by examining a large number of variables with varying measurement levels. Virtually the only suitable multivariate technique for this is categorical principal component analysis. The characteristics of the CdLS phenotype measured were also analysed in relation to parenting stress. Data for 37 children and adults with CdLS were collected. The type of gene mutation and relevant medical characteristics were measured. Information on adaptive functioning, behavioural problems, the presence of the autistic disorder and parenting stress were obtained through questionnaires and semi-structured interviews with the parents. Chronological age and gender were also included in the analysis. All characteristics measured, except gender, were highly interrelated and there was much variability in the CdLS phenotype. Parents perceived more stress when their children were older, were lower functioning, had more behavioural problems, and if the autistic disorder was present. A new perspective was acquired on the relation between the gene mutation type and medical and behavioural characteristics. In contrast with earlier research the severity of medical characteristics did not appear a strong prognostic factor for the level of development. Categorical principal component analysis proved particularly valuable for the description of this small group of participants given the large number of variables with different measurement levels. The success of the technique in the present study suggests that a similar approach to the characterisation of other rare genetic syndromes could prove extremely valuable. Given the high variability and interrelatedness of characteristics in CdLS persons, parents should be informed about this differentiated perspective.

INTRODUCTION

The Cornelia de Lange syndrome (CdLS), is a genetically determined congenital syndrome characterised by a specific facial appearance, limited growth of both head circumference and height, malformations of several organ systems, developmental delay, and behavioural problems (Kline et al., 2007). The combination of a small head circumference, long eyelashes, confluence of the eyebrows and a long philtrum with the

corners of the mouth downturned are the most distinct physical features of the syndrome (Gorlin, Cohen, & Hennekam, 2001). The syndrome can be caused by mutations in one of at least three genes: NIPBL, SMC1A and SMC3 (Deardorff et al., 2007; Krantz et al., 2004; Musio et al., 2006; Tonkin, Wang, Lisgo, Bamshad, & Strachan, 2004). A relation between the type of mutation and the physical and behavioural phenotype has been found (Gillis et al., 2004; Selicorni et al., 2007; Yan et al., 2006), although this difference was not statistically significant in all studies (Bhuiyan et al., 2006). A classical type and a mild type are distinguished in the syndrome, with less marked physical malformations, and less severe growth problems and developmental delay in the mild type (Allanson, Hennekam, & Ireland, 1997; Ireland, Donnai, & Burn, 1993). More severe physical problems, such as lower birth weight and more marked limb anomalies, go together with lower levels of functioning (Berney, Ireland, & Burn, 1999; Goodban, 1993; Hawley, Jackson, & Kurnit, 1985). Kline et al. (2007) found a correlation between the severity composite and the developmental level and mentioned the severity composite to be a predictor of the clinical course. The exact prevalence of the syndrome remains unclear; estimates for the mild and classical type combined range from 1:10,000 to 1:62,000 (Barisic et al., 2008; Opitz, 1985).

Research into the behavioural phenotype, as defined in the probabilistic manner by Dykens (1995), has shown that although normal intelligence can be present, most persons have a moderate to profound intellectual disability (ID) (Basile, Villa, Selicorni, & Molteni, 2007; Beck, 1987; Berney et al., 1999). Many behavioural problems have been reported and especially self-injurious behaviour has received much attention with a reported prevalence between 17% and 64% (Basile et al., 2007; Beck, 1987; Berney et al., 1999; Hyman, Oliver, & Hall, 2002; Sarimski, 1997b). Furthermore, the co-occurence of autism spectrum disorders is often mentioned, with estimates as high as 62% (autistic disorder) to 74% (the whole spectrum) in persons with CdLS (Basile et al., 2007; Berney et al., 1999; Moss et al., 2008). It is still uncertain whether the high occurrence of self-injurious behaviour and autism spectrum disorders is syndrome-specific or only related to the low levels of functioning (e.g. Berney et al., 1999; Oliver et al., 2003).

A limited number of large genetic studies and large behavioural studies using standardised instruments have been carried out in CdLS individuals (Basile et al., 2007; Berney et al., 1999; Gillis et al., 2004; Selicorni et al., 2007). In this study, we aim to provide an in-depth description of the characteristics of people with CdLS, both

behaviourally and physically. A limitation of most earlier studies was their focus on either the behavioural or medical aspects, which very often led to weaker operationalisations of the other aspect. In contrast, the present study was build on expertise in both fields. Furthermore, earlier studies had the description of the characteristics of CdLS persons as primary focus of research. Only Sarimski (1997b) paid particular attention to the way parents perceive the upbringing of their child with CdLS. Such information is, however, crucial in clinical practice in supporting the families with a child with CdLS. Therefore, in the present study also the relationships between parenting stress and the characteristics of the child were studied.

In former studies mainly a bivariate approach was used to investigate the relationships between different aspects of CdLS, which does not seem to coincide with the complexity of the relationships in real life. To delineate the behavioural and physical phenotype further, a multivariate approach using all available information simultaneously is clearly called for. Categorical or nonlinear principal component analysis (PCA) is an extension of standard PCA and is able to handle both numerical (e.g. amount of behavioural problems) and categorical (e.g. presence and nature of a gene mutation) variables. Given the presence of variables with different measurement levels such a technique is ideally suited for the characterisation of CdLS (see e.g. Meulman, Van der Kooij, & Heiser, 2004). Using all the above criteria and techniques, we aim to provide a more in-depth, realistic and comprehensive description of CdLS.

METHOD

Participants and procedure

All participating parents were acquired through the Dutch CdLS Support Group. Of the 71 families known to the support group 42 participated. The main reason not to participate was the distance between their home and the hospital where the medical part of the study was performed. Of the 42 participants, 3 persons were found not to have CdLS, and 2 died during the course of the study. So, 37 persons (21 were male, 16 were female) were admitted to the study. Their age range was 1.4 - 46.2 years, mean age was 18.1 years (*SD* = 13.0), and 62% of the persons were aged 18 years or younger. Behavioural assessment was carried out through questionnaires and interviews with the parents. The participants received an extensive medical evaluation including physical examination and

genetic testing, the details of which have been published elsewhere (Bhuiyan et al., 2006). The study was approved by the medical ethics committee of the Academic Medical Centre in Amsterdam and by the board of the Dutch CdLS Support Group.

Instruments

Behavioural

The Dutch version (Koot & Dekker, 2001) of the *Developmental Behaviour Checklist-Primary Carer* (DBC-P: Einfeld & Tonge, 2002) assesses emotional and behavioural problems in people with an ID. Parents rate 95 items on three-point scales. A total problem behaviour score can be computed, as well as five sub-scale scores (disruptive/antisocial behaviour, self-absorbed behaviour, communication disturbance, anxiety, social relating problems). Inter-rater and test-retest reliability, internal consistency and construct and criterion validity are all satisfactory (Koot & Dekker, 2001). The DBC-P has an Autism Screening Algorithm (DBC-ASA), which reliably screens for autistic disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders fourth edition (American Psychiatric Association, 1994). For children under 48 months the comparable DBC-P Early Screen (Gray & Tonge, 2005) was used.

The expanded interview version of the *Vineland Adaptive Behaviour Scales* (VABS: Sparrow, Balla, & Cicchetti, 1984) measures the level of adaptive functioning on four domains (communication, daily living skills, socialisation, motor skills). An Adaptive Behaviour Composite, based on the four standardised domain scores, can be computed with which a classification in adaptive level can be obtained, ranging from a high level to a profound deficit. US norms were used, which is supported by cross-cultural stability (Fombonne & Achard, 1993). The VABS has good psychometric properties (Sparrow et al., 1984). The VABS interview with the parents was conducted by a trained clinician.

The *Diagnostic Interview for Social and Communication Disorders 10th revision* (DISCO-10: Wing, 1999) is a semi-structured interview used to aid clinicians in diagnosing autism and related disorders in people of all ages and levels of functioning. For research purposes different algorithms exist (Wing, Leekam, Libby, Gould, & Larcombe, 2002). The algorithm we used is based on criteria for childhood autism according to the International Statistical Classification of Diseases 10 (World Health Organization, 1993). This algorithm has a good inter-rater reliability (Nygren et al., 2009) and a good correspondence between a clinical diagnosis of childhood autism/autistic disorder and

DISCO-10 classification has been found (Billstedt, 2007). A trained clinician administered the interview with the parents.

The *Nijmegen Parenting Stress Index-Short* (NPSI-S: De Brock, Vermulst, Gerris, & Abidin, 1992) measures parenting stress in families with children from 2 to 13 years. We have taken this age range as an indication of the developmental level of a child and as the level of functioning of our participants including the older ones fitted in this range, the questionnaire was considered useful. The NPSI-S is a translated and adapted version of the Parenting Stress Index by Abidin (1983 as cited in De Brock et al., 1992). Twenty-five items are scored on six-point scales. Separate Dutch norms for mothers and fathers are available and we used those for the non-clinical norm group. Criterion validity and internal consistency are good. Concurrent and discriminant validity are only investigated for the extended version: concurrent validity is satisfactory and results for discriminant validity are acceptable (De Brock et al., 1992). Both parents were asked to fill out the NPSI-S, but this was only accomplished in 12 cases. In nine of these couples (75%) their raw score belonged to the same norm category and only in one case the result between a mother and father differed more than one norm category. In two cases only results for fathers were available, in the other cases we used results obtained from the mothers.

Physical

All individuals underwent complete and detailed physical examination, and were tested for the presence of either an NIPBL, SMC1A or SMC3 mutation. All physical characteristics, known to be informative for CdLS, were measured (see Table 5.1). A physical severity score was computed, based on criteria for pre- and postnatal growth, skull growth, limb anomalies and facial phenotype. For each characteristic, participants were given a score of 1, 2 or 3: a higher score meant a more severe condition. The comparison values for prenatal growth, i.e. weight, were taken from the general population (Van Wieringen, Roede, & Wit, 1985), if necessary normalized for gestational age, and grouped in accordance with earlier CdLS studies (Hawley et al., 1985; Saal, Samango-Sprouse, Rodnan, Rosenbaum, & Custer, 1993). The comparison values for skull growth were taken from the general population as well (Nellhaus, 1968) whereby a difference between a mild and more severe microcephaly in CdLS was made (Allanson et al., 1997). Grouping for postnatal growth (Gillis et al., 2004; Kline, Barr, & Jackson, 1993) and limb anomalies (Gillis et al., 2004) was based on earlier research in CdLS. Criteria for facial phenotype were taken from Allanson et al. (1997). All persons were classified by the last

author as having a classical, mild or atypical phenotype. This classification was based upon both the information from the physical severity score and the behavioural characteristics and as such was an overall impression of the appearance of the syndrome. Individuals with the atypical variant in this study do have the syndrome, but have an atypical appearance. A more detailed description of the physical findings has been published elsewhere (Bhuiyan et al., 2006).

All ordinal variables were coded in such a way that a higher score means a more severe outcome, for example more behavioural problems and lower levels of functioning.

Table 5.1 *Physical severity score (Bhuiyan et al., 2006)*

Prenatal growth	**Postnatal growth**	**Skull growth**	**Limb malformation**	**Face**
1 > 2500g	1 > P75	1 > - 2SD	1 = no reduction defect	1 = possible CdLS
2 = 1500 - 2500g	2 = P25 - P75	2 = - 2SD to - 4SD	2 = partial reduction defects (absence 1/2 fingers)	2 = mild type
3 < 1500g	3 < P25	3 < - 4SD	3 = severe reduction defects (absence 3 or more fingers or complicated oligo-/polydactyly)	3 = classical type

Data analysis

Data inspection

For the DBC at least 90% of the items have to be filled out for an individual to obtain a reliable scoring. Inspection of data revealed for one person more than 10% was missing, so her DBC data were removed. For persons with less than 10% missing items (5), rounded mean values for the relevant items were substituted. As the amount of items differs substantially between the DBC sub-scales, weighed scores were computed by dividing the sub-scale scores by the number of items on that particular sub-scale. The NPSI-S manual gives a formula to estimate the value for missing items which was used to estimate the values of the three individuals who had one missing item on the NPSI-S. In case information on one aspect of the physical severity score was unknown, a score of 2 was given. No severity score was computed if more than a single item was missing.

Principal component analysis

Standard PCA is generally used to explore the linear relationships between a large amount of numerical variables, and it is a valuable tool for data reduction and description (see e.g. Hair, Black, Babin, Anderson, & Tatham, 2006). However, because this dataset contains both numerical and categorical variables, categorical PCA was employed. Using categorical PCA variables of different measurement levels can be analysed simultaneously, moreover the relationships between the (numerical) variables need not be linear (see e.g. Linting, Meulman, Groenen, & Van der Kooij, 2007). In categorical PCA the categories of the variables are assigned numerical values (category quantifications) such that after quantification (1) the first component explains as much variance as possible, or equivalently; (2) the average squared correlation of the quantified variables and the first component is as high as possible; and (3) Cronbach's alpha for the quantified variables is maximised. For unordered categorical variables it is possible to obtain separate category quantifications on each component, referred to as multiple nominal quantifications.

After the optimal quantifications have been obtained, categorical PCA shares all the properties and interpretations of standard PCA, except that the categorical variables with multiple nominal quantifications take a special position (see below) (De Heus, Van der Leeden, & Gazendam, 2002; Linting et al., 2007; Meulman et al., 2004).

For our analysis we used the CATPCA program contained in SPSS 14.0 (Meulman, Heiser, & SPSS, 2005). An additional feature of this program is that it can portray variables and individuals in a single plot, a so-called biplot (see e.g. Gabriel, 1971). Another special feature is that variables which were not included in the analysis itself (so-called supplementary variables), can be added to the loading plots and biplots. In our study this was particularly useful for adding the type-of-syndrome variable to the plots as this classification was based upon some of the variables already included in the analysis. Detailed specifications of the analysis of the present data are provided in Appendix B.

RESULTS

The description of the results consists of two parts. In the first part information on the sample is provided in terms of the individual measurement instruments. The second

part gives a multivariate description of CdLS by considering all response variables simultaneously via a categorical PCA.

Description of the sample

A summary table containing the univariate statistics of the relevant measured variables is provided in Appendix B (Table B.1).

Persons with CdLS

Most persons were severely disabled in their adaptive functioning. According to the VABS (n = 37) 19 participants functioned in the profound category, six were severely, six moderately and five mildly disabled and only one person functioned in the borderline range. The DBC-P (n = 36) cut-off for total problem behaviour (Einfeld & Tonge, 2002) indicated that nearly half of the participants (47%) showed severe problem behaviour. Most problems appeared on the sub-scales social relating problems (M = 0.68, SD = 0.40) and self absorbed behaviour (M = 0.63, SD = 0.38). The least problems appeared on the communication disturbance scale (M = 0.37, SD = 0.36), with disruptive/antisocial behaviour (M = 0.48, SD = 0.40) and anxiety (M = 0.43, SD = 0.35) in between. The low score on the communication disturbance sub-scale could partly be due to the fact that only a minority of the persons was able to speak, which is required for scoring some of the items in this sub-scale. One item in the DISCO-10 measured self-injurious behaviour at the time of the interview. According to the parents self-injurious behaviour (n = 37) frequently occurred in 22% of the persons, occasionally in 38% and was absent in 41%.

Indications for a co-morbid autistic disorder were present in a large proportion of the sample. By combining the DBC-ASA and the DISCO-10, 20 persons (54%) were classified with the autistic disorder, 6 (16%) had possible the autistic disorder (the instruments disagreed) and 11 (30%) were classified as not having the autistic disorder. Of the 20 persons with autistic disorder, 15 were profoundly disabled in their adaptive functioning, 2 were severely disabled and 3 were moderately disabled.

NIPBL truncating mutations were found in 16 persons (43%), NIPBL missense mutations in 4 (11%), SMC1A in 2 persons (5%), and no mutation in any of these tested genes was found in 15 persons (41%). No SMC3 mutations were found. Physical severity scores (n = 34) ranged from 5 to 14 (M = 9.4, SD = 2.2). As an overall categorisation based on the physical and behavioural characteristics, 7 persons (19%) were classified as mild CdLS, 26 (70%) had classic CdLS and 4 (11%) had atypical CdLS.

Parents

The level of parenting stress (n = 33) was very high for parents with a child with CdLS. None of the parents reported stress in the lowest category of the non-clinical norms. For only 3% of the parents the stress levels were low, and only 9% scored in the norm category 'below the mean'. For 18% of the parents stress levels were average compared to the norms of the NPSI-S. Another 18% perceived their stress above the mean, 15% indicated they experienced high levels of stress. Over a third of the parents (36%) reported very high levels of stress.

Most persons with CdLS, like other people with moderate to profound ID, are dependent on others during their lifespan. This causes their parents to remain their caretakers and/or legal representatives even when their child reaches adulthood or is living in a professional setting. Therefore we consider it appropriate to use the term children in this article, as most adults with CdLS remain in a dependency position with their parents.

Categorical PCA: on child and parental characteristics

For the categorical PCA first the quantification process of the original variables is described, followed by the results of the multivariate analysis. This section ends with the visualisation of the individual persons in relation to the measured variables.

Quantification of the original variables and goodness of fit

A two-component solution for the categorical PCA was chosen as this gave good insight into the data and adding a third component did not contribute much to the interpretability of the data. Table 5.2 shows that all quantified ordinal variables correlated ≥.50 with at least one of the components. Following a rule of thumb for standard PCA this means all contribute well to the description of the characteristics of our sample and all are sufficiently correlated to one another to be useful in the analysis (Hair et al., 2006, p. 128).

Of the unordered categorical variables, gender turned out to be the only variable which contributed poorly to the solution, so it was excluded from further analyses (see Appendix B for details). For the remaining two variables, gene mutation and presence of the autistic disorder, no a priori order existed between the categories, so that they were analysed at a multiple nominal level so that separate quantifications were allowed for each dimension. The total amount of variance accounted for by the two-dimensional solution (63%), implies that after the optimal quantification of the variables the analysis gives a

good description of both the total variability present in the data and the characterisation of persons with CdLS.

Table 5.2 *Component loadings and variance accounted for in the transformed ordinal and multiple categorical variables*

Transformed variables	Component 1	Component 2	Variance accounted for
DBC self-absorbed	**.88**	.22	**.82**
Adaptive functioning	**.80**	.38	**.79**
DBC social relating	**.79**	.27	**.70**
Parenting stress	**.79**	-.21	**.67**
DBC communication disturbance	**.69**	-.31	**.58**
DBC disruptive/antisocial	**.66**	**-.60**	**.80**
Chronological age	**.63**	-.15	.43
DBC anxiety	**.60**	**-.57**	**.69**
Self-injurious behaviour	.40	**.66**	**.59**
Physical severity score	.05	**.84**	**.71**
Gene mutation component 1 [a]	.05		.00
Gene mutation component 2		**.70**	.49
Autistic disorder component 1 [a]	**.62**		.38
Autistic disorder component 2		.26	.07

Note. DBC = Developmental Behaviour Checklist.

[a] As the variables gene mutation and autistic disorder were categorical ones with separate quantifications on each component, they are listed separately for these components.

Graphical representation of transformed ordinal variables

Figure 5.1 shows the two-dimensional plot of the loadings of the variables[2] given in Table 5.2 in which the variables are represented by vectors or arrows. The origin of the plot represents the mean for each variable. The arrows represent the values above the mean. Scores below the mean lie on the extension of the vector in the opposite direction (see Figure 5.3 for examples). In accordance with the loadings shown in Table 5.2 all vectors are more or less equally long, meaning they fit in the solution equally well.

[2] For convenience/readability we will use the words *variable* or *category* from hereon instead of *quantified* or *transformed ordinal variables* or *categories*, as we will only report on the measures after quantification.

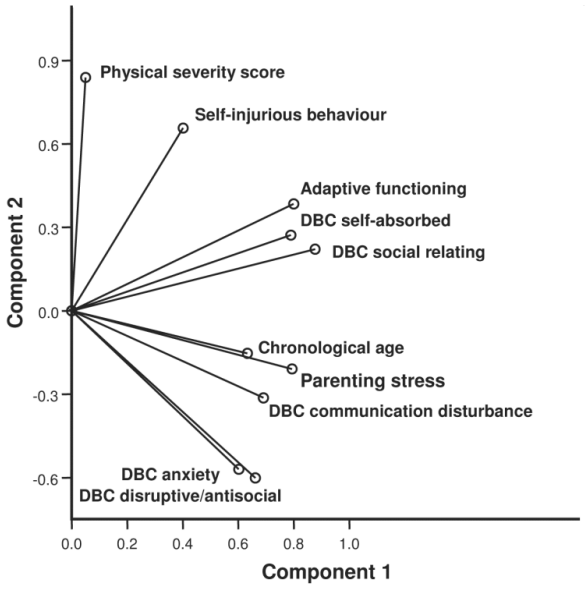

Figure 5.1 Quantified ordinal variables displayed as vectors in a two-dimensional loading plot
Note. DBC = Developmental Behaviour Checklist.

Only chronological age has a somewhat shorter vector, indicating it has somewhat less influence on the solution. That the solution does not represent its variability very well can also be seen in its amount of variance accounted for (see Table 5.2).

As all variables fitted well, the angles between the vectors represent to a reasonable degree the correlations between the transformed variables (Linting et al., 2007). In other words, the plot can be seen as a compact representation of the complete correlation matrix of the ordinal variables. Vectors with small angles between them have high correlations and vice versa. Vectors at an angle of 90° show the variables are uncorrelated, vectors with a 180° angle are closely but negatively related. Three clusters of highly interrelated variables were present. As shown in Figure 5.1 level of adaptive functioning formed a cluster with the DBC sub-scales social relating and self-absorbed. Parenting stress, DBC communication disturbance and chronological age formed a second cluster of variables. The DBC sub-scales disruptive/antisocial and anxiety formed the third cluster. Thus, the plot contains an overview of the relationships between the ordinal variables and as such it provides an overview of the structure of the characteristics of persons with CdLS as far as it is contained in these variables.

Summary of correlations between quantified variables

To provide more numerical information about the relationships of the ordinal variables, the average correlations between and within the aforementioned clusters of variables were added to Figure 5.1 (Figure 5.2); see Appendix B for the correlation table. Not only were variables within the three clusters highly correlated but also the clusters themselves showed considerable correlation as was the case for the variables physical severity score and self-injurious behaviour. All clusters in the solution were highly related with at least one other cluster, underlining the interrelatedness of different characteristics in persons with CdLS. As stated in the introduction, we were specifically interested in the relationships of parenting stress with the child characteristics measured. Parenting stress was higher for persons with lower levels of functioning and more behavioural problems, which applied for all DBC sub-scales. Parents of older persons experienced higher levels of stress. The level of parenting stress was not highly related to the presence of self-injurious behaviour and the severity of physical problems.

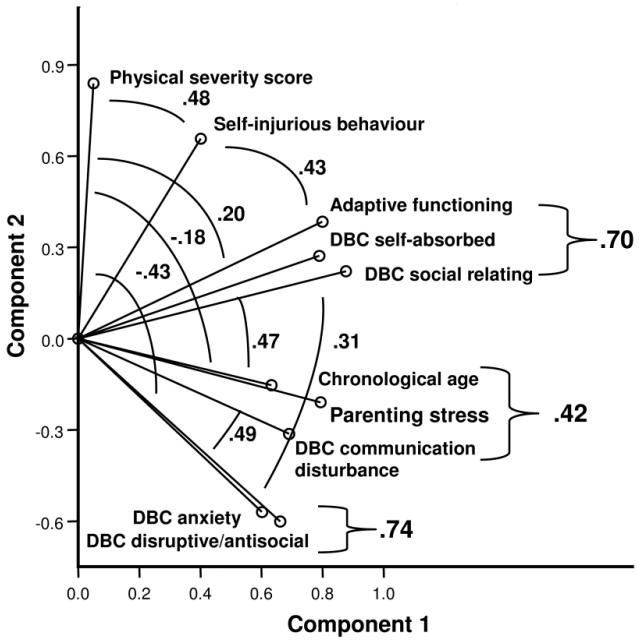

Figure 5.2 Mean correlations between and within (bold) clusters of transformed ordinal variables
Note. DBC = Developmental Behaviour Checklist.

The two unordered categorical variables received different quantifications on each of the two components. Gene mutation type did not correlate highly on component 1 with any of the other variables (ranging from -.01 to .32). On component 2 correlations ranged between -.12 to .67, with high correlations for physical severity score (.67), self-injurious behaviour (.45) and DBC disruptive/antisocial (-.42) and anxiety (-.40). The presence of the autistic disorder on component 1 was strongly correlated with DBC self-absorbed (.74) and social relating (.71), and with the level of adaptive functioning (.63). High correlations were also found with DBC communication disturbance (.43), self-injurious behaviour (.43), and parenting stress (.41). With the other variables correlations ranged between -.01 to .31. On component 2 the presence of the autistic disorder had correlations between .04 to .55 with high correlations for the adaptive level of functioning (.55), and DBC sub-scales social relating (.52) and self-absorbed (.45).

Joint representation of ordinal and categorical variables

For a more detailed insight into the changes in the ordinal variables due to quantifications, Figure 5.1 was redrawn such that the locations of the categories after quantification are shown on the extended vectors (Figure 5.3). Moreover, to give an overview of all available variables, the categories of the two unordered categorical variables were drawn in the plot as well. To complete the plot, the variable type of the syndrome was also added to Figure 5.3 as a supplementary variable. In other words, Figure 5.3 not only contains more details of the ordinal variables of Figure 5.1, but their relationships with the unordered categorical and supplementary variables can now be examined as well.

The values of a categorical variable constitute in fact a classification of the individuals in distinct groups. In the plot the category point lies in between the individuals who belong to that category, so that it represents the average of those persons. Said differently it is the average person of that category (Linting et al., 2007). By drawing a perpendicular line from a category point onto another variable, the projection reflects what score on the ordinal variable was most typical for that category. The three categories of the variable autistic disorder are spread out over the plot, indicating that the measured characteristics were different for CdLS persons with the autistic disorder, those without the autistic disorder, and those with a probable autistic disorder.

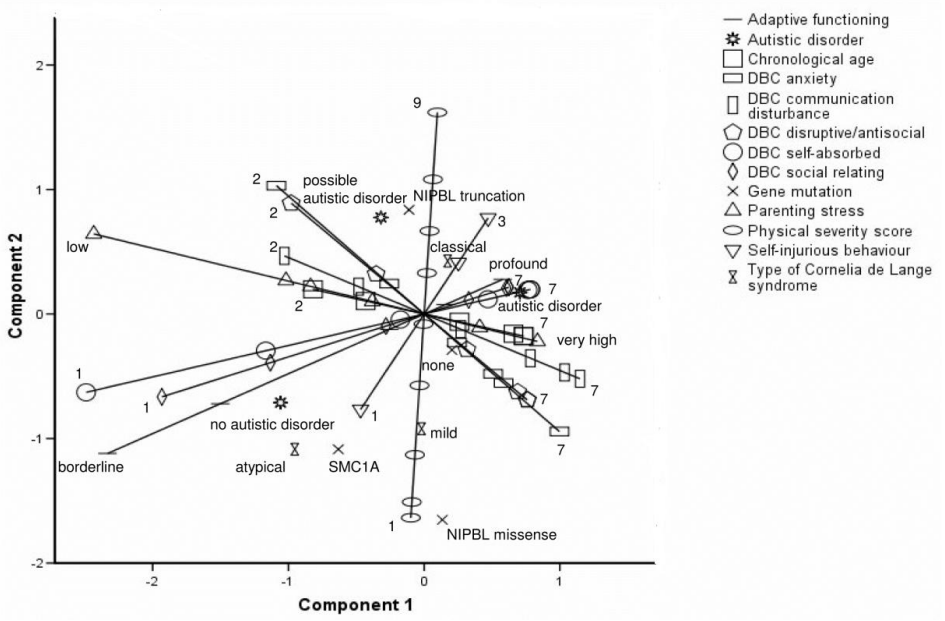

Figure 5.3 Category plot of the ordinal and categorical variables measuring child and parenting characteristics of people with Cornelia de Lange syndrome with type of syndrome added
Note. DBC = Developmental Behaviour Checklist.

To illustrate this we first concentrate on individuals belonging to the autistic disorder category. From the projection of this category on the variable adaptive level, we see that they mostly functioned on the severe to profound adaptive level. Similarly, they showed high levels of behavioural problems. Persons with the autistic disorder showed different values for the separate DBC sub-scales be it that on all sub-scales high scores were obtained, with highest scores on the self-absorbed and social relating problems. Their physical severity score was medium. They often showed self-injurious behaviour. Similar detailed statements can be made for the other two categories of AD. Persons with probable autism and without the autistic disorder differed in their level of behavioural problems, level of functioning and psychical severity score. Focussing on the relation with parenting stress, parents with a child with the autistic disorder perceived very high levels of stress. Parents of a child with a probable presence of the autistic disorder obtained lower but still substantially high levels of stress, and parents of children without the autistic disorder perceived the least stress, scoring closest to average levels of stress compared to the non-clinical norms.

The quantifications for the gene mutation were also spread out over the plot, but the missense NIPBL and SMC1A mutations were more alike, with different characteristics for persons without a mutation or a truncating NIPBL mutation. Because only two persons had a SMC1A mutation, the analysis gives only a first impression of their characteristics and caution about conclusions is needed. It was clear that the mutation type gave differences in the other measured variables, thus CdLS persons with different mutations have different characteristics. After inspecting the plots and the correlations, the biggest differences were seen on the physical severity score and self-injurious behaviour. As for the relation with parenting stress, the differences between the gene mutations were not really large, which was already clear from the low correlations on both components (r = .21 and -.21).

For the supplementary variable, type of syndrome (added in Figure 5.3), atypical and mild CdLS were more alike on their physical severity score and contrasted with persons with classical CdLS. With respect to the level of functioning, the DBC sub-scales self-absorbed and social relating and self-injurious behaviour, the three types of the syndrome clearly differed from each other, whereas on DBC communication disturbance and chronological age the mild and classical type were more alike and contrasted with the atypical type of the syndrome. The mild type differed from the classical and atypical type on the DBC sub-scales disruptive/antisocial and anxiety. With regard to the perceived stress parents of children with the classical and mild type reported higher levels of stress than parents of a child with the atypical type, but differences were not really large.

Individuals and the quantified variables

An important feature in our research is that individuals and their relationships with the variables are of central concern. In categorical PCA each person can be represented in a two-dimensional plot through a point and its position is determined by its (category) scores on all variables. By projecting the individuals onto the variables the spread with regard to these different variables can be seen.

A remarkable result in the light of earlier research was the spread of the level of adaptive functioning of the individuals along the vector of the physical severity score, with which on the level of the variables no high correlation existed (r = .25). Figure 5.4 gives a more detailed insight in the individual scores on these variables. It can be seen that there was a large spread of the level of functioning of individuals on the whole range of physical

severity. Individuals with a very low severity score had a mild, but severe or profound ID as well. Also in the midrange of physical severity the whole spectrum of adaptive functioning of the participants was found. Only in the highest physical severity scores the persons with mild ID were absent. Thus it seemed individuals with a mild ID obtained a low to midrange physical severity score, but at the same time a low severity score could not be taken as a predictor of high levels of adaptive functioning. By using such plots as presented here, differences on an individual level can generate insights which would not have been noticed if only the relationship between variables was inspected.

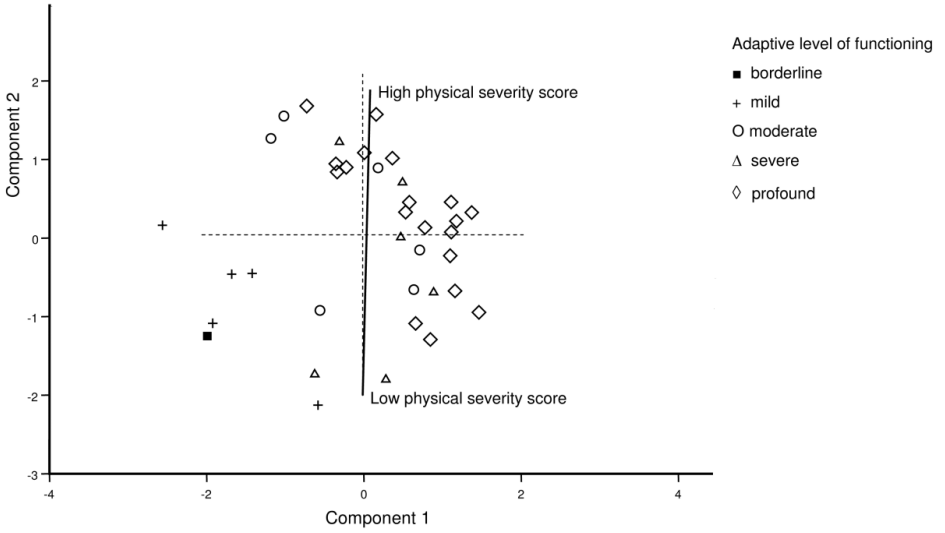

Figure 5.4 Component loading of physical severity score with individual object point labelled by level of adaptive functioning

DISCUSSION

The goal of our study was to provide a comprehensive description of the characteristics of persons with CdLS and their parents using a multivariate approach. The categorical PCA showed all measures except gender were useful in describing the characteristics of persons with CdLS, and did so to a satisfying extent. As the characteristics of the sample were mostly comparable with earlier research (Basile et al., 2007; Beck, 1987; Berney et al., 1999; Deardorff et al., 2007; Hyman et al., 2002; Selicorni et al., 2007), this strengthens the probability of generalisation of the results.

With regard to our first focus, the child characteristics, different types of behavioural problems were highly interrelated. Also social relating problems, self-absorbed and self-injurious behaviours were more prevalent in lower functioning persons, whereas disruptive/antisocial behaviour and anxiety were not closely connected to the level of functioning. The presence of the autistic disorder was strongly associated with lower levels of functioning and more self-absorbed and social relating problems. Also self-injurious behaviour and communication disturbances correlated with the presence of the autistic disorder.

The severity of physical characteristics was closely related to the prevalence of self-injurious behaviour, although a negative relation with disruptive/antisocial behaviour should be noticed as well. It also was linked to the gene mutation type. The physical severity score was not related to the level of functioning, as opposed to results in other studies (e.g. Berney et al., 1999; Goodban, 1993; Hawley et al., 1985; Kline et al., 2007). From the analysis of the individuals it turned out that the physical severity score was low to medium in the persons with higher levels of functioning but it was clearly not a prognostic factor as persons with moderate, severe and profound disabilities obtained severity scores covering the whole range. Most studies that reported a close connection of physical problems and level of functioning measured only one or two physical factors, used less refined operationalisations of the developmental level or included psychomotor measures in their severity score, in which case a distortion of the correlation with the level of functioning appears. These factors may all be related to the difference in results. The type of gene mutation was also related to the level of anxiety and self-injurious and disruptive/antisocial behaviour. Our results indicated comparisons in previous research need to be reconsidered. It appeared that persons with a NIPBL truncating and missense mutation differed the most on the measured characteristics, whereas in the available genetic literature comparisons are made between persons with and without a gene mutation and between missense and truncating mutations (Gillis et al., 2004; Selicorni et al., 2007; Yan et al., 2006). Thus a three-group comparison was more realistic instead of two separate two-group comparisons. Future studies measuring both genetic and behavioural characteristics in a fine-grained way are needed to confirm our results. The age of the persons was important too, although somewhat weaker relations were found. Older persons showed more behavioural problems and had lower levels of functioning. This relation between age and behavioural problems has been reported before (Basile et

al., 2007; Berney et al., 1999; Sarimski, 1997b). The differences between persons with the classical, mild and atypical type of the syndrome were not used in the primary analysis but were used for validation afterwards. It appeared that the classical, mild and atypical type differed from each other on some of the measured variables, whereas on other variables they were more alike. This underlines the observation that no clear-cut difference between the various types exists and thus the classification is not always as straightforward as it is purported to be (Bhuiyan et al., 2006; Selicorni et al., 2007).

Our second aim was to get insight in the relation of parenting stress with regard to the child characteristics. Sarimski (1997b) found that parenting stress was higher in parents with children who were older and had lower levels of functioning. Our participants had a broader age range and a more representative level of functioning, so that Sarimski's results could be extended to older persons and higher functioning persons. Parenting stress was also higher if more behavioural problems were present; however, it was not related to self-injurious behaviour alone, nor to the severity of physical characteristics. Our results do not support the suggestion of Sarimski that self-injurious behaviour may contribute to parenting stress. As self-injurious behaviour is related to the level of functioning which varied more in the present study, this could possibly explain the difference in results. Our results on the physical characteristics expand Sarimski's results, who did not found a significant effect of gastrointestinal problems on parenting stress. For our participants parenting stress was also higher for parents of children with a missense NIPBL mutation compared with no mutation or a truncating NIPBL mutation, though differences were not really large. The presence of an autistic disorder was however important, parents of children with the autistic disorder reported the highest level of stress as opposed to children without or with only a possible autistic disorder. Comparing these results with studies into other genetic ID syndromes, these factors associated with parenting stress are probably syndrome specific. For instance, Fidler, Hodapp, and Dykens (2000) showed factors related to parenting stress differ between parents with children with three different genetic syndromes. This syndrome-specifically parenting stress could be related to the behavioural phenotype of the relevant syndrome, as behavioural problems in people with CdLS will be different from behavioural problems in, for instance, Williams syndrome.

By using a categorical PCA, it became possible to analyse all variables at once, irrespective of their measurement levels. The technique is suitable to generate new insights, such as three-group comparisons for the genetic mutation type instead of two

separate comparisons. Furthermore, the description of the individuals provided more in-depth insights, for instance with respect to the connection between the level of functioning and the physical severity scores. If only mean scores were compared, this could have generated a misleading view of the range of possibilities with regard to this relation. Furthermore, given some contrasting results between our study and previous results, the operationalisations of the physical problems and level of functioning differed considerably between studies, so that it would be helpful to obtain a more homogeneous way of measuring both aspects in order to further delineate the connection in the syndrome.

Although a holistic description of people with CdLS has been given, there are also limitations in this study. First, the specificity of some characteristics is unclear because a control group was lacking in our project. Composing a reliable control group for a syndrome with such a broad range of functioning, appears very difficult to obtain. Second, we only reported the level of parenting stress with regard to child characteristics. Other known influencing factors, such as the family's resources and the support the family is receiving (Perry, 2004), should in future research be taken into account as well. Third, as we only used screening instruments to assess the presence of the autistic disorder, it remains unclear how many persons would get a clinical classification in an individual diagnostic process. Our study seems in line with Berney et al. (1999) and Basile et al. (2007) where a close connection with the level of functioning existed for the presence of an autism spectrum disorder. However, we agree with Moss et al. (2008) that it may be less important whether either a co-morbid autism spectrum disorder is present or the behaviours are seen as part of the syndrome, but instead we should focus on the interventions aimed at the same behaviour. Four of our participants with severe challenging behaviours and behaviours indicative of an autism spectrum disorder were given autism orientated augmentative communication, which lowered the challenging behaviour significantly. Thus it seems future research should not only focus on defining the behavioural phenotype but also study interventions aimed at autism spectrum or autistic-like behaviours. The awareness of the heightened prevalence of autism spectrum or autistic-like behaviours in the syndrome remains equally important. Finally, we refrained from analysing the possible influence of reflux in the present study. Reflux is a significant problem in a large proportion of persons with CdLS (Luzzani, Macchini, Valadè, Milani, & Selicorni, 2003). In the present study group 89% of the participants had reflux at a certain time (past or present) and would thus not allow for a significant

discrimination. Furthermore, determining whether reflux is present or absent at a specific moment in time is extremely difficult and unreliable as reflux can change very quickly. Only if such studies would be performed repeatedly over the total period over which behaviour is assessed could reliable data be provided. As such data are not available for the present study group the possible influence of reflux was not further studied.

The multivariate analysis shows CdLS is not homogenous in the physical and behavioural phenotype, but variability is extensive. This has consequences for the information provided to parents and others caregivers of CdLS individuals. Parents with a newborn or young child with the syndrome can be given a differentiated picture about the possible variation. As suggested before (Clericuzio, 1993) the physical phenotype should not be used as an important prognostic factor for the level of functioning or behaviour of the affected children. In caring for older children and adults with CdLS, understanding the interrelatedness of various characteristics such as adaptive functioning, behaviour and autism spectrum disorders may be of importance. Awareness of the heavy burden the person with CdLS can place on the family, causing high levels of parenting stress, provides insight in the consequences this has on parenting practices and the development of the affected persons. Support to both the persons with CdLS and their parents by well-informed professionals is crucial to create an optimal well-being for all involved.

APPENDIX B

Description of categorical principal component analysis on the data of 37 persons with Cornelia de Lange Syndrome

Categorical PCA is a technique with which nominal, ordinal and numeric variables can be analysed simultaneously. Within this context numeric variables are also often treated as categorical variables with very many categories, so as to allow nonlinear transformations for these variables. If all variables are numerical and are treated as interval-scaled variables standard PCA and categorical PCA are identical (Linting et al., 2007). When using the SPSS program CATPCA (Meulman et al., 2005) to carry out categorical PCA, the analysis level of the variables has to be assigned, and this can be different from the measurement level. This assignment should be guided by the nature of the variables and the judgement of the researcher. Coupled with this choice is the kind of transformations suitable for each variable. For instance, real numerical variables require only a linear transformation, such as standardisations. Ordinal variables can only be monotonically transformed, i.e. the transformations should leave the rank order of the variables in place. A particular variant of this monotone transformation is a spline transformation which induces a smooth transformation from the original category values to the new quantified variables. Such spline transformations provide much smoother transformations, and contribute to the stability of the solution (Linting, 2007). For unordered categorical variables there is much more transformational freedom because the rank order does not have to be preserved. The precise transformation is determined by the relationships with the other variables. Two ways of seeking optimal quantifications for unordered categorical variables have been proposed: either a single quantification is specified irrespective of the number of dimensions of the principal component solution, or each component has a different quantification. This is reminiscent of multiple discriminant analysis in the three-group case, where the first discriminant function can, for instance, indicate the contrast between, say A + B versus C, while the second discriminant function contrasts A versus B. In other words, the mean values of the groups show different patterns on each of the discriminant functions (De Heus et al., 2002; Linting et al., 2007).

In the present analysis, we have assigned multiple nominal scaling levels to the variables measuring the gene mutation and the possible presence of the autistic disorder. The different categories in these variables appeared to be best represented with the least restrictions on the transformations. For all other variables monotonic spline

transformations at an ordinal level were found to be adequate. From the unequal spread of the categories of the ordinal variables in Figure 5.3, it can be seen that the standard assumption of equal intervals for ratings scales such as the DBC is only marginally tenable.

Table B.1 *Univariate description of numerical variables*

Variable	***M***	***SD***	**min/max**	**possible range**
DBC disruptive/antisocial	13 .06	10.71	0 - 39	0 - 54
DBC self-absorbed	19 .55	11.69	0 - 50	0 - 62
DBC communication disturbance	4 .78	4.66	0 - 20	0 - 26
DBC anxiety	3 .89	3.17	0 - 17	0 - 18
DBC social relating	6 .79	4.03	0 - 15	0 - 20
DBC total problem behaviour score	48 .38	30.37	3 - 152	0 - 190
Physical severity score	9 .41	2.23	5 - 14	5 - 15
NPSI-S	78 .52	29.21	32 - 124	25 - 150

Note. DBC = Developmental Behaviour Checklist, raw scores; NPSI-S = Nijmegen Parenting Stress Index–Short, raw scores.

Missing values can be treated in different ways. As in our dataset the number of missing values per variable were small (physical severity score = 3, DBC sub-scales = 1, NPSI-S = 4) we treated them passively. In this way a person with a missing value is only left out in the calculation for that particular variable, but participates in the solution for all other variables.

The variable gender did not contribute very well to the analysis. The total explained variance with gender included as a single nominal variable, lowered to 58%, with component loadings of .08 (first dimension) and -.26 (second dimension). Taking the small transformed correlations of gender with the other ordinal variables (all < | .20 |) into account as well, it was decided to keep this variable outside the analysis. The correlations of the solution of the transformed ordinal and numerical variables are given in Table B.2.

Because nonlinear PCA is relatively sensitive to subjects who have unique or very different patterns across the variables from other subjects, the scores of the individual participants must be examined to detect such subjects which manifest themselves as outliers in the space of the component scores (De Heus et al., 2002). As no serious outliers were evident in the component-score plot, all persons were kept in the analysis.

In summary using categorical PCA as implemented in the SPSS program CATPCA (Meulman et al., 2005) all variables could be analysed together irrespective of their measurement levels. In this way it became possible to give a multivariate coherent description of the sample of persons with Cornelia de Lange syndrome.

Table B.2 *Correlations for the transformed ordinal and categorical variables in the categorical principal component analysis*

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
1 DBC* disruptive/antisocial	1.00													
2 DBC anxiety	.74	1.00												
3 DBC communication disturbance	.68	.59	1.00											
4 Parenting stress	.50	.54	.44	1.00										
5 Chronological age	.41	.23	.33	.49	1.00									
6 DBC self-absorbed	.41	.42	.49	.62	.32	1.00								
7 DBC social relating	.34	.29	.43	.53	.38	.72	1.00							
8 Adaptive functioning	.22	.17	.36	.52	.62	.65	.72	1.00						
9 Self-injurious behaviour	-.15	-.05	-.10	.15	.25	.36	.33	.59	1.00					
10 Physical severity score	-.46	-.40	-.21	-.15	-.19	.16	.17	.25	.48	1.00				
11 Gene mutation component 1	.32	.30	.16	.21	.21	.03	-.12	.02	-.01	.04	1.00			
12 Gene mutation component 2	-.42	-.40	-.12	-.21	-.31	.15	.22	.17	.45	.67		1.00		
13 Autistic disorder component 1	.31	.20	.43	.41	.28	.74	.71	.63	.43	.25	.00		1.00	
14 Autistic disorder component 2	.04	-.11	.32	.21	.19	.45	.52	.55	.33	.38		.37		1.00

Note. DBC = Developmental Behaviour Checklist.

6 Maternal parenting stress in families with a child with Angelman syndrome or Prader-Willi syndrome

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ABSTRACT

Parenting stress was investigated in mothers with a child with Angelman syndrome (AS) or Prader-Willi syndrome (PWS), which are genetically related. Mothers of 24 children with AS and 23 children with PWS (2 – 12 years) completed the Nijmegen Parenting Stress Index–Short, Developmental Behaviour Checklist and Vineland Screener 0-12. Parenting stress was high for 58% AS and 26% PWS cases. For both syndromes, no relationship existed with the child's gender, age, and behavioural problems. In PWS there was no effect of level of functioning. Overall, more mothers with child with AS perceived high parenting stress. When children showed low levels of behavioural problems this difference was contained. However, when children exhibited severe behavioural problems, parenting stress was the same for both syndromes. In AS professional family support is essential, since parenting is stressful for many mothers. In PWS, this is especially the case when behavioural problems are present.

INTRODUCTION

The upbringing of a child, besides being a joyful experience, can at certain times also involve parenting related stress (Deater-Deckard, 2004). Parents with a child with intellectual disability exhibit elevated levels of parenting stress, which tends to be chronic (Hassall & Rose, 2005; Hastings & Beck, 2004; Hatton & Emerson, 2003; Head & Abbeduto, 2007; Olsson, 2008). High levels of parenting stress can have severe implications, such as harsh or withdrawn parenting, and distressed parents are less likely to optimise the child's development (Deater-Deckard, 2004). Parenting stress in families with a child with developmental delays is also associated with negative outcomes for the parent, such as depression (Singer, 2006) and poor physical health (Oelofsen & Richardson, 2006). Children with a developmental disability are particularly susceptible to the influence of a less than optimal family environment (Paczkowski & Baker, 2007; Seligman & Darling, 2007, as cited in Head & Abbeduto, 2007). As such, it is essential to provide the most appropriate support possible in families with a child with intellectual disability when parenting stress is high.

Different theoretical models exist to investigate parental perception, including parenting stress, of the child-rearing experience. Common characteristics of such models

are the incorporation of child characteristics, environmental influences and parental cognitive processes (Hassall & Rose, 2005). In this study, we focus on the perception of maternal parenting stress and the relationship with child characteristics in two different genetic syndromes associated with intellectual disability: Angelman syndrome (AS) and Prader-Willi syndrome (PWS). Both syndromes are caused by changes in the genetic information in the same small area of chromosome 15, and may therefore be called related. In AS the defects are of maternal origin, whereas in PWS they are paternal (Glenn, Driscoll, Yang, & Nicholls, 1997), which results in two distinct (behavioural) phenotypes.

In families with a child with intellectual disability, the child factor most strongly related to parenting stress is the presence of behavioural problems as opposed to, for example, level of cognitive functioning (Hassall & Rose, 2005; Hastings & Beck, 2004; Hatton & Emerson, 2003; Olsson, 2008). Hodapp (1999) states that among children with a genetic syndrome, behavioural problems are also the best predictor of parenting stress. However, he also underlines that children with different genetic syndromes, with their distinct physical and behavioural phenotypes, elicit different reactions from their environment (Dykens, Hodapp, & Finucane, 2000; Hodapp, 1999). It therefore seems important to investigate the relationship between parenting stress and child characteristics for different genetic syndromes separately, since relationships with other child characteristics have been found as well. For instance, higher stress levels in parents of children with Cornelia de Lange syndrome or Joubert syndrome were also related to the child's older age and lower levels of (adaptive) functioning (Farmer, Deidrick, Gitten, Fennell, & Maria, 2006; Sarimski, 1997b; Wulffaert, Van Berckelaer-Onnes, Kroonenberg, Scholte, Bhuiyan, & Hennekam, 2009). Furthermore, a comparison of children with Down syndrome, Williams syndrome, and Smith-Magenis syndrome showed that the influence of child characteristics on stress is syndrome-specific, with different relationships with age and behaviour for the three syndromes (Fidler, Hodapp, & Dykens, 2000). Thus, to provide specific and more individualised support to these families, syndrome-specific investigations are needed.

Angelman syndrome is a rare genetic syndrome; 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, Hansen, & Wulff, 1995; Thomson, Glasson, & Bittles, 2006). A diagnosis of AS can be based on clinical criteria (Williams et al., 2006) but in the majority of cases can be confirmed by genetic testing (Clayton-Smith & Laan, 2003). The

following features are present in 100% of cases: developmental delay, a movement or balance disorder, severe speech impairment (none or only a few words), and behavioural uniqueness including frequent smiling/laughter, happy demeanour, easily excitable personality often with hand-flapping, and hypermotoric behaviour. In 80% of cases epilepsy is found, as well as an abnormal EEG and delayed head growth. According to the diagnostic criteria, a functionally severe developmental delay will be present (Williams et al., 2006). However, somewhat better cognitive and adaptive abilities have been found, although the majority seem to function on the severe delayed level (Peters et al., 2004; Thomson et al., 2006). A behavioural phenotype is just emerging for AS (Horsler & Oliver, 2006). Frequently mentioned, besides the aforementioned behaviours, are eating problems (e.g. eating inedible things), hyperactivity and attention problems, mouthing objects, and sleep disturbances. Persons with AS have an intense fascination for water and other reflective surfaces. It is still unclear whether there is an increased prevalence of autism spectrum disorders (Clayton-Smith & Laan, 2003; Didden, Korzilius, Sturmey, Lancioni, & Curfs, 2008; Dykens et al., 2000; Horsler & Oliver, 2006; Pelc, Cheron, & Dan, 2008). The clinical picture is most distinct in children between 2- to 16-years-old (Buntinx et al., 1995).

Prader-Willi syndrome has been studied much more extensively, especially concerning behavioural aspects. Its population prevalence is estimated to be between 1:8,000 and 1:52,000 (Åkefeldt, Gillberg, & Larsson, 1991; Whittington et al., 2001). A PWS diagnosis can be based on clinical criteria (Holm et al., 1993), but is preferably confirmed by genetic testing. The development of individuals with PWS takes place in two stages. The first phase of life is characterised by hypotonia, with poor sucking and failure to thrive; motor milestones are achieved later in life. The second phase starts at the age of one to six years; problems with gaining weight turn into life-long problems with overeating. This hyperphagia is due to insufficient functioning of the hypothalamus and can lead to life-threatening obesity; nowadays, most children are placed on a strict diet (Dykens et al., 2000; Goldstone, Holland, Hauffa, Hokken-Koelega, & Tauber, 2008). Intelligence quotients (IQ) for most persons with PWS are in the borderline, mild, or moderate 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). The level of adaptive functioning is very often lower than what would be expected according to the IQ due to behavioural problems (Dykens et al., 2000). Apart from food-related problems,

such as hoarding food, other specific behavioural and psychiatric problems can be present. Often mentioned are aggression, oppositional and argumentative behaviours, self-injurious behaviour (skin-picking), stubbornness, and temper tantrums. Obsessive-compulsive symptoms and disorder are highly prevalent in PWS. Furthermore, symptoms of psychoses and affective disorders are frequently described with full-blown co-morbid disorders as well. Results of studies of a heightened risk for autism spectrum disorders and attention-deficit/hyperactivity disorder are contradictory (Cassidy & Driscoll, 2009; Dykens et al., 2000; Dykens & Shah, 2003; Goldstone et al., 2008; Hiraiwa, Maegaki, Oka, & Ohno, 2007; Holm et al., 1993; Walz & Benson, 2002).

This is the first study, as far as we know, to investigate the perception of parenting stress in AS. In PWS two studies on parenting stress have been carried out, in which high stress levels were found (Hodapp, Dykens, & Masino, 1997; Sarimski, 1997a). Furthermore, in PWS, parenting stress appeared to be related to behavioural problems but not to gender, age, IQ, or degree of obesity of the child (Hodapp et al., 1997). For this study we have chosen to report on a relatively homogeneous group: all children are 2- to 12-years-old and are living at home. It is still unclear whether mothers and fathers of children with intellectual disability perceive similar parenting stress levels, since the results are mixed (Hassall & Rose, 2005; Hastings & Beck, 2004; Olsson, 2008). To rule out the unknown effect of gender, only the results for maternal parenting stress are included. Following these choices, the *first aim* of this study was to test the hypothesis that mothers with a child with AS or PWS perceive high levels of parenting stress. The *second aim* was to test the hypothesis that certain child characteristics are related to maternal parenting stress (within-syndrome). The *third aim* was to compare the level of maternal parenting stress between the two syndromes. The investigated child characteristics are: gender, age, behavioural problems, and level of intellectual disability. To our knowledge this is the first study to explore which characteristics of children with AS are related to maternal parenting stress. In PWS, it is expected that there will be no relationship with the child's gender or age, but that there will be a positive relationship with behavioural problems, as described by Hodapp et al. (1997). It appeared that IQ is not related to parenting stress (Hodapp et al., 1997), but the level of adaptive functioning might be a better indicator of the actual functioning of children with PWS. Therefore, adaptive functioning is used to classify the level of intellectual disability and the relationship of this characteristic with maternal parenting stress is explored. With this project we aim to

expand our knowledge about those child characteristics that are of specific relevance to the maternal perception of the child-rearing experience in these two syndromes and also add knowledge about the differences in maternal parenting stress between the syndromes. The ultimate goal is to contribute to better and more specific support for these families.

METHOD

Procedure

With permission of the board of the Dutch PWS/AS Parent Support Group, all its members were invited by means of a letter to participate in the current study. Ethical guidelines of the Royal Netherlands Academy of Art and Sciences (KNAW) were followed to recruit the participants, and written informed consent was obtained from the participants. Of the AS group, 75 parents (53%) joined the project, and 67 PWS parents (30%) reacted positively to the request. In the current study, data were used for children aged 2- to 12-years-old who were living at home, had a definite diagnosis of either AS or PWS, and whose mothers filled out the questionnaires. The percentage and number of participants fitting the criteria were comparable: 24 children with AS (32%) and 23 children with PWS (34%). Parents received the questionnaires by post and were asked to return them in the pre-paid envelope. Parents were requested to identify their child's gene mutation type. If a parent was uncertain about this, written permission was obtained to request this information from the child's medical specialist.

Participants

Twenty-four children with AS (11 boys, 13 girls) and 23 children with PWS (10 boys, 13 girls) and their mothers participated. The distribution of gender did not differ between the syndromes (χ^2 (1) = .03, p = 1.00). The age range was 2 to 12 years (AS M = 8.6, SD = 3.10; PWS M = 7.3, SD = 3.16), and the children of both syndromes did not differ in their age (t (45) = -1.38, p = .18). The following gene mutations were found for the children with AS: in 67% a deletion on the maternal chromosome 15, in 17% a paternal uniparental disomy, in 4% an imprinting defect, in 4% an *UBE3A* gene mutation, and in 8% no gene mutation was found but the AS diagnosis was given by a medical specialist. All children with PWS had gene mutations: in 57% a maternal uniparental disomy, in 35% a deletion on the paternal chromosome 15, in 4% an imprinting defect,

and in 4% a gene mutation was found but further specification of mutation type was absent.

Research instruments

All questionnaires used in this study conform to the official manuals. The following instruments were used.

The *Nijmegen Parenting Stress Index-Short* (NPSI-S; De Brock, Vermulst, Gerris, & Abidin, 1992) is an officially translated and adapted version of the Parenting Stress Index by Abidin (1983, as cited in De Brock et al., 1992). It measures parenting stress in families with children from approximately 2 to 13 years. Parents (in this case mothers) rate 25 items on a 6-point scale. All scores on the 25 items are summed to make up the total score. The total score is classified into seven norm categories defining parenting stress level. Dutch non-clinical and clinical norms are available with separate norms for mothers and fathers. The non-clinical norm group is made up of families from the normal population; the clinical norm group exists of parents with a child who is admitted to mental health services. The non-clinical norms for mothers were used in this study. Cronbach's alpha for internal consistency is .95. The NPSI-S shows good criterion validity with accurate prediction of membership of the clinical and non-clinical population. Construct validity is only investigated for the extended version of the instrument: concurrent validity ranges from satisfactory to good, and discriminant validity is considered reasonable (De Brock et al., 1992).

The Dutch version (Koot & Dekker, 2001) of the *Developmental Behaviour Checklist-Primary Carer* (DBC-P; Einfeld & Tonge, 2002) assesses emotional and behavioural problems exhibited over the past six months by children with intellectual disability. Parents rate 95 items on a 3-point scale. A total behaviour problem score and five subscale scores can be computed. A clinical cut-off point is only available for the total behaviour problem score; it has good sensitivity and specificity to distinguish clinical cases (Einfeld & Tonge, 2002). The intra-class correlation for inter-rater reliability is .55 for the total problem behaviour score. Internal consistency (Cronbach's alpha .95) and test-retest reliability (intra-class correlation .86) are high. Construct and criterion validity are satisfactory (Koot & Dekker, 2001).

The *Vineland Screener 0-12 years* (VS 0-12; Van Duijn, Dijkxhoorn, Noens, Scholte, & Van Berckelaer-Onnes, 2009) is a Dutch screening instrument adapted from

the Vineland Screener by Sparrow, Carter, and Cicchetti (1993). The VS 0-12 measures the level of adaptive functioning of children up to age 12 or older persons with comparable levels of functioning. An adaptive behaviour composite score is based on four domains (Communication, Daily Living Skills, Socialisation, Motor Skills). Unlike the Vineland Screener by Sparrow et al. (1993), the Dutch VS 0-12 does not include an optional section on maladaptive behaviour. Parents indicate on a three-point scale for 90 items whether the child exhibits that particular behaviour in everyday life. Good reliability and validity have been established for a normal population. Inter-rater reliability for the adaptive behaviour composite has an intra-class correlation of .98 and test-retest reliability of .95. Cronbach's alpha is .99 (Van Duijn, Dijkxhoorn, Noens, et al., 2009). The VS 0-12 years is an expansion of the VS 0-6 years which has adequate content, construct, and criterion validity (Scholte, Van Duijn, Dijkxhoorn, Noens, & Van Berckelaer-Onnes, 2008). A regression formula was developed based upon normal population data to estimate the adaptive level of functioning (Van Duijn, Dijkxhoorn, Van Berckelaer-Onnes, Scholte, & Noens, 2010). In the first data wave parents did not fill out the VS 0-12 but were interviewed with the Vineland Adaptive Behavior Scales (Sparrow, Balla, & Cicchetti, 1984). However, the interview appeared to be so time-consuming for the parents that it was replaced by the VS 0-12 questionnaire for the other participants. The relevant items from the interview were used to complete the VS 0-12 for the first 13 mothers with a child with PWS.

Data analysis

The data were analysed with SPSS 16.0, and an alpha of .05 was chosen for all analyses. Univariate outliers were given the next highest score plus or minus one, depending on whether the outlier was at the higher or lower end. The Shapiro-Wilks test was used to check whether the data deviated from a normal distribution and parametric tests could be used. The effect sizes for *t*-tests were given by *r* whereby .10 is viewed as a small effect, a .30 medium effect, and .50 as a large effect. For comparison of categorical data Pearson chi-square tests for association were used. If the expected count in one or more cells was less than 5, Fisher's exact tests were used. Phi was used as effect size for categorical data and the same rule of thumb for the size of the effects was applied (Field, 2009).

The level of intellectual disability was estimated on the basis of the level of adaptive functioning as measured with the VS 0-12. For children up to nine years of age, a developmental quotient (DQ) [VS 0-12 developmental age / chronological age x* 100] was computed and the level of intellectual disability was subsequently classified based upon Došen (2005) (see Table 6.1). Children aged 10 to 12 years can no longer obtain a DQ of 100 with the current VS 0-12 regression formula. For the children the classification was based upon the adaptive developmental age (see Table 6.1). It was decided to dichotomise variables, except age, because of the small number of participants. For the NPSI-S the two highest norm categories, high and very high stress, were coded as high maternal parenting stress. Scores for the other norm categories were coded as the low maternal parenting stress group. For the DBC-P, clinical caseness of behavioural problems was used to define groups with high versus low levels of behavioural problems. The level of functioning was dichotomised into profound/severe/moderate intellectual disability and mild/no intellectual disability.

Table 6.1 *Classification of intellectual disability based on Došen (2005)*

Level of intellectual disability	**Developmental quotient**	**Developmental age**
Severe/profound	0 - 35	0.0 - 4.9 years
Moderate	36 - 50	5.0 - 7.9 years
Mild	51 - 70	8.0 - 12.9 years
None	> 70	> 12.9 years

RESULTS

Maternal parenting stress in AS and PWS

Mothers with a child with AS perceived high levels of parenting stress (see Table 6.2). None of them scored in the norm categories very low to below the mean (norm group 35%). The scores of 29% of mothers fell in the category high parenting stress and another 29% in the category very high parenting stress. In PWS, only 9% of the mothers reported stress levels below the mean. The percentage of mothers who scored in the highest two categories (17% and 9%) was somewhat higher than in the norm group. After

dichotomisation maternal parenting stress was coded as high in 58% of mothers with a child with AS and 26% of mothers with PWS.

Table 6.2 *Parenting stress of mothers with a child with Angelman syndrome (n = 24) or Prader-Willi syndrome (n = 23*

Parenting stress NPSI-S category non-clinical norm group		**Angelman syndrome % (*n*)**	**Prader-Willi syndrome % (*n*)**
Category	Percentiles in norm population		
Very low	0% - ≤ 5% (5%)[a]	-	-
Low	5% - ≤ 15% (10%)	-	-
Below the	15% - ≤ 35% (20%)	-	9 % (2)
Mean	35% - ≤ 65% (30%)	29% (7)	22% (5)
Above the	65% - ≤ 85% (20%)	13% (3)	43% (10)
High	85% - ≤ 95% (10%)	29% (7)	17% (4)
Very high	95% - ≤ 100% (5%)	29% (7)	9% (2)

Note. NPSI-S = Nijmegen Parenting Stress Index-Short.
[a] Percentage of total norm population in parentheses

Child characteristics in AS and PWS

The DBC-P provides insight into which behavioural problems were the most prevalent among the children. In AS (*n* = 24) the following 15 items received a score of 1 or 2 in more than 70% of cases: becomes over-excited; chews or mouths objects, or body parts; easily distracted from task; eats non-food items; impatient; likes to hold or play with an unusual object; makes non-speech noises; overactive; poor attention span; poor sense of danger; repeated movements of hands, body, head, or face; sleeps too little, disrupted sleep; stubborn, disobedient or unco-operative; unrealistically happy or elated; unusual body movements, posture, or way of walking. In PWS (*n* = 23), there was more variation in behavioural problems; only six items were scored in more than 70% of cases: arranges objects or routine in a strict order; easily distracted from task; easily led by others; impatient; poor sense of danger; scratches or picks at skin; stubborn, disobedient or unco-operative; upset over small changes in routine or environment.

Substantial behavioural problems (clinical range) were found for approximately half of the children with AS (13, 54%) and a third of the children with PWS (8, 35%).

There was no significant association between type of genetic syndrome and number of behavioural problems (χ^2 (1) = 1.79, p = .24).

According to the VS 0-12 the adaptive level of functioning ranged in AS (n = 23; for one person, data were missing) from 0 to 2.76 years and in PWS (n = 23) from 0.28 to 8.40 years. On the basis of these data, the level of intellectual disability was estimated. All children with AS were categorised as having a severe/profound intellectual disability. In PWS, 15 children (65%) were categorised as having mild or no intellectual disability, and 8 children (35%) were categorised as having moderate/severe/profound intellectual disability.

Maternal parenting stress within and between AS and PWS

In AS there was no significant association between high or low levels of maternal parenting stress and the child's gender (Fisher's exact p = 1.00). There was no difference in age of the child between mothers with high versus low levels of stress (t (22) = .65, p = .52). No association was found between the level of maternal parenting stress and a high versus low amount of behavioural problems (Fisher's exact p = .70). Since all children with AS had a severe/profound intellectual disability, no association with level of maternal parenting stress could be investigated.

In PWS there was no significant association either between maternal parenting stress and the gender of the child (Fisher's exact p = .18). There was no difference in the child's age between the mothers with high versus low levels of stress (t (21) = -1.56, p = .13). No significant association was found between maternal parenting stress and behavioural problems (Fisher's exact p = .13). Level of maternal parenting stress was compared for children functioning on a moderate/severe/profound level versus children functioning on a mild/no intellectual disability level. There was no significant association (Fisher's exact p = .62).

A comparison was also made between the two syndromes with regard to the level of maternal parenting stress. As shown in Table 6.2, 58% or 14 AS mothers reported high levels of stress, while in PWS the comparable figure was 26% or 6 mothers. These figures suggest that mothers of a child with AS more often perceive high stress than mothers of a child with PWS. Statistical testing confirmed this hypothesis, (χ^2 (1) = 5.00, p = .03). With Φ = -.33, this was a medium effect.

A further analysis revealed that the behavioural problems of the children played a mediating role in the maternal perception of stress in both syndromes, as is shown in Tables 6.3 and 6.4.

If the children had no behavioural problems (see Table 6.3), a comparable picture emerged for the total group. Compared to mothers with a child with PWS, significantly more mothers with a child with AS reported high levels of parenting stress (Fisher's exact p = .01). In the subgroup of children without behavioural problems, this effect can be described as large with Φ = .52.

Table 6.3 *Distribution of maternal parenting stress for children with AS (n = 11) and PWS (n = 15) without behavioural problems*

		Maternal parenting stress		
		Low	**High**	**Total**
AS	*N*	4	7	11
	% within syndrome	36%	64%	100%
	% within maternal parenting stress	23%	78%	42%
PWS	*N*	13	2	15
	% within syndrome	87%	13%	100%
	% Within maternal parenting stress	77%	22%	58%
Total	*N*	17	9	26
	% within syndrome	65%	35%	100%
	% within maternal parenting stress	100%	100%	100%

Note. AS = Angelman syndrome; PWS = Prader-Willi syndrome.

However, when the children had behavioural problems (see Table 6.4), there was no association between the perceived levels of maternal parenting stress and the two syndromes (Fisher's exact p = 1.00), implying that the levels of stress perceived by the mothers are equal for AS and PWS when coping with a behaviourally difficult child is involved.

Table 6.4 *Distribution of maternal parenting stress for children with AS (n = 13) and PWS (n = 8) with behavioural problems at a clinical level*

		Maternal parenting stress		
		Low	**High**	**Total**
AS	*N*	6	7	13
	% within syndrome	46%	54%	100%
	% within maternal parenting stress	60%	64%	62%
PWS	*N*	4	4	8
	% within syndrome	50%	50%	100%
	% Within maternal parenting stress	40%	36%	38%
Total	*N*	10	11	21
	% within syndrome	48%	52%	100%
	% within maternal parenting stress	100%	100%	100%

Note. AS = Angelman syndrome; PWS = Prader-Willi syndrome.

DISCUSSION

To our knowledge, this is the first study to investigate the perceived parenting stress of mothers with a child with AS and to compare the stress between mothers with a child with AS and those with PWS. In line with the *first* hypothesis, the child-rearing experience is related to high levels of maternal parenting stress. Specifically, many more mothers with children with AS reported high stress levels as measured by the NPSI-S (58%) compared to the normal population (15%). In PWS, parenting stress was high for 26% of mothers.

The *second* aim was to investigate the relationship between maternal parenting stress and child characteristics. For AS, gender, age, and behavioural problems were assessed. No relationship was found between maternal parenting stress and these child characteristics. The lack of variation in level of intellectual disability prevented a comparison for that characteristic. The most prominent pattern in families with a child with intellectual disability, and in most genetic syndromes, is higher parenting stress when more behavioural problems are present (Hassall & Rose, 2005; Hastings & Beck, 2004; Hatton & Emerson, 2003; Hodapp, 1999; Olsson, 2008). This was, however, not applicable to AS; mothers with a child with a low amount of behavioural problems

reported the same amount of parenting stress as mothers whose child displayed a clinical amount of behavioural problems. Thus, other child characteristics might be related to parenting stress in this syndrome. It could be that difficulties with communication, both to make things clear to the child and to interpret the child's intentions, is a stress inducing and prominent characteristic. Also, the low level of functioning of the child in general could make the upbringing more stressful. To investigate this hypothesis, a control group with children with the same level of functioning and without speech is needed.

In PWS, maternal parenting stress was not related to the child's gender or age. This is in line with earlier research on PWS (Hodapp et al., 1997). The level of intellectual disability, based on adaptive functioning, was not related to maternal parenting stress in PWS. This result strengthens and extends our knowledge based on Hodapp et al., who found no relationship between parenting stress and IQ. Also, there was no relationship with behavioural problems, and this is at odds with what others have found (Hodapp et al.). There are several possible explanations for this difference. We used an instrument specifically developed for children with intellectual disability. As a proportion of the participants functioned in the borderline range to normal functioning, it might be that some characteristic behavioural problems were not measured by this questionnaire. However, the DBC-P appeared more relevant for the participants with intellectual disability. Another explanation for the difference in results between our study and Hodapp et al. could be the age composition of the two samples. In the current study families with *children* participated, whereas Hodapp et al. included adolescents as well. Steinhausen, Eiholzer, Hauffa, and Malin (2004) found DBC-P behavioural problems in PWS to be more prevalent in the age group 13-29 years compared to the age groups 2-7 and 7-13 years. Thus, more prominent behavioural problems in adolescents could give rise to the different results for the relationship between parenting stress and behavioural problems. However, further studies with different age cohorts are needed to confirm this hypothesis.

The *third* aim was to compare stress levels between mothers with a child with AS and those with PWS. Overall, more mothers with a child with AS reported high stress levels due to the child-rearing experience. However, the presence of a clinical behaviour problems was a mediating factor for maternal parenting stress in the two syndromes. Among children with low levels of behavioural problems, mothers with a child with AS perceived more stress. When the child had a clinical amount of behavioural problems, there was no difference in parenting stress between mothers with a child with AS and one

with PWS. Thus, it can be said that mothers with a child with AS have overall high stress levels, whereas mothers with a child with PWS experience this only when their child has significant behavioural problems. This result could be added to the knowledge that parents with a child with AS have higher levels of loss of control compared to parents with a child with PWS (Van den Borne et al., 1999). Although the syndromes are genetically related, they differ in many respects, such as the level of functioning and behaviour. AS in general seems to be stress-inducing, whereas in PWS more specific behavioural problems relate to stress. We hypothese that some of the most prominent characteristics of AS, severe/profound intellectual disability and absence of speech, might explain why raising a child with this syndrome is a heavy burden, independent of the presence or absence of behavioural problems.

The findings suggest that professional support for families with a child with AS is needed, because stress levels are high in a large proportion of mothers, which can have a negative influence on parenting behaviour (Deater-Deckard, 2004). In PWS, the need for support is more prominent when the child exhibits substantial behavioural problems. In that case, parents should get additional support to manage the behavioural problems, which may result in reduced parenting stress (Hastings & Beck, 2004). It seems important to provide parents with information on parenting stress as related to their child's syndrome. Parents with a child with AS or PWS have a substantial need for information on other child-related issues (Van den Borne et al., 1999). Information on parenting stress in young families might give a realistic description of family life and consequently might better prepare them for future challenges. Wigren and Hansen (2003) reported that parents with a child with PWS mainly wanted general information and support as opposed to family-directed support. It is important that future studies measure parenting stress *and* the desire for support of parents simultaneously. If both components are studied concurrently, professional care and parental satisfaction with this care might be improved. Furthermore, for families with a child with one of the two syndromes, professional support should be a continuous process, since the perception of stress is not related to the child's age. Professional aid is presumably also needed during adolescent years, since Hodapp et al. (1997) found no relationship between parenting stress and the child's age for children with PWS from 3 to 18 years.

There are some limitations of the current project. First, we used only a limited set of child characteristics to relate to maternal parenting stress, while important

environmental and parental characteristics also influence the stress process; for example the socio-economic status of the family and parental cognitions (Hassall & Rose, 2005; Perry, 2004). In addition, measuring positive outcomes among parents is also crucial because it has been shown that there is a large variation in parental experiences with raising a child with intellectual disability. Many parents adapt well to the highly specific demands of parenting a child with disability and, for instance, experience personal growth (Hassall & Rose, 2005, Hatton & Emerson, 2003; Head & Abbeduto, 2007; Olsson, 2008). When more of the relevant child, parental, and environmental characteristics are included in an analysis, a more coherent description of these families will be obtained. Second, causality could not be established because of the cross-sectional nature of the study. For persons with intellectual disability in general the results are mixed whether the child's behaviour problems cause parenting stress or whether there is a bi-directional effect (Hassall & Rose, 2005; Hastings & Beck, 2004; Olsson, 2008). To investigate the causality of relationships, a longitudinal study is needed (Hatton & Emerson, 2003). This is an important aim since it can refine the design of family support. Third, the information with regard to the child's behavioural problems and parenting stress was provided by the same type of informant; that is the mother. This may have influenced the results. Further studies are needed with additional informants like fathers and/or teachers to assess independently of the mother the child's behavioural problems and to relate these findings to the behavioural problems the mothers report and the stress they perceive. Fourth, like other studies of rare genetic syndromes, the small number of participants results in a lack of statistical power. According to Cohen (1992) with an alpha of .05, preferred power of .8 and 26 participants, large effect sizes are needed to obtain statistically significant outcomes with chi-square tests (1 *df*). Results should thus be interpreted with caution. Finally, participants were gathered by the Dutch PWS/AS Parent Support Group. Parents who belong to such support groups are very often highly motivated and from middle to high socio-economic background (Dykens, 1999), and thus may not be representative of all Dutch families with a child with AS or PWS. In addition, only a proportion of all members of the support group agreed to participate. Families in this self-selected sample may have additional specific characteristics which unfortunately remain unknown. However, concerning the children's behaviour we assume to have had a representative sample of children with AS and PWS. The behavioural problems most frequently encountered in this study showed roughly the same pattern as in other studies of the AS

and PWS behavioural phenotypes. It is, however, remarkable that the item on overeating was not scored for more than 70% of the children with PWS, which is contrary to expectations. Possibly parents are so used to this behaviour, as it is a core symptom of the syndrome, that they do not report it any more. In sum, although the behaviour of the children seems representative, caution is needed concerning generalisation of the results as these may be biased by the selection procedure.

In conclusion, this study contributes to our knowledge about the maternal perception of raising a child with AS or PWS. In clinical practice these results can guide the intervention process and ultimately optimise the development of children with these syndromes and the families they grow up in. We should aim to capture the interplay of a lot of different factors to better approach the situation in real life. We agree with Olsson (2008) that it is most important to focus on the processes that lead to different outcomes in families and to include negative and positive outcomes at the same time. Why do some families adapt well to their specific situations? Unraveling these complex processes can provide important clues for clinical practice.

7 General conclusions and discussion

INTRODUCTION

The main aim of this study was to expand our knowledge of the behavioural phenotypes of five genetic syndromes associated with intellectual disabilities (ID) and to determine the relationship with perceived parenting stress, in order to improve support through recommendations for clinical practice. The five syndromes are Rett syndrome, CHARGE syndrome, Cornelia de Lange syndrome, Angelman syndrome, and Prader-Willi syndrome. We have reported on the syndromes *separately* in chapters 2 to 5 (only in chapter 6 are two syndromes compared directly). In this final chapter we will present an overview of our findings with regard to the child characteristics and parenting stress, and compare the five syndromes in this respect. Thereafter, a critical reflection of the present study is given and suggestions for future research are provided. The chapter ends with implications for clinical practice.

OVERVIEW OF FIVE GENETIC SYNDROMES

For all five syndromes the behavioural characteristics were investigated by the same assessment instruments, but for each syndrome specific emphasis has been placed upon *different* child characteristics in chapters 2 to 6. Subsequently, a description is provided of the behavioural phenotype of the same aspects for all five syndromes, based upon the shared data presented in chapters 2 to 6, i.e. on adaptive functioning and level of ID, the presence of the autistic disorder, and behavioural problems. The similarities and differences between the syndromes will be discussed and remarkable findings per syndrome will be highlighted as far as these were not already mentioned in chapters 2 to 6. Finally the relationships between the behavioural phenotype and the perceived parenting stress will be compared between the genetic syndromes investigated.

The behavioural phenotypes of five genetic syndromes

A summary of the different child characteristics per syndrome is given in Table 7.1. The behavioural phenotypes for the genetic syndromes are compared, although this comparison is somewhat hampered by the uneven age range and gender composition of the samples and therefore must be viewed with some reserve.

With regard to the level of **adaptive functioning**, a clear distinction emerges for the maximum level reached. Those with Rett syndrome or Angelman syndrome reach adaptive developmental ages of two to three years. Those with CHARGE syndrome, Cornelia de Lange syndrome, or Prader-Willi syndrome have a much higher maximum level, i.e. adaptive developmental ages of eight to nine years.

By estimating the level of **intellectual disability**, based on the adaptive functioning and taking chronological age into account (see e.g. chapter 4), a similar distinction was found. All individuals with Rett syndrome or Angelman syndrome have a severe to profound ID. In the other three syndromes there is more variation and all levels of functioning (profound ID to no/mild ID) are present. However, in these syndromes the distribution of ID level is syndrome-specific. For CHARGE syndrome the lowest (severe to profound ID) and highest levels of functioning (no to mild ID) are equally present. Thus, for children with CHARGE syndrome the level of functioning is hard to predict. Persons with Cornelia de Lange syndrome mostly function in the severe to profound disabled range, although higher functioning individuals are also present. The majority of the children with Prader-Willi syndrome have no to a mild ID, but a proportion functions at the lower levels.

In other studies of both Rett syndrome and Angelman syndrome higher levels of functioning have occasionally been found (Demeter, 2000; Duker, Van Driel, & Van de Bercken, 2002; Peters et al., 2004; Thomson, Glasson, & Bittles, 2006), but these levels of abilities seem exceptional and were not seen in our study. For CHARGE syndrome a broad range of functioning has been described (Johansson et al., 2006; Salem-Hartshorne & Jacob, 2005; Smith, Nichols, Issekutz, & Blake, 2005), but the current study indicates that there is a *substantial* percentage that functions in the (near) normal range.

In the literature on the general population of people with ID, the prevalence rate of the **autistic disorder** is linked to the level of ID, but the exact prevalence is unclear because rates differ considerably between studies. Deb and Prasad (1994) found that 37% of the children with severe to profound ID had the autistic disorder, 16% of the children with moderate ID, and 8% of the children with mild ID. De Bildt, Sytema, Kraijer, and Minderaa (2005) found a prevalence rate of pervasive developmental disorders (including the autistic disorder and PDD-NOS) of 26% for children with moderate to profound ID and 9% for children with mild ID. The global outcome is that the highest prevalence rates

for the autistic disorder are found at the lower end of the ID spectrum (De Bildt et al., 2005).

In the current study we screened for the autistic disorder with the Developmental Behaviour Checklist - Autism Screening Algorithm (DBC-ASA; Einfeld & Tonge, 2002) and the Diagnostic Interview for Social and Communication Disorders - 10th Revision (DISCO-10; Wing, 1999). Table 7.1 shows the percentage of agreement (autistic disorder present or not present) and disagreement on classification (uncertain) between the instruments. The two instruments suggest that the autistic disorder is present in somewhat more than a third of the females with Rett syndrome and this is a similar to somewhat higher proportion expected for persons with this level of ID (Deb & Prasad, 1994; De Bildt et al., 2005). For a discussion on the controversial issue to classify the autistic disorder in females with Rett syndrome, see chapter 2. When a child has Angelman syndrome, the autistic disorder is suspected to be present in two-thirds of the individuals. This is a much higher proportion than in the general population of children with severe to profound ID. For the three other syndromes, the comparison is more complicated since a broad range of ID levels is thereby present. In Cornelia de Lange syndrome in more than half of the cases a co-morbid autistic disorder is suspected. This is a higher proportion than expected, even if the highest prevalence rates, related to severe and profound ID, are taken into account. For CHARGE syndrome and Prader-Willi syndrome percentages are considerably lower, although still substantial.

In all of the syndromes investigated, with the exception of Rett syndrome, there seems to be an increased risk of a co-morbid autistic disorder given the level of functioning within the syndromes. However, these figures for the presence of the autistic disorder need to be considered cautiously. In the current study screening instruments were used and thus only estimates can be given; individual assessment should always follow the screening to obtain a diagnosis. This step is certainly needed to be definite about the risk for co-morbidity with the autistic disorder in these genetic syndromes.

A population study of individuals with ID revealed that 41% had a severe amount of **behavioural problems**, i.e. measured as the percentage of individuals with scores in the clinical range (Einfeld & Tonge, 1996). In our study, a higher percentage of individuals with Cornelia de Lange syndrome and Angelman syndrome exhibited a severe amount of behavioural problems (see Table 7.1). A lower percentage of persons with Rett

Table 7.1 *Overview of child characteristics per syndrome based upon chapters 2 to 6*

		RS	CS	CdLS	AS	PWS
N		52	22	37	24	23
Gender	Male	-	16	21	11	10
	Female	52	6	16	13	13
Age in years	range	2 - 49	1 - 22	1 - 46	2 - 12	2 - 12
	(*M; SD*)	(16.5; 11.8)	(11.0; 5.5)	(18.1; 13.0)	(8.6; 3.1)	(7.3; 3.2)
Adaptive functioning	range	2 - 28	3 - 103	4 - 112	0 - 33	3 - 101
(in months)	(*M; SD*)	(7.6; 4.4) [a]	(53.5; 38.9) [b]	(26.4; 26.1) [c]	(9.4; 10.3) [b]	(53.6; 24.5) [b]
Intellectual disability [d]	severe-profound	100%	40%	68%	100%	26%
	moderate	-	15%	6%	-	9%
	no-mild	-	45%	16% [c]	-	65%
Autistic disorder [e]		39%	36% [g]	54%	67%	22%
	uncertain [f]	23%	9%	16%	25%	26%
	not present	38%	55% [g]	30%	8%	52%
Severe behavioural problems [h]		25%	27%	47%	54%	35%

RS=Rett syndrome; CS=CHARGE syndrome; CdLS=Cornelia de Lange syndrome; AS=Angelman syndrome; PWS=Prader-Willi syndrome.

[a]Based on Vineland Screener 0-6;

[b]Based on Vineland Screener 0-12;

[c]Based on VABS.

[d]For children aged 1 to 9 years a developmental quotient was calculated based upon relevant version of Vineland Screener. For children aged 10 years and older the developmental age was used to classify the level of intellectual disability, see chapter 4 for more explanation.

[e]Based upon DBC-ASA and DISCO-10;

[f]The two instruments disagree about classification of autistic disorder;

[g]For one individual based upon only DBC-ASA.

[h]Clinical number of behavioural problems based on cut-off DBC.

syndrome, CHARGE syndrome, or Prader-Willi syndrome showed clinically significant behavioural problems in comparison to the general ID population. Thus, the presence of Angelman syndrome or Cornelia de Lange syndrome can be seen as factors that heighten the risk of severe behavioural problems. To get more insight into the behavioural problems that are specific for each syndrome, in Table 7.2 problems are tabulated which are prevalent in more than 70% of the individuals (i.e. receive a rating that the behaviour is 'somewhat or sometimes true' or 'very true or often true'). Those with CHARGE syndrome show the most variation in behavioural problems; only one behavioural problem (impatience) is present in more than 70% of the individuals. In Rett syndrome, Cornelia de Lange syndrome, and Prader-Willi syndrome six to eight behavioural problems are highly prevalent. Some of these behaviours are highly prevalent in one of the other syndromes as well, but in all three syndromes some *specific* problems appear highly prevalent. Children with Angelman syndrome are the most alike as far as behavioural problems are concerned. For them, 15 behaviours are prevalent in the majority of the children; eight of these behaviours are not present in the majority of any of the other four syndromes, i.e. can be marked as a unique characteristic of the syndrome.

Because the behavioural problems were measured with the same instrument, and the ID level is taken into account, valid between-syndrome comparisons can be made. Of the two syndromes associated with severe to profound ID, those with Angelman syndrome are more alike in their behavioural problems than individuals with Rett syndrome. For the three syndromes with mixed levels of functioning, those with CHARGE syndrome are much more varied in their behavioural problems than those with Cornelia de Lange or Prader-Willi syndrome. Overall, the behavioural phenotype is most distinct for Angelman syndrome, whereas in CHARGE syndrome one can barely speak of a behavioural phenotype.

Parenting stress and associated child characteristics in five genetic syndromes

The level of parenting stress that is perceived by parents with a child with one of the syndromes is depicted in Table 7.3. Parenting stress is rated as high when the scores fall into the two highest categories of the normal population norm group, covering 15% of parents in the general population who report stress related to the child-rearing situation. Raising a child with one of the genetic syndromes investigated is a substantial risk factor

Table 7.2 *Developmental Behaviour Checklist items that are applicable to more than 70% of the participants per syndrome*

Rett syndrome (*N* = 52; 2 - 49 years)	
Item	**%**
Repeated movements of hand, body, head, or face	92
Poor attention span	87
Laughs or giggles for no obvious reason	81
Makes non-speech noises	79
Underreacts to pain	75
Aloof, in her own world	73

Angelman syndrome (*N* = 24; 2 - 12 years)	
Item	**%**
Chews or mouths objects, or body parts	96
Poor attention span	96
Easily distracted from his/her task	92
Makes non-speech noises	92
Sleeps too little, disrupted sleep	92
Overactive	88
Poor sense of danger	88
Unusual body movements, posture, or way of walking	83
Likes to hold or play with unusual object, overly fascinated with something e.g. water	79
Repeated movements of hand, body, head, or face	79
Becomes over-excited	75
Eats non-food items	75
Impatient	75
Stubborn, disobedient, or unco-operative	75
Unrealistically happy or elated	75

Cornelia de Lange syndrome (*N* = 37; 1- 46 years)	
Item	**%**
Prefers to do things on his/her own, tends to be a loner	81
Mood changes rapidly for no apparent reason	78
Aloof, in his/her own world	75
Makes non-speech noises	75
Poor attention span	75
Avoids eye contact	72

Prader-Willi syndrome (*N* = 23; 2 - 12 years)	
Item	**%**
Arranges objects or routine in a strict order	91
Easily distracted from his/her task	87
Impatient	83
Poor sense of danger	83
Upset over small changes in routine or environment	83
Easily led by others	74
Scratches or picks at his/her skin	74
Stubborn, disobedient, or unco-operative	74

CHARGE syndrome (*N* = 22; 1 - 22 years)	
Item	**%**
Impatient	86

Note. Items that are applicable are given a score 1 or 2. Items in italics are 'unique' in being prevalent in more than 70% of the syndrome compared to the other syndromes.

for experiencing high levels of parenting stress. Parents with a child with Prader-Willi syndrome report less stress than parents with a child with one of the four other syndromes, although the percentage who perceive high stress is still higher than in the normal population. However, in addition to underlining this risk factor, it should be mentioned that there are also a lot of parents with a child with one of the syndromes who do not perceive the child-rearing situation as highly stressful.

Having investigated the (sometimes problematic) characteristics of the children, it is a logical step to assume that there are relationships between child characteristics and parenting stress. Hodapp (1999) has suggested that the degree of parenting stress in genetic syndromes is best predicted by the child's behavioural problems. Table 7.3 shows that for the various syndromes different child characteristics relate to parenting stress. For example for parents with a child with Cornelia de Lange syndrome, stress is significantly higher when the child functions at a lower level, whereas in CHARGE syndrome the level of functioning is not related to parenting stress. Although in both syndromes considerable variation in level of functioning exists, it depends on the syndrome whether this factor relates to parenting stress or not. This suggests that relationships between child characteristics and parenting stress are syndrome-specific.

CRITICAL REFLECTIONS AND DIRECTIONS FOR FUTURE RESEARCH

Some limitations became apparent in the current research project, that can be used to improve future studies. In this study the *relationship* between child characteristics and parenting stress was investigated by means of a cross-sectional descriptive design. Carrying out detailed descriptive research is as important as searching for causality in stress research (Lazarus, 2000). However, knowledge about causes can lead to better well-aimed interventions. In the current study, Perry's model (2004) (see Figure 1.1) was used as a framework wherein child characteristics are depicted as stressors with parenting stress as a negative outcome, and thereby suggest causality. But using this model to investigate these variables does not imply that conclusions about *relationships* in the current study can be extended to conclusions about *causality* without direct testing. For children with ID in general, the issue of causality of parenting stress and child characteristics is as yet not resolved. In some studies child characteristics, often behavioural problems, are found to cause parenting stress, whereas a substantial number of studies has reported a bi-

Table 7.3 *Overview of parenting stress per syndrome based upon chapters 2 to 6*

	RS	CS	CdLS	AS	PWS
N	24 [a]	22	37	24	23
High parenting stress [b]	46%	59%	51%	58%	26%
Child characteristics tested on relationship with parenting stress	- age -adaptive functioning - behavioural problems - autistic disorder - Rett-specific behaviours	-gender - age -adaptive functioning - intellectual disability - behavioural problems - ability to speak - auditory and visual problems - deafblindness	- gender - age - intellectual disability - behavioural problems - autistic disorder - severity of physical problems - gene mutation type	- gender - age - behavioural problems	- gender - age - intellectual disability - behavioural problems
Relationships between child characteristics and parenting stress	more total behavioural problems and in subscales self-absorbed, autism, social relating, anxiety and disruptive behaviour, more Rett-specific general mood problems → higher parenting stress	more behavioural problems in subscales depression, autism, self-absorbed, and disruptive behaviour → higher parenting stress	older age, more severe intellectual disability, more behavioural problems, presence autistic disorder → higher parenting stress	no relation between measured child characteristics and parenting stress	no relation between measured child characteristics and parenting stress

RS=Rett syndrome; CS=CHARGE syndrome; CdLS=Cornelia de Lange syndrome; AS=Angelman syndrome; PWS=Prader-Willi syndrome.
[a]Based upon a subgroup of females with Rett syndrome, 24 children aged 2 to 18 years, see chapter 4.
[b]Scores falling in the two highest norm categories of normal population on Nijmegen Parenting Stress Index - Short.

directional effect (Hassall & Rose, 2005; Hastings & Beck, 2004; Hastings, Daley, Burns, & Beck, 2006; Olsson, 2008). Therefore, longitudinal studies in the field of genetic syndromes are needed to test causal directions in these specific populations.

The behavioural phenotype of five genetic syndromes was described (see Table 7.1 and Table 7.2). If the definition of Dykens (1995) for behavioural phenotypes is used, the statement that a particular behavioural problem belongs to the behavioural phenotype requires an adequate control group (e.g. on level of functioning and age) (Einfeld & Hall, 1994). We were able to compare syndromes with comparable levels of functioning (i.e. Rett and Angelman syndrome; CHARGE, Cornelia de Lange and Prader-Willi syndrome) and as such statements about syndrome-specific behaviour can be made. However, the individuals were not directly matched for level of functioning, age, and gender and those with a genetic syndrome were compared mutually. In future studies a matched control group with a non-specific cause for ID is required and more in-depth comparisons between the five syndromes are needed to reconfirm the statements about the behavioural phenotypes that became evident in the current study.

In Perry's model (2004; see Figure 1.1) our focus was on child characteristics as stressors because these are the core and distinguishing features of children with genetic syndromes. We have chosen to investigate child characteristics that were relevant because they can be highly disturbing, i.e. behavioural problems, autistic disorder symptoms, and low levels of independence. In future studies it is essential to broaden the child characteristics measured. Although numerous child characteristics can be mentioned, a few syndrome-specific recommendations are provided. In both Rett syndrome and CHARGE syndrome physical disabilities are often present and can be very severe. Measurement of the relationship between physical characteristics and parenting stress could shed light on the impact of the child's physical problems on the upbringing situation. In Cornelia de Lange syndrome the autistic disorder is highly prevalent. Parents with a child with Cornelia de Lange syndrome and the autistic disorder perceive more parenting stress. To improve support it would be helpful to investigate which specific aspects of the autistic disorder are perceived as stressful. In Angelman syndrome an important child characteristic to include in studies would be a detailed measure of non-verbal communication abilities. Having a child who does not talk and is also unable to communicate non-verbally might be a strong influencing factor; this is highly relevant for the Angelman syndrome since non-verbal abilities differ substantially in this population.

In Prader-Willi syndrome it would be useful to measure the intensity of support that is needed to manage the child's eating habits and to determine the extent to which this poses a burden for the child-rearing situation.

Besides expanding and specifying child characteristics, research will also improve by including additional elements of Perry's model (2004) to gain more insight into risk as well as protective factors. Other stressors than characteristics of the child with the genetic syndrome can be influential. Some of these stressors are specific for families with a child with ID (e.g. additional expenses for adapting the home) whereas others can appear in every family (e.g. unemployment) and both types should be investigated in future studies. The inclusion of measures for mediating resources and (in)formal support (see Figure 1.1) will provide a more comprehensive description of the stress process. Measurement of parental coping strategies and the amount and type of formal and informal support seem thereby to be the minimum essentials needed to gain insight into stress protective factors. Although our focus was on negative outcomes for parents (i.e. parenting stress), positive outcomes should be measured simultaneously since parents can also experience positive aspects of having a child with a genetic syndrome. If more measurements of all aspects of Perry's model are included, this will do more justice to the reality of the child-rearing situation in these families. We follow Olsson's (2008) view that in future studies it is important to focus on the *processes* that lead to different outcomes in families with a child with a certain genetic syndrome. Why do some families adapt well to their specific situation and others do not? There is still a lot to discover about causality and influencing risk and protective factors by means of research in families with genetic syndromes.

Limitations are further posed by the size and recruitment of the samples. The numbers of participants included in the analyses (see chapters 2 to 6) were, respectively, 52, 24, 22, 37, 24, and 23 families. Given the rarity of the five genetic syndromes and the size of the Netherlands population, these are acceptable figures. However, the small sample sizes result in a lack of statistical power. This poses serious threats for the conclusions that can be drawn from this study; this is a challenge for a lot of other studies into genetic syndromes as well. It remains thus uncertain whether there truly is no effect or whether our group was simply too small to detect it. Therefore, closer international collaboration between researchers investigating genetic syndromes is needed to expand sample sizes. Although worldwide data bases are already used for research into gene mutations, e.g. in Rett syndrome, a comparable initiative is needed in the behavioural

sciences. There are research instruments that have been translated world-wide and that have clearly been proven to be useful within the ID population, such as the Developmental Behaviour Checklist (Einfeld & Tonge, 2002). Solely by using such instruments and sharing data world-wide will behavioural studies of genetic syndromes be able to make a big step forward.

Recruitment of the participants took place via the various Dutch Parent Support Groups. Members of such support groups have been characterised as being highly motivated and of middle to high socio-economic status (Dykens, 1999). Only a proportion of the members of the support groups participated in our project. The problem is that one cannot know the representativeness of members of a support group, in particular the self-selected sample of the support group. In CHARGE syndrome we collaborated with a specialised outpatient clinic to gather more participants. Again, it is not known what specific characteristics these families have, but it is highly likely that there is also a selection of people who visit such a clinic. The investigated genetic syndromes are rare and both ways of recruiting people induce uncertainty about the representativeness of the sample. Using all available tracks simultaneously, parent support groups, specialised clinics, organisations and institutions for people with ID, seems the best way to gather as many participants as possible, because the perfect way for recruitment in this field simply does not exist (Finegan, 1998).

CLINICAL IMPLICATIONS

Based upon the results of the present study, the following recommendations for clinical practice can be given. First, the general implications applicable to all the five syndromes will be presented, then some additional syndrome-specific recommendations will be discussed (see also chapters 2 to 6).

General recommendations

Because the behavioural phenotypes of the syndromes investigated in the present study vary considerably, it is important that professionals provide parents of a child with a genetic syndrome with a detailed description of the behavioural strengths and weaknesses that are associated with their child's syndrome. Specialised psychoeducation can show that associated behavioural problems are not displayed on purpose by the child and parents are

not to blame for the presence of these behaviours. Parents can then also try to anticipate the child's behaviour and developmental abilities (Finegan, 1998; Skuse, 2000).

Awareness of the seemingly high prevalence of a co-morbid autistic disorder in at least a proportion of the syndromes is essential because this has a big impact on those with ID (De Bildt, 2003; Van Berckelaer-Onnes, 1996). Although we only *screened* for the autistic disorder, our results nevertheless suggest that in all the syndromes investigated, except Rett syndrome, there is a heightened prevalence of autistic disorder symptoms compared to those with the same level of functioning without a genetic syndrome. However, there are ongoing discussions whether the autistic disorder should be classified in people with genetic syndromes or whether the symptoms in genetic syndromes have different profiles and thus should be labelled as autistic traits (see Moss & Howlin, 2009, for a detailed discussion). Regardless of the outcome of this discussion, the advice for clinicians will be the same: Individuals with a genetic syndrome and a co-morbid autistic disorder (*or* autistic traits) should be given the same support and interventions as people with ID and the autistic disorder with additional adaptations needed per genetic syndrome. Kraijer (2004) provides three core strategies for people with autism spectrum disorders and ID. First, structure and predictability are essential in daily life routine. Second, the demands that are placed upon people with this double diagnosis should be adapted to their often disharmonic functioning. Third, alternative ways of communication are necessary. The quality of life for this population can be increased when augmentative communication is attuned at the right level of sense-making (Noens & Van Berckelaer-Onnes, 2004). Adaptation of the environment is thus essential. Clinicians should thereby integrate the specific approaches for people with these three diagnoses (i.e. a genetic syndrome, ID, and the autistic disorder) and tune into the individual's need for support.

Professionals involved in the support of a child with a genetic syndrome should not only focus on the child's needs, but also on the family system. Although there are parents who do not perceive the child-rearing situation as stressful, our study also shows that there are many parents who perceive high levels of parenting stress. Parenting stress can have severe negative consequences for both parents and child (e.g. Deater-Deckard, 2004; Oelofsen & Richardson, 2006; Pazcowski & Baker, 2007; Singer, 2006). Therefore, professionals should give family assessment a prominent place in order to detect highly distressed parents for whom support is needed. If this is the case, several steps can be taken. First, it is important to provide parents with information concerning their child's

genetic syndrome (Bass, 1990). Providing information on the child's strengths and weaknesses in behaviour has been mentioned before, but information should also be provided on e.g. the aetiology, medication, and possible therapies. A parent support group for the particular syndrome can be a very important additional source of information for parents. Professionals therefore need to inform parents about the existence of such groups and encourage membership. This is especially important since parent support groups not only provide information, but members can provide emotional support for each other. Sharing experiences with someone who experiences similar problems (i.e. other parents) can give a sense of belonging and enhances the caregivers abilities to cope with stress. Parent support groups thus can give parents more confidence concerning their caring tasks and as such play an important role in empowerment of parents (Bass, 1990). Second, in three of the currently investigated syndromes parenting stress is higher when children exhibit behavioural problems. Parents with a child with Rett syndrome, CHARGE syndrome, and Cornelia de Lange syndrome with high levels of behavioural problems need support to manage these behavioural problems which in turn will reduce parenting stress (Hastings & Beck, 2004). Third, parents should be supported to limit the levels of stress and highly distressed parents should be offered stress management strategies which can be helpful in coping with different situations throughout the upbringing process. This is needed, as in all five syndromes parenting stress did not reduce when the child grew older. Having a child with a genetic syndrome remains stressful and this emphasizes the need for the family support to be a continuous process in order to provide information and advice at different stages of life.

Many different disciplines are involved in the care of children with genetic syndromes associated with ID, because both medical and behavioural problems often exist. A lot of the children participating in the current project were seen not only by many different experts but also by a lot of different disciplines. This corresponds to, for example, the finding that in CHARGE syndrome on average 17 different professionals were seen on a regular basis in caring for these children (Hartshorne, 1993 in Hartshorne & Hartshorne, 1998). It can be distressing for parents to obtain (sometimes contrasting) information from so many experts. For some parents it takes a vast amount of time to manage all information and appointments for their child and this is often experienced as highly distressing. It is important that these families are supported by one professional

who becomes a key figure in streamlining and, most importantly, integrating all of the information and thus relieves some of the heavy burden these parents face.

Additional syndrome-specific recommendations

Rett syndrome There is discussion concerning the placement of Rett syndrome under the pervasive developmental disorder section in the major classification systems for mental and health disorders (see chapter 2; Wulffaert, Van Berckelaer-Onnes, & Scholte, 2009). Our results suggest that some females with Rett syndrome have an additional autistic disorder and professionals need to be alert for the presence or absence of this co-occurrence. The prevalence of this co-morbid disorder is in line with studies of individuals with severe to profound ID without Rett syndrome. We underline this co-morbidity explicitly as in the major classification systems the presence of Rett syndrome precludes the possibility of a co-morbid classification of the autistic disorder. For the next version of the Diagnostic and Statistical Manual of Mental Disorders, the DSM-V, it is already proposed to remove Rett syndrome from the pervasive developmental disorders (American Psychiatric Association, 2010).

As mentioned before, parents need support to manage the behavioural problems of their child with Rett syndrome. Additionally, we adopt the advice by Sarimski (2003) and Laurvick, Msall et al. (2006) that support should also focus on the challenges caused by the physical disabilities in Rett syndrome. Furthermore, in these studies a positive impact on the family system was found when mothers had time for their own activities besides caretaking, such as having work outside the house and free time, which thus should be encouraged.

CHARGE syndrome Parents and professionals working with children with CHARGE syndrome need to be aware of the variability in level of functioning in the syndrome. A substantial proportion of these individuals function in the normal to near normal range. In the early years of family life the focus lies mainly on the child's medical problems, and understimulation of the cognitive development is a substantial risk. Given the broad range of abilities, the cognitive and behavioural development of these individuals should be given attention as soon as possible after medical problems are stable or under control. The autistic disorder is suspected to be present in a substantial proportion of those with CHARGE syndrome. In addition, a lot of them have sensory deficits which severely affect development. The combination of these problems, which both have an

impact on the perception of daily life, makes communication an important domain for early intervention in this syndrome.

Cornelia de Lange syndrome Parents of children with Cornelia de Lange syndrome and professionals working with them should be aware of the highly variable behavioural and physical phenotypes. When working with families with a young child, professionals should know that the physical phenotype is not to be used as a prognostic factor for the level of functioning of the children. Given the broad range of functioning of individuals with the syndrome, it is important to monitor the development of young children closely and offer stimulation adjusted to the level of functioning. Severe behavioural problems are present in a large proportion of those with Cornelia de Lange syndrome and parents should obtain professional support to manage and/or reduce these problems.

Half of the parents with a child with Cornelia de Lange syndrome experience high stress levels. Risk factors in families with a child with Cornelia de Lange syndrome are a low level of functioning of the child, high level of behavioural problems, the presence of the autistic disorder and older age of the child. Professionals need to be alert when these risk factors are present in order to provide early support and prevent problems from getting worse.

Angelman syndrome In Angelman syndrome severe behavioural problems are also present in a large proportion of the children. Their parents should obtain professional support to manage and/or reduce these problems. Parenting stress is high in a large proportion of the families with a child with Angelman syndrome. In our study no specific child characteristics in Angelman syndrome were found that were related to parenting stress. However, we provide some hypotheses in which domains families could receive support. We hypothesized that support should focus on optimising the communication abilities of the child, which we discussed at the national family day 2009 of the Dutch Angelman Parent Support Group. Parents agreed that poor communication abilities of their child were a source of stress, and some commented that they were even more concerned whether professionals could understand their child as well as they themselves did. Another target for intervention in order to reduce parenting stress is to focus on the sleep problems suffered by the majority of these children, which also was discussed at the national family day. These suggestions give rise to further investigations. The stress

process in Angelman syndrome needs to be unravelled further to give more specific advice.

Prader-Willi syndrome The majority of the children with Prader-Willi syndrome have a mild to no ID. However, there is also a substantial number of children who function at lower levels. It is therefore important to investigate the abilities at an early age in order to choose the most appropriate level of schooling for these children, in order to prevent under- as well as overstimulation. Most parents with a child with Prader-Willi syndrome perceive a somewhat heightened level of parenting stress (i.e. above the mean of the normal population norm group), but a quarter perceives high levels of parenting stress. However, in our project no specific child characteristics were found that were related to parenting stress. Further investigations are needed to shed more light on this issue and provide more syndrome-specific recommendations for support.

Final remark

To conclude, we studied *groups* of children with genetic syndromes and their families. We emphasize that therefore only general guidelines can be given. Genetic determinism should thereby be avoided; the presence of a genetic syndrome is only a predisposition for certain outcomes. Individuals with the same syndrome differ from each other in e.g. behavioural characteristics (Hodapp & Dykens, 2004, 2009) and the families differ from each other. Parents value professionals who see the individuality and uniqueness of a family (Lärka Paulin, Bernehäll Claesson, & Brodin, 2001 in Olsson, 2008). Support for families with a child with a genetic syndrome should therefore be based on scientific knowledge, but comprise individual assessment to get insight into the challenges and influencing factors in *that* particular family. By expanding specific knowledge on these children and their families, it will become possible to formulate syndrome-specific guidelines for diagnostics and treatment of both medical and behavioural aspects throughout the lifetime, such as Kline et al. (2007) already did for persons with Cornelia de Lange syndrome. This will improve the care and support that people with genetic syndromes associated with ID receive.

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Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Binnen de zorg voor mensen met een verstandelijke beperking is steeds meer aandacht voor de gevolgen van een genetisch syndroom op de ontwikkeling van deze personen. Momenteel zijn ongeveer 1500 syndromen die gepaard gaan met ontwikkelingsproblemen genetisch geïdentificeerd (Oliver & Hagerman, 2007), maar voor een groot deel hiervan ontbreekt een duidelijk beeld van het kenmerkende gedrag ofwel van het gedragsfenotype. Kennis omtrent dit gedragsfenotype is echter een eerste vereiste om syndroomspecifieke interventies te kunnen ontwikkelen en de zorg aan deze mensen te verbeteren. Nog minder is bekend over de opvoedingscontext van personen met specifieke genetische syndromen. Daarbij is de mate van stress die ouders ervaren rondom de opvoeding een belangrijk aandachtsgebied. Het is immers bekend dat de aanwezigheid van ouderlijke stress een positieve ontwikkeling van zowel het kind als de ouders kan belemmeren. Ouders die veel stress ervaren blijken bijvoorbeeld minder goed in staat te zijn om hun kind in de ontwikkeling te stimuleren. Juist bij kinderen met een verstandelijke beperking kan dit veel invloed hebben (Deater-Deckard, 2004; Pazcowski & Baker, 2007). Ouders zelf kunnen als gevolg van stress onder andere een depressie ontwikkelen of lichamelijke klachten krijgen (Oelofsen & Richardson, 2006; Singer, 2006). Ook voor het domein ouderlijke stress geldt dat uitbreiding van kennis hieromtrent bij verschillende syndromen een eerste vereiste is om de (preventieve) zorg aan deze gezinnen te kunnen verbeteren.

Dit proefschrift richt zich op vijf genetische syndromen namelijk het Rett syndroom, CHARGE syndroom, Cornelia de Lange syndroom, Angelman syndroom en Prader-Willi syndroom. Het doel van de studie is om 1) de gedragsfenotypes voor de vijf syndromen nader in kaart te brengen, 2) inzicht te verwerven in de beleving van ouderlijke stress gerelateerd aan de opvoeding van het kind met het specifieke syndroom en 3) de relatie tussen een aantal kindkenmerken en ouderlijke stress te onderzoeken. De onderzochte kindkenmerken zijn: het niveau van adaptief functioneren, de aanwezigheid van probleemgedrag, de aanwezigheid van de Autistische Stoornis, het geslacht en de leeftijd. Daarnaast zijn in een aantal gevallen nog syndroomspecifieke kindkenmerken in het onderzoek betrokken.

Alle participerende ouders zijn benaderd via de betreffende oudervereniging met een verzoek tot deelname aan het onderzoek. Voor het onderzoek naar het CHARGE

syndroom zijn extra ouders geworven door samenwerking met de CHARGE-polikliniek van het Universitair Medisch Centrum Groningen.

Bij alle in het onderzoek betrokken ouders is een uitgebreid interview afgenomen over het gedrag en de ontwikkeling van hun kind, het Diagnostic Interview for Social and Communication Disorders - 10de revisie (DISCO; Wing, 1999). Hiermee kan onder andere gescreend worden op de Autistische Stoornis. Om adaptief gedrag in kaart te brengen is aanvankelijk de uitgebreide interviewversie van de Vineland Adaptive Behaviour Scales (Sparrow, Balla, & Cicchetti, 1984) afgenomen. Aangezien dit interview in combinatie met de DISCO erg veel tijd van ouders in beslag nam, is overgestapt op een screenende vragenlijst. Zowel de Vineland Screener 0-6 (Scholte, Van Duijn, Dijkxhoorn, Noens, & Van Berkcelaer-Onnes, 2008) als de Vineland Screener 0-12 (Van Duijn, Dijkxhoorn, Noens, Scholte, Van Berckelaer-Onnes, 2009) is gebruikt. Probleemgedrag is in kaart gebracht met de Vragenlijst over Ontwikkeling en Gedrag van Kinderen - Ouderversie (Koot & Dekker, 2001). Ten slotte hebben ouders een vragenlijst ingevuld over hun beleving van stress gerelateerd aan de opvoedingssituatie, de Nijmeegse Ouderlijke Stress Index - Kort (De Brock, Vermulst, Gerris, & Abidin, 1992).

Dit proefschrift bestaat uit een algemene introductie, vijf artikelen en een hoofdstuk met discussie en aanbevelingen. In de algemene introductie (hoofdstuk 1) zijn de onderzoeksvragen weergegeven en is een omschrijving van de vijf syndromen gegeven. In de hoofdstukken 2 tot en met 6 zijn de resultaten van de onderzoeken naar de verschillende syndromen weergegeven. Hoewel voor alle syndromen dezelfde instrumenten zijn gebruikt, ligt in elk hoofdstuk de nadruk op een ander aspect, afhankelijk van het onderzochte syndroom. In hoofdstuk 7, de algemene discussie, is daarom voor alle syndromen een overzicht gegeven van overeenkomstige kindkenmerken om vervolgens een vergelijking tussen de verschillende syndromen te maken.

In deze samenvatting zijn allereerst de belangrijkste bevindingen uit de hoofdstukken 2 tot en met 7 per syndroom weergegeven. Daarna volgen aanbevelingen voor vervolgonderzoek en de praktijk.

BELANGRIJKSTE BEVINDINGEN

De hoofdstukken 2 en 3 zijn gewijd aan het Rett syndroom, dat vrijwel alleen voorkomt bij vrouwen. In hoofdstuk 2 wordt voor 52 vrouwen (2 tot en met 49 jaar) met het Rett syndroom een beschrijving gegeven van de aanwezigheid van autistische gedragingen. Theoretisch bezien is het niet onomstreden om onderzoek te doen naar de eventuele aanwezigheid van een bijkomende Autistische Stoornis bij deze vrouwen. In de huidige classificatiesystemen voor psychische stoornissen is het niet mogelijk het Rett syndroom en de Autistische Stoornis bij één persoon vast te stellen. Beide vallen in de classificatiesystemen onder de pervasieve ontwikkelingsstoornissen. Er wordt echter door sommige onderzoekers aangegeven dat niet bij alle vrouwen met het Rett syndroom autistische gedragingen aanwezig zijn. Er heerst twijfel over plaatsing van het Rett syndroom binnen de pervasieve ontwikkelingsstoornissen (Gillberg & Billstedt, 2000; Wing, 2005), hetgeen mede geleid heeft tot het huidige onderzoek. Alle 52 vrouwen in het onderzoek hadden een ernstige tot zeer ernstige verstandelijke beperking. Bij 42% tot 58% van hen waren aanwijzingen voor comorbiditeit met de Autistische Stoornis, ongeveer een gelijk tot een wat hoger percentage dan verwacht wordt op dit functioneringsniveau. Daarnaast bleek in dit onderzoek dat bij 19% van de vrouwen het gedrag dat zij in het verleden vertoonden geclassificeerd kon worden als indicatief voor de Autistische Stoornis, maar dat hun huidige gedrag dusdanig is veranderd dat deze classificatie niet meer van toepassing is. Dit ondersteunt eerdere bevindingen, gebaseerd op gevalsbeschrijvingen, dat bij sommige personen met het Rett syndroom autistisch gedrag slechts een beperkte periode aanwezig is, om dan weer af te nemen of helemaal te verdwijnen. Om inzicht te krijgen in specifiek probleemgedrag is in hoofdstuk 7 voor deze vrouwen in kaart gebracht welk gedrag bij meer dan 70% voorkomt, zie de tabel in deze samenvatting voor een overzicht.

De belangrijkste consequentie van bovenstaande resultaten is dat het conform andere genetische syndromen *mogelijk* moet zijn om de Autistische Stoornis bij mensen met het Rett syndroom te classificeren. Het feit dat de kans op comorbiditeit met de Autistische Stoornis bij andere genetische syndromen even groot of zelfs groter is en het feit dat het autistische gedrag bij een deel weer verdwijnt, pleit binnen de classificatiesystemen voor verwijdering van het Rett syndroom uit de pervasieve ontwikkelingsstoornissen. Naar verwachting is de volgende versie van één van de twee

grote classificatiesystemen, de DSM, in het voorjaar van 2013 gereed. Voor de DSM-V is het voorstel om het Rett syndroom te verwijderen uit de pervasieve ontwikkelingsstoornissen (American Psychiatric Association, 2010). De resultaten uit het huidige onderzoek pleiten voor procesdiagnostiek om de aanwezigheid van de Autistische Stoornis bij deze vrouwen met zo'n laag ontwikkelingsniveau vast te stellen.

In hoofdstuk 3 wordt de mate van ouderlijke stress beschreven die moeders van 24 meisjes (2 tot en met 17 jaar) met het Rett syndroom ervaren. Deze 24 kinderen maken allen deel uit van de 52 deelnemers in het onderzoek naar autistische gedragingen. Bijna de helft van de moeders (46%) rapporteerde een mate van stress die geclassificeerd kon worden als hoog tot zeer hoog, tegenover 15% in de normgroep uit de normale populatie. De leeftijd van het kind en diens niveau van adaptief functioneren waren niet gerelateerd aan de mate van stress bij de moeders. Echter, hoe meer probleemgedragingen en in zichzelf gekeerd gedrag, autistische gedragingen, sociale beperkingen, angst en storend gedrag de kinderen vertoonden, des te meer stress de moeders rapporteerden. De gevonden relaties hadden kleine tot middelgrote effectgroottes. Wat betreft Rett-specifieke gedragingen waren alleen gedragingen met betrekking tot de *'general mood'* gerelateerd aan ouderlijke stress. Meer stemmingsproblemen hingen samen met een hogere mate van stress, hoewel het effect klein was. De mogelijke aanwezigheid van een comorbide Autistische Stoornis was niet gerelateerd aan de ouderlijke stress.

In hoofdstuk 4 wordt het gedragsfenotype van 22 kinderen (1 tot en met 22 jaar) met het CHARGE syndroom en de beleving van ouderlijke stress binnen de gezinnen beschreven. Uit het onderzoek bleek dat op basis van de adaptieve vaardigheden 45% van de kinderen geen of slechts een lichte verstandelijke beperking had. Hoewel een breed bereik in functioneren verwacht werd, is nog niet eerder een dusdanig groot percentage kinderen beschreven dat op de hogere niveaus functioneert. Dit impliceert dat voor kinderen met het CHARGE syndroom moeilijk te voorspellen is hoe zij zich zullen ontwikkelen. Wat betreft de probleemgedragingen kwam ook een grote variatie naar voren, alleen 'ongeduldig zijn' was voor meer dan 70% van de kinderen kenmerkend. In hoofdstuk 7 bleek dat bij 36% van de kinderen vermoedelijk de Autistische Stoornis aanwezig was. Gezien de vele bijkomende problemen op auditief en visueel gebied dienen de resultaten van deze screening echter met de nodige terughoudendheid te worden geïnterpreteerd. De beleving van ouderlijke stress werd voor 59% van de ouders geclassificeerd als hoog tot zeer hoog. Er werd geen relatie gevonden met de

kindkenmerken niveau van adaptief functioneren, mate van verstandelijke beperking, auditieve en visuele problemen, doofblindheid, geslacht en leeftijd. Ouders rapporteerden echter meer stress naarmate de kinderen meer depressieve gedragingen, autistische gedragingen, in zichzelf gekeerd gedrag en storend gedrag vertoonden. De effectgroottes konden geclassificeerd worden als middelgroot tot groot.

In hoofdstuk 5 wordt een gedetailleerd beeld geschetst van de fysieke- en gedragskenmerken van 37 personen (1 tot en met 46 jaar) met het Cornelia de Lange syndroom en de stress die hun ouders ervaren. Er kwam een grote variatie in het (gedrags)fenotype naar voren en alle kindkenmerken, behalve sekse, vertoonden onderling een sterke samenhang. Het merendeel (84%) van de personen had een matige tot zeer ernstige verstandelijke beperking. De Autistische Stoornis was vermoedelijk bij 54% aanwezig. In hoofdstuk 7 zijn de probleemgedragingen beschreven die bij meer dan 70% aanwezig waren, zie de tabel in deze samenvatting voor een overzicht. Bij 51% van de ouders kon de ervaren ouderlijke stress als hoog tot zeer hoog geclassificeerd worden. Ouders rapporteerden meer stress als de kinderen een ernstigere verstandelijke beperking hadden, ouder waren, meer gedragsproblemen vertoonden en bij hen vermoedelijk de Autistische Stoornis aanwezig was. Een opmerkelijk resultaat was dat, in tegenstelling tot eerdere beschrijvingen, de ernst van de fysieke problemen bij mensen met het Cornelia de Lange syndroom niet direct gekoppeld was aan het functioneringsniveau. Daarom dienen professionals in de toekomst terughoudend te zijn in het uiten van voorspellingen omtrent de ontwikkelingsmogelijkheden van een kind met dit syndroom op basis van het uiterlijk en de ernst van de fysieke problemen.

In hoofdstuk 6 wordt het gedragsfenotype van het Angelman syndroom en het Prader-Willi syndroom beschreven in relatie tot de ouderlijke stress. Aan dit onderzoek namen 24 moeders met een kind (2 tot en met 12 jaar) met het Angelman syndroom en 23 moeders met een kind (2 tot en met 12 jaar) met het Prader-Willi syndroom deel. Bij het Angelman syndroom was zoals verwacht bij alle kinderen sprake van een ernstige tot zeer ernstige verstandelijke beperking. Zij vertoonden een grote gelijkenis in type probleemgedrag, zoals te zien is in de tabel. In hoofdstuk 7 is beschreven dat bij 67% van de kinderen vermoedelijk de Autistische Stoornis aanwezig was. Maar liefst 58% van de moeders rapporteerde hoge tot zeer hoge ouderlijke stress-scores. De ouderlijke stress hing niet samen met het geslacht, de leeftijd of de mate van probleemgedrag van kinderen met het Angelman syndroom. Van de kinderen met het Prader-Willi syndroom functioneerde

35% op het niveau van een matige tot zeer ernstige verstandelijke beperking, de overige kinderen hadden een minder ernstige of vrijwel geen achterstand. In de tabel zijn de probleemgedragingen beschreven die meer dan 70% van de kinderen vertoonden. In hoofdstuk 7 is beschreven dat bij 22% vermoedelijk de Autistische Stoornis aanwezig was. Bij 26% van de moeders was sprake van een hoog tot zeer hoog stressniveau. De mate van stress bij moeders hing niet samen met het geslacht, de leeftijd, hoeveelheid probleemgedrag of niveau van adaptief functioneren van het kind met het Prader-Willi syndroom.

Moeders met een kind met het Angelman syndroom rapporteerden vaker dan moeders met een kind met het Prader-Willi syndroom een hoog tot zeer hoog niveau van stress; de effectgrootte kon geclassificeerd worden als middelgroot. Bij vergelijking van de twee syndromen bleek de hoeveelheid probleemgedrag echter van invloed op de stress. Indien kinderen met één van beide syndromen weinig probleemgedrag vertoonden, beleefden meer moeders met een kind met het Angelman syndroom een hoog stressniveau in vergelijking met moeders met een kind met het Prader-Willi syndroom. Het gevonden effect werd geclassificeerd als groot. Als de kinderen echter een klinisch significante mate van probleemgedrag vertoonden, was de stressbeleving tussen moeders met een kind met het Angelman syndroom en het Prader-Willi syndroom gelijk. Dit betekent dat het omgaan met een kind met veel probleemgedrag zowel bij het Angelman syndroom als het Prader-Willi syndroom gepaard gaat met een gelijke mate van stress.

In hoofdstuk 7 wordt ook een overzicht gegeven van de resultaten wat betreft de gedragsfenotypes en ouderlijke stress voor de vijf verschillende syndromen. Hierbij lijkt bij alle syndromen behalve het Rett syndroom een verhoogd risico aanwezig te zijn van comorbiditeit met de Autistische Stoornis, waarbij het functioneringsniveau in acht is genomen. Deze resultaten dienen echter met voorzichtigheid geïnterpreteerd te worden, aangezien in het huidige onderzoek alleen screeningsinstrumenten ten aanzien van de Autistische Stoornis zijn gebruikt. Aanvullende individuele diagnostiek is een vereiste om een definitieve classificatie voor een persoon te kunnen geven. Wat betreft de mate van probleemgedrag lijken het Angelman syndroom en het Cornelia de Lange syndroom samen te gaan met een hoog risico op een ernstige hoeveelheid probleemgedrag. Bij de overige syndromen is de mate van probleemgedrag niet hoger dan verwacht wordt bij mensen met een verstandelijke beperking zonder een genetisch syndroom. Wat betreft de aard van probleemgedrag blijkt het gedrag van mensen met het Angelman syndroom sterk

overeenkomstig te zijn (15 gedragingen), terwijl bij mensen met het CHARGE syndroom nauwelijks probleemgedrag voorkomt dat kenmerkend is voor het merendeel van de personen (1 gedragsomschrijving). De overige drie syndromen nemen daarbij een middenpositie in met zes tot acht probleemgedragingen die bij meer dan 70% voorkomen. Op het gebied van ouderlijke stress is de aanwezigheid van elk van de vijf syndromen een behoorlijke risicofactor voor het ontwikkelen van ouderlijke stress. Hierbij is het echter belangrijk dat men zich ervan bewust is dat niet alle ouders met een kind met een genetisch syndroom een hoog stress niveau ervaren. Ten slotte is in onderhavig onderzoek aangetoond dat per syndroom verschilt welke kindfactoren met de stressbeleving van ouders samenhangen.

AANBEVELINGEN VOOR VERVOLGONDERZOEK

In het huidige onderzoeksproject zijn enkele beperkingen naar voren gekomen (zie hoofdstuk 7), op basis hiervan is een aantal aanbevelingen geformuleerd voor vervolgonderzoek. In dit onderzoek is de *relatie* tussen ouderlijke stress en kindkenmerken onderzocht. Hoewel het gebruikte model van Perry (2004; zie hoofdstuk 1) *causaliteit* tussen de stressoren (kindkenmerken) en de uitkomst (ouderlijke stress) suggereert, dient men terughoudend te zijn met deze interpretatie. Door het cross-sectionele design van de studie kunnen er geen uitspraken over causaliteit worden gedaan. Aangezien ook binnen het onderzoeksveld met betrekking tot mensen met een verstandelijke beperking de richting van de oorzaak-gevolg relatie omtrent ouderlijke stress en kindkenmerken nog niet helder is, moet longitudinaal onderzoek hierin meer duidelijkheid geven.

Meer inzicht omtrent de opvoedingssituatie in gezinnen met een kind met een genetisch syndroom zou in vervolgonderzoek verkregen moeten worden door factoren uit meerdere componenten van Perry's model (2004) te betrekken. De onderzochte kindkenmerken kunnen verbreed worden, bijvoorbeeld door voor het Rett syndroom en het CHARGE syndroom de relatie tussen ouderlijke stress en de veelvoorkomende fysieke problemen te onderzoeken (zie hoofdstuk 7 voor meer suggesties). Ook dient de invloed van andere mogelijke stressoren dan kindkenmerken onderzocht te worden, zoals de invloed van een laag gezinsinkomen. Meer inzicht in opvoedingsgerelateerde stress kan verkregen worden door mediërende factoren zoals de hoeveelheid (in)formele steun die

een gezin ontvangt en persoonlijke eigenschappen van de ouders zoals copingstrategieën mee te nemen in onderzoek. Daarnaast is het belangrijk niet alleen stressoren en negatieve uitkomsten in kaart te brengen, maar juist de focus te leggen op protectieve factoren en positieve uitkomsten. Er zijn immers ook ouders die weinig stress ervaren in de opvoeding van hun kind met een genetisch syndroom of die aangeven een positieve ontwikkeling door te maken, vaak in de vorm van persoonlijke groei. Het doel van het onderzoek dient daarbij te zijn om te achterhalen waarom sommige gezinnen zich goed aan kunnen passen aan hun specifieke gezinssituatie en waarom dat in andere gezinnen niet of minder goed lukt. Meer inzicht in deze processen kan de hulpverlening ten goede komen.

Ten slotte is het belangrijk in vervolgonderzoek te streven naar grotere onderzoeksgroepen. Hoewel de aantallen per genetisch syndroom in het huidige onderzoek voor Nederland acceptabel zijn, dient men toch voorzichtig te zijn met conclusies vanwege de kleine onderzoeksgroepen. Het is binnen gedragsonderzoek daarom belangrijk te streven naar een brede internationale samenwerking om meer personen met eenzelfde syndroom bij een onderzoeksproject te kunnen betrekken. Het vergroten van de onderzoeksgroep in vervolgonderzoek is ook mogelijk door ouders via meer uiteenlopende kanalen te benaderen. Waar nu voornamelijk leden van de oudervereniging benaderd zijn om aan het onderzoek deel te nemen, zouden ouders bijvoorbeeld ook via zorginstanties voor mensen met verstandelijke beperkingen of specialistische centra benaderd kunnen worden. Op die manier kan een meer diverse en daarmee representatieve en grotere groep geworven worden.

KLINISCHE IMPLICATIES

Op basis van het huidige onderzoek is een aantal klinische aanbevelingen geformuleerd. Uit huidig onderzoek kwam duidelijk naar voren dat bij elk syndroom eigen typerende kenmerken aanwezig waren. Het is belangrijk om ouders van een kind met een genetisch syndroom voor te lichten over de specifieke sterke en zwakke kanten van het gedragsprofiel, kenmerkend voor het syndroom. Psycho-educatie kan daarbij duidelijk maken dat bepaald probleemgedrag vaak voorkomt bij een bepaald syndroom en dat het kind dit gedrag niet met opzet laat zien. Daarnaast dient aandacht besteed te worden aan het gegeven dat ouders zich niet verantwoordelijk moeten voelen voor het voorkomen van deze syndroomspecifieke probleemgedragingen. Ouders zullen dan naar verwachting de

problemen makkelijker kunnen accepteren en vervolgens beter in staat zijn te anticiperen op het gedrag van het kind, waardoor ze hun kind gerichter kunnen stimuleren op die gebieden waar dit specifiek nodig is (Finegan, 1998; Skuse, 2000).

Professionals dienen alert te zijn op de hoge prevalentie van een comorbide Autistische Stoornis bij de onderzochte syndromen. Hoewel benadrukt dient te worden dat er in het huidige onderzoek alleen *gescreend* is op de Autistische Stoornis, is het belangrijk alert te zijn op deze mogelijk bijkomende stoornis gezien de grote impact die dit heeft op mensen met een verstandelijke beperking. Omtrent dit onderwerp is op dit moment onder wetenschappers en clinici een discussie gaande. Sommigen menen dat de Autistische Stoornis ook bij mensen met een genetisch syndroom geclassificeerd dient te worden, anderen menen dat meestal een ander profiel van symptomen bij mensen met een genetisch syndroom zichtbaar is en daarom beter over autistische trekken gesproken kan worden (zie Moss & Howlin, 2009). Voor de praktijk is het echter minder belangrijk welke positie men inneemt in de discussie (classificeren of beschrijven), maar moet men zich wel bewust zijn van de implicaties voor de benadering van deze mensen. Interventies dienen daarbij afgestemd te worden op de combinatie van de drie aspecten, namelijk het genetische syndroom, de verstandelijke beperking en de Autistische Stoornis (of autistische trekken). Integratie van interventies voor de drie diagnoses is daarbij essentieel om de omgeving optimaal aan te passen aan de ondersteuningsbehoefte van een persoon.

Professionals die betrokken zijn bij de zorg voor mensen met een genetisch syndroom dienen niet alleen aandacht te hebben voor de persoon met het syndroom, maar ook voor het hele gezinssysteem. Hoewel er ouders zijn die de opvoedingssituatie niet als stressvol beleven, ervaart een groot deel van de ouders wel degelijk veel stress. Gezien de mogelijke negatieve consequenties van stress voor ouders en kind, is het van belang een hoog stressniveau in gezinnen tijdig te signaleren en daar vervolgens naar te handelen. Een eerste mogelijkheid is om ouders specifieke informatie te verschaffen over het betreffende syndroom, zowel wat betreft het verwachte gedragsprofiel alsook medische problemen en mogelijke interventies. Een belangrijke aanvullende bron van informatie voor ouders is een specifieke oudervereniging. Professionals dienen ouders hierop te attenderen en lidmaatschap te stimuleren. Deze oudervereniging zijn niet alleen een bron van up-to-date informatie, maar juist ook uiterst belangrijk voor het bieden van emotionele ondersteuning. Het kunnen delen van soortgelijke ervaringen met andere ouders kan een gevoel van saamhorigheid bieden en helpen om beter om te kunnen gaan met stress.

Oudervereningingen vervullen daarbij een belangrijke functie om ouders meer zelfvertrouwen te geven omtrent de opvoeding (Bass, 1990). Ook werd in het huidige onderzoek aangetoond dat ouderlijke stress bij ouders met een kind met het Rett syndroom, het CHARGE syndroom en het Cornelia de Lange syndroom hoger is naarmate de kinderen meer probleemgedrag vertonen. Ouders dienen daarom ondersteund te worden in het hanteren van dit probleemgedrag, om te voorkomen dat er (te) hoge stressniveau's ontstaan (Hastings & Beck, 2004). Ten slotte dienen ouders die veel stress ervaren ondersteund te worden door middel van stress management technieken zodat zij nu en op latere momenten in de opvoeding beter met stress om kunnen gaan.

In de opvoeding van een kind met een genetisch syndroom dat gepaard gaat met een verstandelijke beperking komen ouders vanwege de diversiteit van medische en gedragsproblemen van het kind in aanraking met professionals uit veel verschillende disciplines. Hierbij komt het regelmatig voor dat ouders veel informatie op deelgebieden van professionals krijgen en daarbij soms tegenstrijdige adviezen van verschillende professionals ontvangen. Voor sommige ouders is het coördineren van de zorg rond hun kind bijna een dagtaak en juist dit kan veel stress opleveren. Het is daarom belangrijk dat deze gezinnen begeleid worden door een professional die ouders ondersteunt bij de coördinatie van de zorg, bij voorkeur gedurende de levensloop. Juist een gedragswetenschapper kan de informatie integreren om de zorg voor het kind te optimaliseren en de ouders te ontlasten.

Items van de Vragenlijst over Ontwikkeling en Gedrag van Kinderen die van toepassing zijn bij meer dan 70% van de participanten per syndroom

Rett syndroom (52 personen; 2 - 49 jaar)	
Item	**%**
Herhaalde bewegingen van handen, lichaam, hoofd of gezicht	92
Kan zich slecht concentreren	87
Lacht of giechelt zonder duidelijke reden	81
Maakt geluiden die geen spraak zijn	79
Reageert te weinig op pijn	75
Afstandelijk, zit in haar eigen wereldje	73

Angelman syndroom (24 personen; 2 - 12 jaar)	
Item	**%**
Kauwt op voorwerpen of lichaamsdelen of stopt ze in de mond	96
Kan zich slecht concentreren	96
Snel afgeleid van zijn/haar taak	92
Maakt geluiden die geen spraak zijn	92
Slaapt te weinig, verstoorde slaap	92
Overactief, rusteloos of kan niet stilzitten	88
Te weinig gevoel voor gevaar	88
Ongewone lichaamsbewegingen, houding of manier van lopen	83
Vindt het prettig om een ongewoon voorwerp vast te houden of ermee te spelen, is overdreven gefascineerd door iets bijvoorbeeld water	79
Herhaalde bewegingen van handen, lichaam, hoofd of gezicht	79
Raakt te zeer opgewonden	75
Eet dingen die eigenlijk niet eetbaar zijn	75
Ongeduldig	75
Koppig, ongehoorzaam of werkt niet mee	75
Is blij of opgetogen zonder dat dit met de werkelijkheid in overeenstemming is	75

Cornelia de Lange syndroom (37 personen; 1- 46 jaar)	
Item	**%**
Doet het liefst dingen in zijn/haar eentje, is een beetje een eenling	81
Verandert snel van stemming zonder duidelijke reden	78
Afstandelijk, zit in zijn/haar eigen wereldje	75
Maakt geluiden die geen spraak zijn	75
Kan zich slecht concentreren	75
Vermijdt oogcontact	72

Prader-Willi syndroom (23 personen; 2 - 12 jaar)	
Item	**%**
Schikt voorwerpen in een vaste volgorde of houdt vast aan een vaste gang van zaken	91
Snel afgeleid van zijn/haar taak	87
Ongeduldig	83
Te weinig gevoel voor gevaar	83
Raakt overstuur bij kleine veranderingen in de gebruikelijke gang van zaken of omgeving	83
Wordt gemakkelijk beïnvloed door anderen	74
Krabt of pulkt aan zijn/haar huid	74
Koppig, ongehoorzaam of werkt niet meer	74

CHARGE syndroom (22 personen; 1 - 22 jaar)	
Item	**%**
Ongeduldig	86

Noot. Schuingedrukte items komen alleen bij dat syndroom in meer dan 70% van de personen voor in vergelijking met de andere vier syndromen. Ze kunnen hiermee als 'unieke' gedragingen worden beschouwd.

DANKWOORD

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CURRICULUM VITAE

Josette Wulffaert was born on July 28th 1981 in Bramsche, Germany. She started secondary school at the Sint Oelbert Gymnasium in Oosterhout and continued in the second semester of her second year at the Johan de Witt Gymnasium in Dordrecht. After receiving her diploma in 1999, she started studying at the Department of Pedagogical and Educational Sciences of the University of Amsterdam. She obtained her propedeuse (cum laude) in 2000. In 2001 she continued her studies at the Department of Clinical Child and Adolescent Studies of Leiden University and obtained her master's degree (cum laude) in 2005.

After graduation she joined the staff of the Department of Clinical Child and Adolescent Studies, Leiden University. In 2006 she started her PhD project on the behavioural phenotypes of people with genetic syndromes and the parenting stress involved. She also started to work at the Ambulatorium, an outpatient clinic for clinical assessment and treatment of children and their families at Leiden University. She worked mainly with the team for children with severe developmental disorders. In July 2010 Josette commenced working as a clinician at the FortaGroep Child and Adolescent Clinic, Schiedam.

Josette Wulffaert is geboren op 28 juli 1981 te Bramsche, Duitsland. Na anderhalf jaar voortgezet onderwijs op het Sint Oelbert Gymnasium te Oosterhout, heeft ze haar middelbare schooltijd voortgezet op het Johan de Witt Gymnasium te Dordrecht. Na het behalen van haar diploma in 1999, studeerde ze Pedagogische en Onderwijskundige Wetenschappen aan de Universiteit van Amsterdam. Ze behaalde haar propedeuse (cum laude) in 2000. In 2001 zette ze haar studie voort bij de afdeling Orthopedagogiek aan de Universiteit Leiden en studeerde daar in 2005 cum laude af.

Na haar afstuderen werkte zij als onderwijsmedewerker aan de afdeling Orthopedagogiek, Universiteit Leiden. In 2006 startte ze haar promotieonderzoek naar het gedragsfenotype van mensen met genetische syndromen en de opvoedingsstress bij de ouders van deze kinderen. Tevens werkte zij op het Ambulatorium, een kliniek voor diagnostiek en behandeling van kinderen en hun gezinnen, onderdeel van de Universiteit Leiden. Ze werkte daar voornamelijk bij het team voor kinderen met ernstige ontwikkelingsstoornissen. Sinds juli 2010 werkt Josette als orthopedagoog bij het kinder- en jeugdcentrum FortaGroep te Schiedam.