RESEARCH ARTICLE

The Impact of Rare Genetic Disorders on Family Functioning

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Abstract:
The increasing presence of genetic neurodevelopmental disorders (NDDs) results in greater demands for counseling. Many studies focus on the characteristics of patients, but less on family functioning. The aim of this study is to objectify parental stress and to study its relationship with child characteristics and environmental factors across several syndromes.
56 individuals with NDD participated: 24 with Kleefstra Syndrome, 13 with Koolen-de Vries Syndrome, and 19 with other rare (mono) genetic disorders. Parents were asked to complete the General Functioning subscale of the Family Assessment Device (FAD-GF), the Child Behavioral Checklist, and a questionnaire about demographic parental data.
25.5% of the families scored above the cut-off for pathological stress (>2.17). The mean FAD–GF score was 1.84. There was no significant difference between mean FAD-score of the subgroups (p=0,70).
(Para)medical counselors should address this high amount of parental stress during counseling and consider these genetic syndromes as complex chronical illnesses.

Introduction:

Parents of children with developmental delay experience higher levels of stress[1]. This is due to issues related to a) the delayed development and diagnosis itself, b) accessing and finding their ways in the service system, c) transition phases, like starting school, and d) managing behavioral challenges[2]. Especially the relationship between challenging behaviors in the child and stress in the parents, has been subject of research[3,4]. Parental stress is assumed to have a negative influence on family functioning, whereas family functioning is a mediator in quality of life of the child as well as in levels of psychopathology[5]. Here we use the concept of "family" to describe a group consisting of one or two parents and their children (one or more), which if functioning well, is the principal institution for the socialization of children. In case of children with chronic diseases, a positive family functioning can mediate in controlling the disease burden, like in chronic somatic illness such as diabetes mellitus type I. Family dysfunction on the other hand, is for instance associated with higher level of blood glucose (HbA_{1c})[6].

In research on neurodevelopmental disorders (NDD), most studies focus on broad patient diagnostic categories such as intellectual disabilities (ID) and autism spectrum disorders (ASD). However, differentiation of subgroups with specific genetic causes of NDD may be of extra value within this broad category. Each genetic syndrome is associated with its own pattern of needs, concerns, associated disease(s) and behavior[7]. Consequently, etiological differentiation is a prerequisite not only for adequate diagnosis and treatment in general[8,9], but also for a syndrome specific approach to parental stress and to improve family functioning. Such studies are already performed in well-established genetic syndromes. For instance, mothers of children

with Down syndrome experience less stress than mothers of children with other developmental disabilities. On the other hand, previous research indicated higher stress levels in families with Down syndrome compared to families with typically developing children[10,11].

In our previous study[12] we have focused on child factors in several rare monogenetic neurodevelopmental disorders, in particular on the level of adaptive functioning and presence of psychopathology (e.g., in Kleefstra syndrome) and found great variation across syndromes. Specifically, we observed that parents struggled with the burden of care that co-occurs with raising a child with both intellectual disability as well as psychiatric symptoms. Since the prevalence of these rare monogenetic disorders is rapidly increasing[13,14], there is a need for leads in counseling these families. (Para)medical counseling is typically focused on the (somatic) phenotype of these syndromes, which is centered on child factors.

Hence, the primary objective of this study is to identify the prevalence of pathological stress within parents of children with (very) rare monogenetic neurodevelopmental disorders as well as its prevalence within the specific syndromes. Our second objective is to study its relationship with child characteristics and family environment factors across several syndromes.

Method:

Participants:

Patients were recruited from the department of Human Genetics (HG), Radboud university medical center in Nijmegen and from the department of child and adolescent psychiatry for intellectual disabilities (ID) at Karakter in Horst, both in the Netherlands. All known subjects diagnosed with KS (n=24) and KdVS (n=13) in the Netherlands and Belgium were invited to participate from the department of Human Genetics(HG), Radboud University Medical Centre in the Netherlands. Due to the rarity of these syndromes this number was the maximum to achieve.

We created a mixed control group (MG)with subjects, who have very rare genetic variants. They were recruited both from the department of HG and the department of ID.

Participant characteristics have already been described in our previous study[12] and listed in **Table I**. In this study, 56 of the 58 participants of our previous study on Kleefstra syndrome and other rare genetic disorders[12] were included. In two participants, Whole Exome Sequencing did not show a causative genetic defect, hence they were excluded. The participants in this study can be subdivided into 3 categories: 24 with KS, 13 with KdVS and 19 with other rare genetic neurodevelopmental disorders. Participant characteristics are summarized in **Table I**.

Table I: Patient Characteristics

Group	**Genetic Defect**	**Male: Female ratio (%)**	**Biological age: mean (SD; min-max) in years**
Kleefstra Syndrome (n=24)	*EHMT1* gene 16x Microdeletions 8x Mutations	**9:15 (38% vs 62%)**	15.42 (±10.421; 3-37)
KoolendeVries Syndrome (n=13)	*KANSL* gene microdeletions (12x) *KANSL* gene mutation (1x)	**6: 7 (46% vs 54%)**	18.31 (± 10.696; 5-34)

Contrast Group (n=19)	6x *GATAD2B* gene microdeltion 3x *ANKRD11* gene mutation 3x *SIN3A* gene mutations 2x *PACS1* gene mutations 1x *FOXP2* gene mutation 1x *FBOX17* gene microdeletion (2p16.3) 1x *AUTS2* gene microdeletion (7q11.22) 1x *YWHAE* microduplication (17p13.3)	**11:8 (58% vs 42%)**	12.21 **(**± 9.461; 3-40)
Total (n=56)		**26: 30 (46% vs 54%)**	**15.00 (**± 10.248; 3-40)

Informed consent was obtained by legal representatives and included in the patient file. The regional medical ethical committee (medical research ethics committee CMO/METC Arnhem-Nijmegen, the Netherlands) approved the study (NL43187.091.13), which was performed in full accordance with the Declaration of Helsinki.

- Kleefstra Syndrome (KS, n=24): This is a rare genetic syndrome, which is caused by haploinsufficiency of the *EHMT1* gene, resulting in a clinical phenotype characterized by ID, childhood hypotonia and a typical facial appearance[15-17]. The course of this syndrome is complicated by several psychiatric disorders, like autism spectrum disorder (prevalence of almost 100%) and psychotic episodes, which occur in the context of primary psychotic disorder or bipolar disorder, with a lifetime prevalence of 29.2% in these patients[12] .
- KoolendeVries Syndrome (KdVS, n=13) results from 17q21.1 and is associated with an ID, expressive language problems and in about half of the patients there are behavioral problems[18-20]. In a small sample, the (lifetime) prevalence of anxiety disorders was high, with 69.2% suffering from (a range of) anxiety disorders. In contrast, the prevalence of obsessive-compulsive disorder was extremely low in this cohort compared to other rare genetic syndromes[12].
- Mixed group of other very rare genetic disorders (MG, n=19). Individuals in this group carry causative mutations for their condition as listed in ***Table I***.

Instruments:

The instruments we used focus on the one hand on family characteristics and on the other hand on child-centered factors.

1. Family functioning and characteristics of the family

a. ***Mc Master Family Assesment Device****: General Functioning Scale (FAD-GF), Dutch version:* The McMaster Model of family functioning originates from clinical psychiatric experience and research. It covers the continuum from healthy to unhealthy family functioning in six dimensions: (a) problem solving, (b) communication, (c) roles, (d) affective responsiveness, (e) affective involvement and (f) behavioral control. The complete family assessment device (FAD, 60-items) is based on this model. The FAD-GF is a shorter version and measures the overall health and pathology of the family. It consists of 12 questions about healthy (6) and unhealthy (6) family functioning and is scored by the parents. Each item is scored on a 4-point scale (ranging from strongly agree to strongly disagree). The sum scores of these items

are divided by the number of questions answered to calculate an overall score. An overall score of 2.17 is regarded as unhealthy[21,22].

b. Data on ***educational level and psychopathology in parents*** were obtained in an additional Dutch questionnaire. Educational level was scored in the Verhage categories[23]. Presence of psychopathology was scored in accordance with the overall categories of the DSM-IV (for example: psychotic disorders, mood disorders etc). We dichotomized this variable into 'present' or 'absent'. We did not include the number of psychiatric diagnoses in our analyses, because only very few parents had multiple diagnosis.

2. Child-related factors

a. ***Vineland Adaptive Behavior Scale (VABS, In Dutch adaptation Vineland-Z)***, which is a widely used clinical interview is to determine the level of adaptive functioning of people with an intellectual disability. This instrument has a good reliability and validity in this specific population[24]. Primary caregivers were interviewed about the participants.

b. The mini Psychiatric Assessment Schedules for Adults with Developmental Disabilities (mini PAS-ADD[25]); in Dutch translation[26,27] This instrument determines behavioral problems and psychiatric disease in subjects with an intellectual disability by interviewing the proxy.

c. ***Autism Diagnostic Observation Schedule, second version (ADOS-2)*** is a semi-structured play to assess autism features[28,29]. It has proven psychometric properties in the ID-population (30) and also in genetic ID-syndromes[31].

d. ***Child Behavior Checklist (CBCL/1,5-5)[32];*** Dutch version[33]. This questionnaire measures problem behavior on a 3-point scale: 0= symptom is absent, 1= sometimes present, 2= often present. It is intended for children between 1,5 and 5 years of (developmental) age and is completed by the parent(s). It consists of 100 items, which reflect problem behaviors. The psychometric properties of this questionnaire were proved in a population sample of Dutch normally developing children[33] as well as in a sample of children with an intellectual disability[34]. This questionnaire (1.5-5) best suited the developmental ages of the participants.

In our previous work, we have reported on results of the first three child-related interviews and the observation schedule (2 a-c) and their subsequent results in more detail[12].

Procedure:

Parents were asked to complete the questionnaires, comprising FAD-GF, CBCL1,5-5 and additional questionnaire on educational level and psychopathology, together (in cases where both parents have legal parental authority; if there was only one parent with legal parental authority, than only this parent was asked to complete the questionnaire). The clinical interviews were performed by the first author, who is a certified child psychiatrist.

For the FAD-GF, questionnaires with less than 10 questions answered were regarded as not completed and therefore not included in the statistical analysis.

Statistical analysis

Mean FAD scores for the total group as well as the subgroups were calculated. To determine whether specific child and parent-related factors contribute to this, bivariate correlations were calculated and correction for multiple testing was applied.

Results

In total, 51 out of 56 FAD-GF forms were completed with ten or more answers. The mean FADscore was 1.84 with a median of 1.83. There was no significant difference between mean FADscore of the several subgroups (p=0,70). Raw scores, including confidence intervals (CI) and standard deviations (SD), are presented in ***Table II***.

Bivariate correlations between the overall FADscore and child-related factors as well as parent-related factors were calculated for nominal variables and displayed in ***Table III*.**

Table II: FADscores

	Subgroup	FAD score mean (median)	95%-CI (SD)	% families with pathological stress (n)
Total (n= 51)		1,84 (1,83)	1,69-1,99 (0,53)	25,5% (13)
	Kleefstra Syndrome (n=23)	1,90 (1,92)	1,65-2,14 (0,57)	30,4% (7)
	KoolendeVries Syndrome (n=12)	1,76 (1,79)	1,56-1,95 (0,31)	8,3% (1)
	Control group (n=16)	1,83 (1,82)	1,50-2,16 (0,62)	31,3% (5)

Table III: correlations between stress in the families and child- and parent-related factors

		N=	p-value	Correlation coefficient (Pearson's *r*)
Child related factors				
	Gender	51	0,936	-0,012
	Biological age	51	0,076	-0,251
	Developmental age[1]	51	0,073	-0,253
	Autism traits[2]	50	0,853	0,027
	Sleep problems (at present)[3]	48	0,245	-0,171
	Depressive traits[3]	48	0,909	-0,17
	Anxiety traits[3]	48	0,759	0,045
	Bipolar traits[3]	N=48	0,676	0,062
	Psychotic traits[3]	N=48	0,969	-0,006
	Unspecified psychiatric traits[3]	N=48	0,887	-0,021
	Total score CBCL[4]	N=42	P=0,004**	0,438
	Internalizing score CBCL[4]	N=42	P=0,016*	0,371
	Externalizing score CBCL[4]	N=42	P=0,003**	0,443
Parent-related factors				

	Educational level father	N=47	P=0,07	-0,266
	Educational level mother	N=48	P=0,021*	-0,332
	Psychopathology father	N= 47	P=0,023*	0,331
	Psychopathology mother	N=46	P=0,000**	0,595

[1] measured as the total score on the VABS
[2] measured with the comparison score on the ADOS-2
[3] measured with the mini PAS-ADD interview, which is scored by a clinician
[4] measured with the CBCL, which is completed by the parents

Presence of psychopathology in one of the parents was highly correlated to the level of stress within the family (p= 0,002 to p=<0,0001). Educational level of mother was slightly negative correlated to the stress level, with lower educated mothers experiencing more stress compared to higher educated mothers. Several categories of the CBCL were also related to stress within the family.
Child-related psychiatric factors, like presence or absence of traits of autism, anxiety, mood disorders or psychosis did not show statistical significant correlation. The dichotomous variables (gender of the child, living at home or in an institution) were tested using an independent t-test and showed no significant results, respectively p=0,936 for gender (*r*=-0.012; 23 males/ 28 females) and p=0,207 (*r*=-0.180) for place of living with a slightly higher mean FADscore for the ones living at home (1,90 versus 1,69; 14 patients were institutionalized). There was no significant differentiation in stress level between these groups (p=0,685): 27% of the families, whose child is living at home, have pathological stress levels compared to 21% of the families, whose child is living at an institution. In addition to this, an analysis was performed for each of the syndromes, because their mean scores substantially deviated. This also did not show a significant difference.

Discussion:

This study focuses on the stress levels experienced by the parents of children with rare genetic NDD syndromes. Subsequently it aims at the relationship between child and family characteristics across several syndromes. In our cohort, a mean of 1.84 was scored on the GF-subscale of the FAD. Furthermore, our results indicate a mean prevalence of 25.5% of parents with pathological stress levels. Compared to other chronic diseases of childhood, these are both markedly high scores. For instance, families of children with diabetes mellitus type I, which also requires a lot of (family) adjustments in daily life, had a mean score of 1.76 and a standard deviation of 0.39 (6), suggesting that at most ~15% (> +1 standard deviation) of the parents have a pathological level of stress. A study in a small sample of families with a child diagnosed with ADHD scored also around 1.75[35] on the FAD-GF. For the subgroup of parents of KS-children in our cohort, the average was even higher at 1.90 with almost one out of three parents reporting pathological stress. The mean score on the FAD-GF did not differ significantly between the various groups in our cohort. Nor did the percentage of parents with pathological stress. However, differences between the several syndromes are still

visible (**Table II**). This raises the question whether specific factors can be identified that increase the risk of pathological stress.

Risk factors that directly correlate to the experienced level of stress in the family were: 1. The presence of psychopathology in (one of) the parents, 2. Educational level of the mother and 3. The several domains on the CBCL. Though these correlations indicate coherence, they do not necessarily give direction to this coherence. For example, stress enhances the risk to develop psychopathology, but psychopathology itself does also generate stress. The presence of psychopathology in (one of) the parents is strongly correlated (respectively fathers versus mothers: r= 0.023 and r=<0.001) to the presence of pathological parental stress. This can be understood from facing dual strain as they have to deal with their own disease burden and, on top of that, the disease burden of their child. In addition, raising a child requires a certain degree of flexible adaptation to the child's needs[36]. The presence of psychopathology in one of the parents may interfere with this ability to adapt. The DSM-5 manual[37] describes this by means of the criterion D, in which current functioning needs to be affected in several areas of daily life.

Furthermore, in this study, the educational level of mothers significantly connects to higher parental stress levels, with an inverse correlation in our cohort. Lower educated mothers face more stress than the higher educated mothers. A study of Parkes et al. [38] has shown that parental stress was higher at both ends of the educational spectrum, with lower educated mothers having most parental stress followed by the higher educated mothers. The latter was explained by difficulties fulfilling the needs of both work and the child. Intermediate educated mothers showed the lowest stress levels in this study. Although we expected to find same results, this was not the case in our cohort. The highest educated mothers showed the lowest mean FAD scores as well as low scores for the presence of pathological stress. Although the results of educational levels of fathers were not significant in our cohort, a same trend was evident.

It is a well-known fact that lower educational levels are associated with lower socioeconomic status (SES) and vice versa. Several stressors, like financial problems, health problems, unhealthy lifestyle as well as social isolation and psychopathology are associated with lower SES[39]. Moreover, the capacity of executive functioning (EF) is vulnerable to stress. EF comprises attention, memory, working memory capacity and emotion regulation capacity[40]. So one can hypothesize that parenting stress results in less flexibility to provide care. Moreover, it was found that a lower SES is associated with a reduced well-being and alterations in brain development of the child[41,42]. As a consequence, the sum of stressors could be detrimental to these parents and their children.

Finally, the significant correlation between overall-domains (total score, internalizing score and externalizing score) of the CBCL requires some explanation. The CBCL is a parent-based questionnaire, designed to detect symptoms of psychopathology in the child[32]. The significant correlations at all domains are suggestive that this instrument in this population is subject to bias. Higher levels of stress in the parents seem to be related to significant higher scores (indicative) for psychopathology in the child. This presumption is strengthened by the lack of even a single correlation between psychopathology, scored by an independent informant (mini PAS-ADD subscales).
Besides those statistical significant correlations, the factors biological and developmental age do also show a trend

towards significant correlation. These inverse correlations can be understood from the fact that young children, whether they are biologically young or developmentally young, need a lot of sensitivity and responsiveness from their parents. Critical in sensitive parenting is the ability to adapt parental behavior in a flexible way to the child's needs.

(Para)medical counselors, like clinical geneticists and pediatricians working with children diagnosed with a genetic syndrome, should be aware of these high levels of stress in the families. In medicine, genetic disorders resulting in NDD are still considered to be a fixed state rather than a chronical developmental disorder, with a fluctuating course during the span of life. The disease burden, as our data clearly indicate, is considerable and especially the stress, experienced by parents and caregivers, is extensive. An optimal organization of care for these children and their families should take the complexity of these factors into account and pay attention to both child factors, adaptive factors, as well as maladaptive (e.g. psychiatric and somatic), and environmental factors. Specific attention should be paid to the transition phases, like starting school and puberty.

Besides the way in which professionals regard and cope with the disease, which is primarily focused on child characteristics, it is also important to help parents deal with the diagnosis as well as the associated daily life problems. Parents should receive education about their child's developmental level, including cognitive, psychological and behavioral features, but also about the disease burden (recognition) and opportunities to find support for themselves. Ideally, short training modules for parents should be offered to promote better coping and acceptance of their child's diagnosis (for example mindful parenting[43,44]). The parents should be familiarized with, as well as to gain access to, the web of care requests and agencies for their child. Besides, extra attention should be on psychopathology in the parents and referral for this. The well-being of the parent does relate to well-being of the child[2,45]. Therefore, it is of clinical importance to identify maladaptive family functioning. This study provides a first step for detecting parental stress in daily clinical practice of managing monogenetic disorders.

Limitations of this study are the relatively small sample size, although it is already a fairly large group for rare syndromes. Ideally, we feel that the groups would all have included over 20 participants. Another limitation is the single moment at which the FAD questionnaire was completed by both parents. The question is whether these results are equal or fluctuate in time. Additional, we question whether there are differences in the scoring between each of the parents. For instance in autism spectrum disorders, parental scores may differ significantly between fathers and mothers[46]. We recommend considering these issues in future research on this topic. In order to properly interpret the results, it is necessary to have repeated measures of the FAD as well as other parameters, related to stress. Additional socio-economic factors, for example the family income, amount of involved health care workers and temperament features can be of value to further specify risk factors. However, this deserves a separate/ follow-up study. Furthermore, repetition in a larger number of participants is recommended. Specific attention in future research should be on stress sensitivity of parents.

Conclusion:

The data from this study implicate strongly that more attention should be paid to stress levels in the parents, who raise a child with a (rare) genetic syndrome. Although the heterogeneity of maladaptive family

functioning is high, the average level of stress in the parents should raise concerns. Indeed, these are even higher than in a number of other chronic diseases, which are associated with major changes in daily life. A sum of factors plays a role in the pathological development of this stress and threatens the well being of the child (as well as other family members). Screening for increased stress levels in the patient's parents should therefore be an essential part of the medical consultation.

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