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

Wulffaert, J.

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

Josette Wulffaert
Ina A. van Berckelaer-Onnes
Pieter M. Kroonenberg
Evert M. Scholte
Zahurul A. Bhuiyan
Raoul C.M. Hennekam

Journal of Intellectual Disability Research, 2009, 53, 604-619

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.

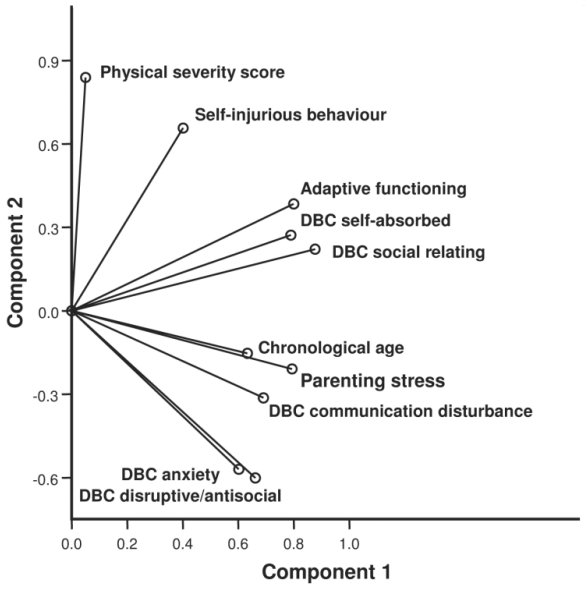

Figure 5.1 Quantified ordinal variables displayed as vectors in a two-dimensional loading plot
Note. DBC = Developmental Behaviour Checklist.

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.

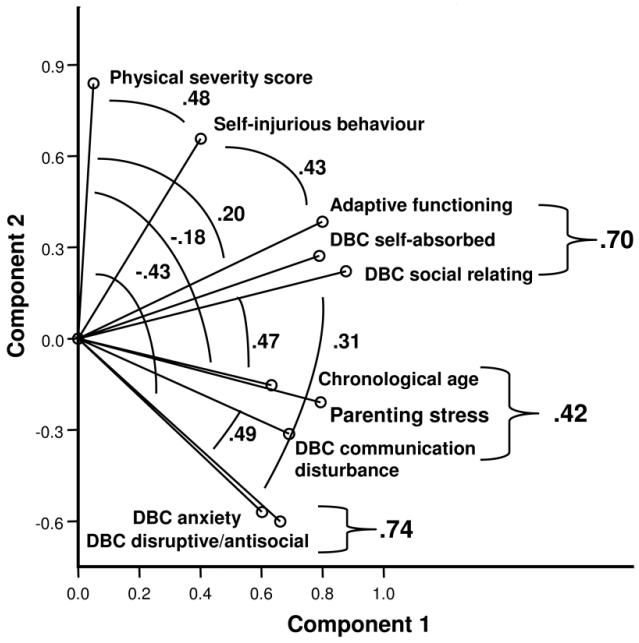

Figure 5.2 Mean correlations between and within (bold) clusters of transformed ordinal variables
Note. DBC = Developmental Behaviour Checklist.

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.

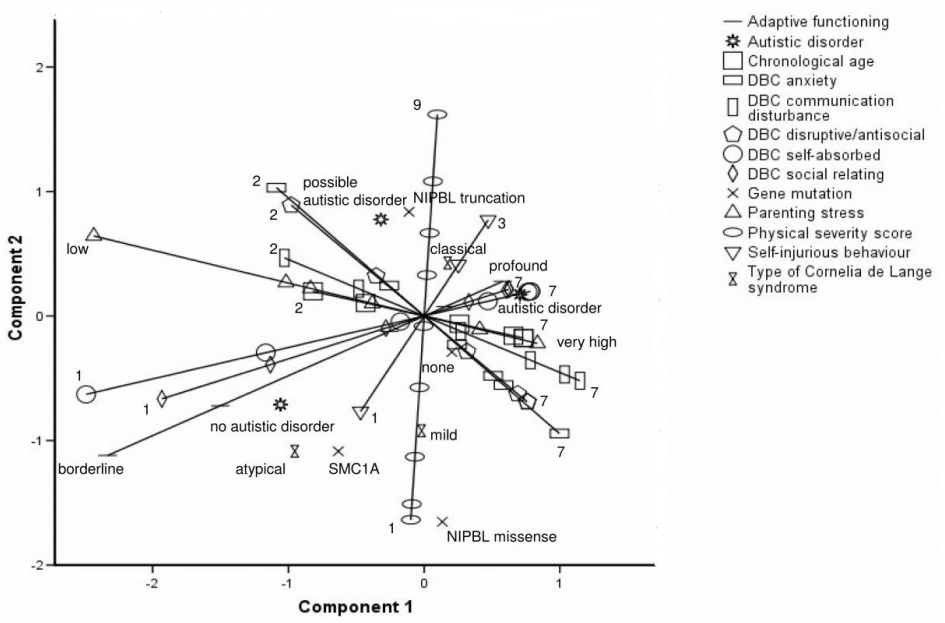

Figure 5.3 Category plot of the ordinal and categorical variables measuring child and parenting characteristics of people with Cornelia de Lange syndrome with type of syndrome added
Note. DBC = Developmental Behaviour Checklist.

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.

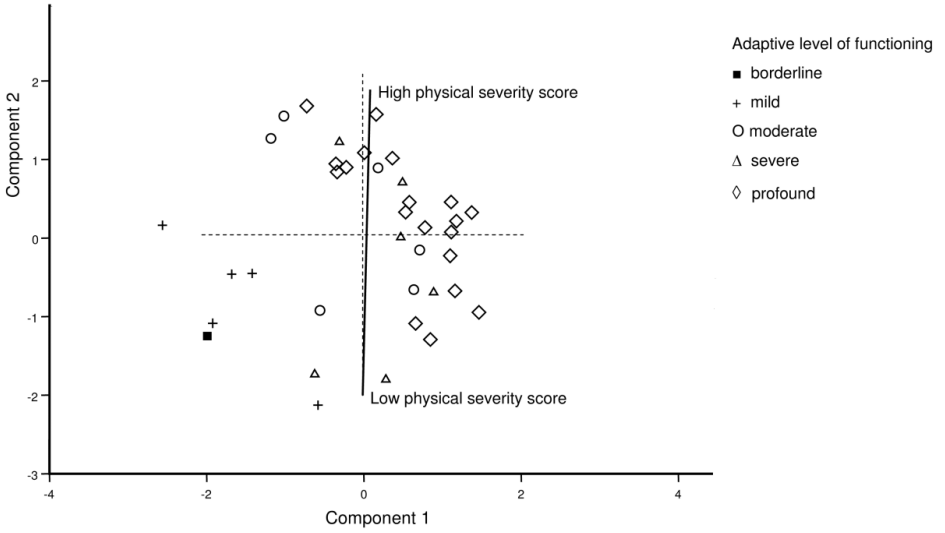

Figure 5.4 Component loading of physical severity score with individual object point labelled by level of adaptive functioning

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.