JIMD Reports
DOI 10.1007/8904_2013_233

RESEARCH REPORT

Socio-emotional Problems in Children with CDG

K.F.E. van de Loo • L. van Dongen • M. Mohamed • T. Gardeitchik • T.W. Kouwenberg • S.B. Wortmann • R.J.T. Rodenburg • D.J. Lefeber • E. Morava • C.M. Verhaak

Received: 27 February 2013 / Revised: 05 April 2013 / Accepted: 12 April 2013 / Published online: 4 June 2013

Abstract *Background*: Congenital disorders of glycosylation (CDG) form a group of inherited metabolic diseases. Although the clinical presentation shows extreme variability, the nervous system is frequently affected. Several parents of our patients diagnosed with CDG reported behavioral problems, including mood swings, depressive behavior, and anxiety. This raised the question whether patients with CDG have an increased risk for socio-emotional problems.

Methods: We evaluated 18 children with confirmed CDG. The Child Behavior Checklist (CBCL) was used to screen for socio-emotional problems. To determine the disease progression and severity in CDG, the Nijmegen Paediatric CDG Rating Scale (NPCRS) was used. Results were compared to "norm scores" and to children with mitochondrial disorders and children with other chronic metabolic disorders with multisystem involvement.

Results: Results showed a high prevalence of socio-emotional problems in children with CDG. Mean total scores, scores on withdrawn/depressed behavior, social problems, and somatic complaints were significantly increased. More than two thirds of our CDG patients have abnormal scores on CBCL. The mean score on social problems was significantly higher compared to our two control groups of patients with other chronic metabolic disorders.

Conclusions: Patients with CDG have an increased risk of developing socio-emotional problems. A standard screening for psychological problems is recommended for the early detection of psychological problems in CDG patients.

Communicated by: Verena Peters
Competing interests: None declared

Authors van de Loo, van Dongen contributed equally;
Authors Morava and Verhaak contributed equally
We state no conflict of interest and the authors are all in agreement with the submission of the manuscript

K.F.E. van de Loo · C.M. Verhaak
Department of Medical Psychology, Radboud University Medical Centre, Nijmegen, The Netherlands

L. van Dongen · M. Mohamed · T. Gardeitchik · T.W. Kouwenberg · S.B. Wortmann · R.J.T. Rodenburg
Department of Pediatrics, Institute for Genetic and Metabolic Disease, Radboud University Medical Centre, Nijmegen, the Netherlands

M. Mohamed · T. Gardeitchik · T.W. Kouwenberg · S.B. Wortmann · R.J.T. Rodenburg · D.J. Lefeber · E. Morava
Laboratory of Genetic Endocrine and Metabolic Diseases, Institute for Genetic and Metabolic Disease, Radboud University Medical Centre, Nijmegen, the Netherlands

D.J. Lefeber
Department of Neurology, Institute for Genetic and Metabolic Disease, Radboud University Medical Centre, Nijmegen, the Netherlands

E. Morava (✉)
Department of Pediatrics, Institute for Genetic and Metabolic Disease, Hayward Genetics Centre, Tulane Medical School, New Orleans, Louisiana, USA
e-mail: emoravakozicz@tulane.edu

E. Morava
Department of Pediatrics, Radboud University Medical Centre, Nijmegen, the Netherlands

Abbreviations

CBCL	Child Behavior Checklist
CDG	Congenital disorders of glycosylation
MCD	Mitochondrial disease
NPCRS	Nijmegen Paediatric CDG Rating Scale
NPMDS	Newcastle Paediatric Mitochondrial Disease Scale

Introduction

Glycosylation is a biologically essential enzymatic multi-step process, which has impact on the folding, secretion, transport, and function of proteins and lipids (Freeze 2006;

Jaeken 2010). Defects in the glycosylation cause congenital disorders of glycosylation (CDG), which is now approaching 50 different defects (Jaeken 2010; Jaeken et al. 2009; Theodore and Morava 2011). Each disorder is called after the corresponding gene symbol followed by "-CDG".

PMM2-CDG (CDG-Ia), MPI-CDG (CDG-Ib), and ALG6-CDG (CDG-Ic) are the most common reported types of CDG, with over 700 patients, over 20 patients, and over 30 patients affected worldwide, respectively. Other CDG subtypes are rare and in some cases only reported in a single patient (Mohamed et al. 2011; Sparks and Krasnewich 2005).

Because of the ubiquitous requirement of glycoproteins, CDGs usually present as a multisystem disease. Neurologic involvement, failure to thrive, liver dysfunction, coagulation abnormalities, and dysmorphic features are frequent. Typical CDG type I features include inverted nipples, fat pads, low serum thyroxin-binding globulin, and strabismus. Neurological involvement is common and differs in severity in CDG-I patients. Some CDG subtypes present with specific symptoms. For example, MPI-CDG is characterized by hepatic-intestinal problems (Liem et al. 2008), and ATP6V0A2-CDG (cutis laxa type IIA) and COG7-CDG patients often show cutis laxa (Morava et al. 2007, 2009a, b).

In medical literature, patients with CDG are generally described as very social extrovert children, of warm character (Grünewald 2009). However, this hypothesis is based on observations and has never been studied in diverse forms of CDG. Until now, there is no literature available regarding the socio-emotional functioning in patients with CDG. In our own patient group, however, socio-emotional problems, including mood swings, depressive behavior, or possible anxiety, have been reported by parents. This raised the question whether patients with CDG have an increased risk of socio-emotional problems like mood disorders and social problems.

The prevalence of socio-emotional problems in children with chronic diseases is higher compared to healthy children. In the Netherlands, at least 14 % of the children suffer from a chronic disease (Mokkink et al. 2007). Literature shows that children with chronic diseases show more internalizing problems like socio-emotional problems and depressive symptoms (Boekaerts and Röder 1999; Evans et al. 2005). This is also described in metabolic and endocrine diseases. Children with a genetic cause of hyperandrogenism, phenylketonuria, and type 1 diabetes show more socio-emotional problems than healthy controls (Mueller et al. 2010; Northam et al. 2006; Waisbren and White 2010). Endocrine disorders like hypothyroidism can manifest with depression as a first symptom (Davis and Tremont 2007). Furthermore, children with mitochondrial disorders show a higher rate of withdrawn, depressive behavior, compared to norm scores and children with other metabolic disorders (Koene et al. 2009; Morava et al. 2010). These results suggest that depression is more likely the result of the mitochondrial disorder itself, rather than due to the fact that this metabolic disorder is a chronic disease.

The aim of this study is to assess if children with CDG have more socio-emotional problems compared to norms and if these problems are inherent to CDG. Based on the literature and observations in the clinical practice, it is expected that children with CDG show more internalizing problems compared to healthy children and compared to children with other chronic diseases. To test this hypothesis, we compared children with CDG to population norm scores and to children with other chronic metabolic diseases with multisystem presentation, to evaluate whether the symptoms can be partially due to a chronic disease. We also compared the children with CDG to patients with mitochondrial disorders, who have been shown to present with inherent psychological problems.

Methods

For this study, we included patients with a biochemically and genetically confirmed diagnosis of congenital disorders of glycosylation aged 1 to 18 years. Patients with different subtypes of CDG were included in the study (Table 1). The study was conducted upon initiative from several parents attending a CDG patient/parent information day. Subsequently, CBCL screening and psychological evaluation and consult were offered to 26 of our patients of pediatric age. Eighteen patients responded to the interviews. In all 18 patients, a psychological screening was performed using the Child Behavior Checklist (CBCL) to screen for socio-emotional problems (Achenbach and Rescorla 2000; Achenbach and Rescorla 2001). The primary caretaker was invited to answer the CBCL interview questions. Because intellectual disability is common in CDG patients, we decided to also include intellectually disabled patients in our study. Patients were scored on IQ by WPPSI/WISC and an IQ of 70 was used as cut-off score for intellectual disability. In patients younger than 2.6 years, a developmental assessment was performed using the BSID. In the group of 18 patients, 8 children (44%) (5 girls and 3 boys) are intellectually disabled.

Clinical Studies

To determine the severity of the metabolic disorder, two of our investigators scored the patients with the Nijmegen Paediatric CDG Rating Scale (NPCRS) (Achouitar et al. 2011) by reviewing the medical history and clinical examination. Three different questionnaires are available for three age groups: 0–24 months, 2–11 years, and 12–18 years (Achouitar et al. 2011). These questionnaires consist of three sections. Section I (Current function) includes seven questions regarding seven general functions (vision, hearing, communication, feeding, self-care, mobility, and

Table 1 Characteristics, NPCRS, and CBCL scores of CDG patients

Id	Sex	Age	IQ	Diagnose	Visual involvement	Communication problems	Gastrointestinal	Muscle hypotonia, weakness	Liver involvement	Growth retardation	Impaired development	Strabismus	Ataxia	CDG score	Total CBCL score	CBCL T-score internalizing	CBCL T-score externalizing	CBCL T-score anx/dep	CBCL T-score with/dep	CBCL T-score social problems	CBCL T-score somatic complaints
1	M	15	<70	ALG6-CDG	-	+	-[b]	+	-	+	+	+	+	22	64	47	63	50	53	70	58
2	M	17	>70	ALG13-CDG	-	-	-	-	-	+	+	+	-	4	56	52	57	50	54	63	61
3	F	10	<70	ATP6V0A2-CDG	-	+	+[b]	+	+	-	+	+	-	18	57	61	53	60	60	59	57
4	M	15	>70	PMM2-CDG	-	-	-	+	+	-	+	+	-	8	67	69	63	65	70	66	61
5	F	13	>70	PMM2-CDG	-	+	+	+	+	+	+	-	+	11	70	75	63	78	66	78	76
6	M	14	<70	ALG6-CDG	-	+	+	+[c]	-	+	+	+	+	27	70	65	66	50	66	70	72
7	F	6	>70	SRD5A3-CDG	-	+	-	+	+	-	+	+	-	16	50	39	47	50	52	59	50
8	F	1	<70	PMM2-CDG	+	+	+[b]	+	+	-	+	+	-	22	50	62	39	50	60		70
9	M	17	<70	PMM2-CDG	+[a]	+	-	+[c]	-	-	+	+	+	30	47	34	43	50	50	67	50
10	F	12	<70	PMM2-CDG	+[a]	+	+[b]	+[c]	-	+	+	+	+	33	66	53	65	50	57	73	59
11	F	2	>70	PMM2-CDG	+	+	+[b]	+	+	+	+	+	-	23	49	56	44	51	63		50
12	F	3	>70	PMM2-CDG	-	-	-	+	+	-	+	+	+	14	36	29	42	50	50		50
13	F	14	>70	ATP6V0A2-CDG	-	-	-	-	-	-	+	-	+	6	69	69	63	67	66	87	68
14	F	8	<70	ALG6-CDG	-	-	+[b]	+[c]	-	-	+	+	-	19	73	67	64	63	68	77	64
15	M	8	>70	PMM2-CDG	+	+	+[b]	+[c]	+	+	+	+	+	28	72	69	58	54	68	77	74
16	M	14	>70	PMM2-CDG	-	+	-	+	-	-	+	+	+	13	40	40	34	50	53	51	50
17	F	10	<70	MPI-CDG	-	+	+[b]	+	+	+	+	-	+	18	71	52	71	50	64	72	57
18	M	8	>70	MPI-CDG	-	+	+[b]	+	+	+	+	+	+	19	65	59	59	54	60	57	61

Gray: increased score for social problems

All patients had impaired educational achievement

[a] Also hearing problems

[b] Also feeding problems

[c] Wheelchair use

educational achievement). The scale for 0–24 months only has five questions in this section (vision, hearing, communication, feeding, and mobility). Section II (System Specific Involvement) consists of questions to review central nervous system, blood, gastrointestinal, endocrine, respiratory, cardiovascular, renal, and liver functions over the preceding six months. Section III (Current Clinical Assessment) includes nine questions related to the current status of the patient (growth, development, vision, strabismus and eye movement, myopathy, ataxia, pyramidal, extrapyramidal, and neuropathy) (Achouitar et al. 2011). All items have four answer options: normal (0), mild (1), moderate (2), and severe (3), except the assessment of development. On this item, a score of 0–7 is possible. The total scale consists of 26 questions and the maximum score is 82.

Psychological Studies

Primary caretakers of the CDG patients completed the CBCL concerning the child. The CBCL is a widely used screening questionnaire for behavioral, emotional, and social functioning in children aged 1.5–18 years (Achenbach and Rescorla 2000, 2001). In this study, the CBCL was filled in by one parent.

We were interested in the total score of the CBCL as a measure of overall problems, as well as the internalizing and externalizing score, for children aged 1.5–18 years. Furthermore, of the syndrome profile, we used the subscales anxious/depressed (1.5–18 years) and withdrawn/ depressed (1.5–18 years) to investigate depressed behavior, social problems (only in CBCL 6–18 years), and somatic complaints (1.5–18 years). The remaining subscales were also analyzed to screen for possible other behavioral problems.

The raw scores were analyzed and assigned to T-scores using the ASEBA Windows software Assessment Data Manager (ADM) (Achenbach and Rescorla 2000, 2001). For the total, internalizing, and externalizing scores, we used T-score of 60 (93rd percentile) as cut-off point. For the subscales, we used a T-score of 65 (93rd percentile) as cut-off point.

Control Group 1

Our first control group consisted of 18 children with other inborn errors of metabolism (of other metabolic disorders), namely, mitochondrial disorders. These disorders also have a multisystem nature, in which organs are affected in variable severity. The patients are under regular outpatient follow-up at our hospital. Psychological screening using the CBCL is performed as routine care in this group of patients. We selected 18 patients for our control group, matched with the CDG group based on age, sex, and IQ. Equal to the

CDG group, in this group 8 children are intellectually disabled (IQ < 70) (5 girls and 3 boys). Comparable to the CDG group, we determined the severity of the metabolic disorders in this control group using the Newcastle Paediatric Mitochondrial Disease Scale (NPMDS) (Phoenix et al. 2006). The NPCRS, used in the CDG group, is derived from this scale. Most questions overlay and the scoring system is equal. The scale also consists of three sections, 26 items, and the maximum score is 82.

Control Group 2

Our second control group consisted of 18 patients with inborn errors of metabolism, other than CDG and mitochondrial disorders. We selected these children due to the multisystem nature of their disease. This group included children diagnosed with amino acidopathies (phenylketonuria, homocysteinemia), carbohydrate metabolism disorder (glycogen storage disease, galactosemia), organic acidemia (isovaleric acidemia, methylmalonic acidemia, propionic acidemia), urea cycle disorder (carbamyl phosphate synthetase deficiency), and fatty acid oxidation disorders (short-chain acyl-CoA dehydrogenase deficiency). Psychological screening using the CBCL has been performed as routine care in this group of patients. From this database we selected 18 consecutive patients, also matched on age, sex, and IQ. Seven out of the eighteen children are intellectual disabled, 4 girls and 3 boys.

Analysis

For the data analysis, SPSS version 18 software has been used. Significance was set at a p-value <0.05. To determine normal distribution, we used the Kolmogorov-Smirnov test. This test confirmed normal distribution on all scores on the CBCL and on the NPCRS and NPMDS. We compared the CBCL scores, including the total, internalizing, and externalizing scores and the subscores anxious/depressed, withdrawn/depressed, social problems, and somatic complaints, of our study group to norm scores of the American population using the one sample *T*-test, in absence of the Dutch norms. We compared the CBCL scores of our study group to the control groups with multiple independent sample T-ests. We evaluated possible correlations between clinical symptoms, severity and disease progression, and socio-emotional problems based on disease severity and progression (NPCRS scores) and the CBCL total, internalizing, and externalizing scores, using the Pearson Correlation.

Results

CDG Group

The CDG group consists of 18 patients with confirmed congenital disorders of glycosylation, 8 boys and 10 girls. The mean age is 10 years and 10 months.

The severity of the disease was scored by the NPCRS, as described above (Achouitar et al. 2011). Mean scores were 7.3 (1–15) (Section I), 2.4 (0–4) (Section II), 8.7 (3–16) (Section III), and 18.4 (4–33) (Total). The clinical features and CBCL scores of the CDG patients are demonstrated in Table 1.

Out of the 18 patients, 13 (72%) had an abnormal score on the CBCL. Ten children (56%) scored above the cut-off point on the total score, 8 (44%) children on the internalizing scale, and 8 (44%) children on the externalizing scale. On the subscales, three children (17%) scored above the cut-off point on anxious/depressed, 6 (33%) on withdrawn/depressed, and 5 (28%) on somatic complaints. Because the subscale social problems is not included in the CBCL 1.5–5 years, data of only 15 patients is available on this subscale. Ten of these 15 children (67%) showed social problems.

All of the children with CDG with an IQ of <70 (100%) show problems on one or more measures of the CBCL compared to 50% of the children with CDG with a normal IQ.

More than half of the PMM2-CDG patients have an aberrant CBCL score (6 out of 9). With four children showing total and internalizing problems, three showed external problems. Five of them have an abnormal score on the subscale social problems, two on anxious/depressed behavior, three on withdrawn/depressed behavior, and three on somatic complaints. The two patients with MPI-CDG showed an abnormal total score on the CBCL. One of them also had abnormal scores on externalizing problems and social problems. All three patients with ALG6-CDG in our study group have abnormal total and externalizing scores and abnormal scores on social problems. Two of them also have abnormal scores on internalizing scores and withdrawn/depressed behavior. One of them also had an abnormal score on somatic complaints. One of two children diagnosed with ATP6V0A2-CDG in our study group had abnormal scores on all four subscales, except social problems, and on total, internalizing, and externalizing scores. The other child had only an abnormal score on internalizing problems on the CBCL. The two children diagnosed with ALG13-CDG and SRD5A3 had normal CBCL scores.

Table 2 Characteristics, NPMDS, and CBCL scores of MCD patients

Id	Sex	Age	IQ	Diagnose/Complex deficiency*	Visual involvement	Communication problems	Gastrointestinal	Muscle hypotonia, weakness	Liver involvement	Growth retardation	Impaired development	Ptosis	Ataxia	MCD score	Total CBCL score	CBCL T-score internalizing	CBCL T-score externalizing	CBCL T-score anx/dep	CBCL T-score with/dep	CBCL T-score social problems	CBCL T-score somatic complaints
1	F	9	>70	C III and IV def.	+	+	-[a]	+	-	-	+	-	-	18	72	78	70	68	70	67	80
2	M	18	>70	C I and III def.	+	-	-[a]	+	-	+	+	+	+	27	60	57	56	57	57	67	54
3	F	5	>70	C I def.	-	+	-[a]	+	-	-	+	+	-	15	60	62	51	50	67		62
4	M	7	<70	C I, II and III def.	-	-	+[a]	+	-	-	+	-	-	12	68	52	64	50	66	62	50
5	F	3	>70	C I, II and III def.	-	-	+	+	-	-	+	-	-	9	67	72	58	63	76		74
6	F	11	<70	C I and III def.	-	+	+[a]	+	-	-	+	-	+	15	64	64	62	66	66	54	50
7	M	11	<70	C V def.	-	+	+[a]	+[b]	+	+	+	+	-	25	47	52	33	50	62	56	57
8	M	12	>70	C III def.	-	+	-	-	+	-	+	+	-	10	67	70	58	68	70	82	64
9	M	17	<70	C I def.	-	+	-	-	-	-	+	-	-	8	57	67	46	54	86	58	54
10	F	9	>70	C I, III and V def.	+	-	-	+	-	+	+	-	-	14	46	52	34	52	56	51	53
11	M	12	>70	C I def.	-	+	-	-	-	-	+	-	-	3	52	69	40	63	70	54	64
12	F	17	>70	C V def.	-	-	+	+	-	-	+	-	-	8	29	33	34	50	50	50	50
13	M	6	>70	C I and III def.	-	-	-	-	-	-	+	-	-	10	53	65	48	57	54	53	72
14	F	19	<70	C I and IV def.	+	+	+[a]	+[b]	-	+	+	-	-	27	59	58	49	50	60	61	68
15	F	16	<70	C I and IV def.	+	+	+[a]	+[b]	-	+	+	-	-	29	70	70	66	57	85	54	68
16	F	2	<70	C I def.	+	+	-[a]	+	-	-	+	-	-	20	57	58	59	50	63		53
17	F	6	<70	C II and III def.	-	-	+[a]	+	+	+	+	-	-	16	77	70	80	57	77	77	68
18	M	6	>70	C III def.	-	-	+[a]	-	-	+	+	-	-	9	53	41	50	50	50	58	53

Gray: increased score for social problems

*All patients, except 5, 10, and 11, had impaired educational achievement. The diagnosis is made based on measurements in a muscle biopsy according to established diagnostic procedures (Janssen et al. (2006) Chemistry 52: 860)

[a] Also feeding problems

[b] Wheelchair use

Control Group 1

The first control group consisted of 18 patients with a mitochondrial disease, 8 boys and 10 girls, with a mean age of 10 years and 8 months. The severity of the disease was scored by the NPMDS (see Methods) (Phoenix et al. 2006). Mean scores on Section I, II, and III are, respectively, 6.2 (0–17), 1.7 (0–4), and 7.4 (2–16) and the mean total score was 15.3 (3–29). Independent T-tests show no significant differences in scores between the CDG group and the MCD group. Clinical features and the CBCL scores of the MCD patients are demonstrated in Table 2. Twelve (67%) out of the 18 patients had an abnormality on the CBCL. Nine children (50%) scored above the cut-off point on the total score, 10 (56%) on the internalizing, and 5 (28%) on the externalizing scale. Three children (17%) had a score above the cut-off point on the subscale anxious/depressed, 10 (56%) on withdrawn/depressed, and 6 (33%) children on the subscale somatic complaints. Four out of 15 children (27%) showed social problems.

Control Group 2

The second control group consists of 18 patients with inborn errors of metabolism, including amino acidopathies, carbohydrate metabolism disorder, organic academia, urea cycle disorder, and fatty acid oxidation disorders. Mean age was 10 years and 4 months, with ages varying from 3 years and 9 months to 18 years and 5 months. No instrument was available to score disease severity. CBCL scores of the second control group are demonstrated in Table 3.

Eleven (61%) out of the 18 patients had an abnormality on the CBCL. Eight children (44%) scored above the cut-off point on the total score, six (33%) on the internalizing scale, and 5 (28%) on the externalizing scale. Three children (17%) showed problems on the subscale anxious/depressed, two (11%) on withdrawn/depressed, and five (28%) on somatic complaints. Five out of 15 children (33%) showed social problems.

Correlation Clinical Severity and Organ Involvement with CBCL Scores

No correlations were found between the CBCL total score and the NPCRS total score (Pearson Correlation = 0.068, $p = 0.790$), NPCRS section I (Pearson Correlation = 0.088, $p = 0.728$), or NPCRS section III (Pearson Correlation = −0.143, $p = 0.572$). There is a small positive correlation between Section II on the NPCRS and total score on CBCL in CDG as measured by the Pearson Correlation (Pearson Correlation = 0.482, $p = 0.043$). However, regarding the small sample sizes we do not consider this result as statistically significant.

Table 3 Characteristics and CBCL scores of the patients of control group 2

Id	Sex	Age	IQ	Diagnose	Total CBCL score	CBCL T-score internalizing	CBCL T-score externalizing	CBCL T-score anx/dep	CBCL T-score with/dep	CBCL T-score social problems	CBCL T-score somatic complaints
1	M	4	<70	Methylmalonic aciduria	55	51	59	50	56		50
2	M	10	>70	Glycogenosis type Ia	71	71	65	66	76	69	67
3	M	7	<70	Propionic acidemia	50	41	44	50	54	56	50
4	M	9	>70	Glycogenosis type IX	64	58	66	57	66	65	50
5	M	6	>70	Carbamoyl phosphate synthetase I deficiency	62	58	58	57	62	53	53
6	M	12	<70	Glycogenosis type Ia	58	62	53	63	53	58	67
7	F	15	>70	Cobalamin C deficiency	67	58	64	50	63	70	62
8	F	18	<70	Cobalamin C deficiency	62	64	51	62	57	61	65
9	F	10	<70	Isovaleric aciduria	69	64	70	66	64	62	53
10	F	9	<70	Glycogenosis type IX	53	48	47	50	50	51	61
11	F	5	>70	Isovaleric aciduria	42	49	39	56	51		50
12	F	8	>70	Ketotic hypoglycemia	53	56	44	54	52	54	61
13	F	10	>70	Glycogenosis type IX	55	61	51	57	50	51	68
14	M	3	<70	Glycogenosis type IX	48	55	44	56	60		53
15	M	10	>70	Glycogenosis type IX	36	45	33	50	50	50	57
16	F	7	>70	Phenylketonuria	62	58	64	54	64	57	53
17	F	18	<70	Galactosemia	52	58	34	55	63	73	53
18	F	15	>70	Methylmalonic aciduria	68	74	59	72	60	70	84

Gray: increased score for social problems

Table 4 Mean behavior T-scores in the patients with CDG compared to norm scores. $N = 18$

	Total score (CBCL 1.5–18 years)	Internalizing score (CBCL 1.5–18 years)	Externalizing score (CBCL 1.5–18 years)	Anxious/ depressed (CBCL 1.5–18 years)	Withdrawn/ depressed (CBCL 1.5–18 years)	Social problems (CBCL 6–18 years)	Somatic complaints (CBCL 1.5–18 years)
Mean T-score	59.6	55.4	55.2	55.1	60.0	68.4	60.4
Mean diff. (95% CI)	9.6 (3.7–15.4)	5.4 (–1.2–12.1)	5.2 (–0.2–10.7)	1.1 (–2.9–5.2)	6.0 (2.7–9.3)	14.4 (9.1–19.7)	6.4 (2.1–10.8)
p-value	**0.003**	0.101	0.059	0.571	**0.001**	**0.000**	**0.006**

For the standard CBCL scales, a subscale score of <65 is normal, 65–69 scores are borderline, and from the score >70 indicate a clinical problem (normative ranges are different for girls and for boys) (Achenbach and Rescorla 2000, 2001)

CDG Patients Scores Compared to Norm Scores

Mean CBCL total score is significantly higher in children with CDG compared to norm scores ($p = 0.003$; Table 4). The internalizing and externalizing scales were not significantly higher ($p = 0.101$ and $p = 0.059$, respectively). The mean score of anxious, depressive behavior in our study group was not statistically significantly increased ($p = 0.571$).

Compared to the norms scores, in children with CDG the mean score was significantly higher on withdrawn/ depressed behavior ($p = 0.001$), social problems ($p = 0.000$), and on somatic complaints ($p = 0.006$). Furthermore, we screened the other subscales for possible problems. Results showed more thought problems ($p = 0.044$), attention problems ($p = 0.004$), aggressive behavior ($p = 0.011$), affective problems ($p = 0.003$), anxiety problems ($p = 0.032$), somatic problems ($p = 0.031$), ADHD problems ($p = 0.008$), and conduct problems ($p = 0.016$) in the CDG group compared to the norms.

Table 5 shows the mean differences between CDG patients with an IQ of > 70 and an IQ <70 and the norm scores. In CDG patients with a normal IQ, results still show a significantly increased mean score on the

Table 5 Mean behavior T-scores in the patients with CDG and an IQ of >70 and < 70 compared to norm scores

	Total score (CBCL 1.5–18 years)	Internalizing score (CBCL 1.5–18 years)	Externalizing score (CBCL 1.5–18 years)	Anxious/ depressed (CBCL 1.5–18 years)	Withdrawn/ depressed (CBCL 1.5–18 years)	Social problems (CBCL 6–18 years)	Somatic complaints (CBCL 1.5–18 years)
Patients with CDG and an IQ of >70. $N = 10$							
Mean T-score	57.4	55.7	53.0	56.9	60.2	67.3	60.1
Mean diff. (95% CI)	7.4 (–2.0–16.8)	5.7 (–5.4–16.8)	3.0 (–4.5–10.5)	2.9 (–4.1–9.9)	6.2 (0.9–11.5)	13.3 (3.0–23.5)	6.1 (–1.1–13.3)
p-value	0.108	0.275	0.386	0.371	**0.027**	**0.019**	0.089
Patients with CDG and an IQ of <70. $N = 8$							
Mean T-score	62.3	55.1	58.0	52.9	59.8	69.7	60.9
Mean diff. (95% CI)	12.3 (4.0–20.5)	5.1 (–4.1–14.3)	8.0 (–1.8–17.8)	–1.1 (–5.6–3.4)	5.8 (0.5–11.0)	15.7 (10.5–20.9)	6.9 (0.7–13.0)
p-value	**0.010**	0.229	0.094	0.573	**0.035**	**0.000**	**0.033**

For the standard CBCL scales, a subscale score of <65 is normal, 65–69 scores are borderline, and from the score >70 indicate a clinical problem (normative ranges are different for girls and for boys) (Achenbach and Rescorla 2000, 2001)

Table 6 Mean behavior T-scores in the patients with CDG compared to T-scores in the control groups

	Total score (CBCL 1.5–18 years)	Internalizing score (CBCL 1.5–18 years)	Externalizing score (CBCL 1.5–18 years)	Anxious/ depressed (CBCL 1.5–18 years)	Withdrawn/ depressed (CBCL 1.5–18 years)	Social problems (CBCL 6–18 years)	Somatic complaints (CBCL 1.5–18 years)
Mean behavior T-scores in the patients with CDG compared to T-scores in control group 1. $N = 18$							
Mean T-score CDG group	59.6	55.4	55.2	55.1	60.0	68.4	60.4
Mean T-score control group 1	58.8	60.6	53.2	56.2	65.8	60.3	60.8
Mean diff. (95% CI)	0.8 (–7.0–8.6)	–5.1 (–13.5–3.3)	2.0 (–6.1–10.1)	–1.1 (–6.2–3.9)	–5.8 (–11.9–0.2)	8.1 (1.1–15.2)	–0.3 (–6.5–5.8)
p-value	0.841	0.226	0.621	0.658	0.058	**0.026**	0.913
Mean behavior T-scores in the patients with CDG compared to T-scores in control group 2. $N = 18$							
Mean T-score CDG group	59.6	55.4	55.2	55.1	60.0	68.4	60.4
Mean T-score Control group 2	57.1	57.3	52.5	56.9	58.4	60.0	58.7
Mean diff. (95% CI)	2.5 (–4.7–9.7)	–1.8 (–9.4–5.8)	2.7 (–4.8–10.3)	–1.8 (–6.8–3.2)	1.6 (–3.1–6.3)	8.4 (1.9–14.9)	1.7 (–4.3–7.8)
p-value	0.487	0.626	0.469	0.461	0.489	**0.013**	0.565

For the standard CBCL scales, a subscale score of <65 is normal, 65–69 scores are borderline, and from the score >70 indicate a clinical problem (normative ranges are different for girls and for boys) (Achenbach and Rescorla 2000, 2001)

subscales withdrawn/depressed behavior ($p = 0.027$) and social problems ($p = 0.019$) compared to norms, even though less patients are included ($n = 10$). Children with CDG with an IQ of <70 show more total problems ($p = 0.010$), withdrawn/depressed behavior ($p = 0.035$), somatic complaints ($p = 0.033$), and social problems ($p = 0.000$) compared to the norms.

Comparison Between CDG Group and the Control Groups

The mean CBCL total, externalizing, and internalizing scores in our study group was not significantly aberrant from both control groups (Table 6). The same was true for the subscales anxious/depressed, withdrawn/depressed behavior, and somatic complaints.

The occurrence of social problems was significantly higher in our study group compared to children with mitochondrial disorders ($p = 0.026$) and children with other metabolic disorders ($p = 0.013$).

Conclusions

The aim of this study was to investigate whether children with CDG have more socio-emotional problems compared to the norm group and compared to children with other chronic metabolic diseases with multisystem presentation. As observed in our clinic, results showed that children with CDG show more overall problems compared to norms. Furthermore, they show more withdrawn/depressive behavior, social problems, somatic complaints, affective problems, and anxiety problems compared to the norms. As previously described, this is in line with children with other metabolic diseases who also show more socio-emotional problems compared to healthy controls (Koene et al. 2009; Morava et al. 2010; Mueller et al. 2010; Northam et al. 2006; Waisbren and White 2010). Compared to children with other metabolic diseases, children with CDG, however, show more social problems. This could mean that social problems are inherent to CDG. However, regarding the small sample sizes, more research is needed to draw such a firm conclusion.

One might hypothesize that a more severely affected child would have higher scores on the CBCL. However this was not the case, there was no correlation found between total score on NPCRS and the scores on the CBCL. Results suggest that socio-emotional problems are more a result of the disease itself rather than of the disease severity or progression.

In our study, all of the children, with CDG with an IQ below 70, show one or more socio-emotional problems. This is even higher as described in literature, which shows that the prevalence of socio-emotional problems is three to five times higher in the intellectually disabled compared to the normal population (Došen 2008). Therefore, children with CDG who are also intellectually disabled have an even higher risk of socio-emotional problems. According to Koskentausta et al. (2004), the CBCL is reliable in mild intellectually disabled children, but is less reliable in children with moderate, severe, or profound intellectual disability. A study of Borthwick-Duffy et al. (1997) showed, however, that CBCL is reliable in children with an intellectual disability and supports the use of the CBCL in these children. Furthermore, Masi et al. (2002) report that the CBCL overall measure shows a high correlation with other measures of socio-emotional problems in mentally retarded children and could therefore be used as a reliable screenings instrument. A limitation is that this study did not make a subdivision in IQ values below 70 due to small sample sizes; in future studies, this is recommended to draw firm conclusions.

By evaluating the relatively small CDG subpopulation with normal intelligence, the scores are still significantly higher on subscales withdrawn/depressed behavior and social problems compared to the population (Table 5). Therefore, the occurrence of withdrawn/depressed behavior and social problems in children with CDG seems to be independent of intelligence.

Surprisingly, we found no differences regarding anxious/depressed behavior in children with CDG compared to the population. Even in the intellectually disabled children, there were no differences found, while according to the literature, mentally retarded children are more vulnerable to socio-emotional problems, especially anxiety and depression (Masi et al. 1999, 2000). According to Masi et al. (2002) the anxious/depressed subscale of the CBCL, however, does not correlate with other depression measures in questionnaires developed solely for mentally retarded children. So it is questionable if the results regarding the anxious/depressed subscale could be partially explained by the questionnaire used. Future studies must take mental retardation into account and use multiple diagnostic instruments to investigate depression.

Results in our mixed cohort showed that in almost all types of CDG, children showed one or more socio-emotional problems. PMM2-CDG patients are described as happy children and no mood disorders have been reported yet. Nevertheless in our study, six out of the nine PMM2-CDG patients showed abnormal scores on CBCL. PMM2-CDG is the largest CDG group, with over 700 patients reported worldwide. Furthermore, all three ALG6-CDG patients showed significant psychological problems. In literature, observations regarding behavior in this patient group are lacking. However, these results should be interpreted with caution regarding the small sample size of the group. Therefore, future research is recommended to investigate whether the prevalence, degree, and nature of psychological problems are variable between different subtypes of CDG.

This study suggests that CDG patients could suffer from untreated psychological problems. However, one should be cautious with drug therapy. CDG effects liver function and most drugs used in psychiatric treatment are eliminated by the liver. The effect of these drugs on glycosylation is not yet evaluated. Because of the possible side effects of psychopharmaca in inborn errors of metabolism, psychological therapy is of first choice in children with metabolic disorders and socio-emotional problems.

Congenital disorders of glycosylation form a relatively young but growing group of inborn errors of metabolism. Future studies are needed to further elucidate the psychological aspects of the disease and are essential for optimal interpretation and treatment of socio-emotional problems in children with CDG.

In summary, our study results show an increased prevalence of socio-emotional problems in patients diagnosed with CDG compared to norm scores. Mean total scores, scores on withdrawn/depressed behavior, social problems and somatic complaints were significantly increased. More than two thirds of our CDG patients have abnormal scores on CBCL. Compared to children with other metabolic disorders, CDG patients show more social problems. Therefore, it can be concluded that patients with CDG have an increased risk of developing socio-emotional problems. Based on our results, a standard screening for psychological problems is recommended in CDG patients for the early detection of psychological problems and to provide adequate treatment at an early stage.

Synopsis

A standard screening for psychological problems is recommended for the early detection of psychological problems in CDG patients.

Contributors

Eva Morava and Chris Verhaak designed and supervised the study and commentated on the text. Lotte van Dongen and Kim van de Loo managed the data, the statistical analyses, and wrote the article.

M. Mohamed, T. Gardeitchik, T.W. Kouwenberg, S.B. Wortmann and D.J. Lefeber - were involved in the conception and design, and reviewed the manuscript.

R.J.T. Rodenburg- was involved in the conception and design, and responsible for the laboratory diagnostic analysis of the mitochondrial patients and reviewed the manuscript.

Guarantor

E. Morava

Role of Funding Source

No financial support was used by this study.

Ethics Approval

There was no ethics approval required.

Patient Consent Statement

No patient consent was required.

Conflicts of Interest

The authors disclose any financial conflict of interest.

References

Achenbach TM, Rescorla LA (2000) Manual for the ASEBA preschool forms and profiles. University of Vermont Department of Psychiatry, Burlington, VT

Achenbach TM, Rescorla LA (2001) Manual for the ASEBA school-age forms and profiles. University of Vermont, Research Center for Children, Youth, and Families, Burlington, VT

Achouitar S, Mohamed M, Gardeitchik T et al (2011) Nijmegen paediatric CDG rating scale: a novel tool to assess disease progression. J Inherit Metab Dis 34:923–927

Boekaerts M, Röder I (1999) Stress, coping, and adjustment in children with a chronic disease: a review of the literature. Disabil Rehabil 21:311–337

Borthwick-Duffy SA, Lane KL, Widaman KF (1997) Measuring problem behaviors in children with mental retardation: dimensions and predictors. Res Dev Disabil 18:415–433

Davis JD, Tremont G (2007) Neuropsychiatric aspects of hypothyroidism and treatment reversibility. Minerva Endocrinol 32:49–65

Došen A (2008) Psychische stoornissen, gedragsproblemen en verstandelijke handicap. Koninklijke van Gorcum, Assen

EvansDL CDS, Lewis L et al (2005) Mood disorders in the medically ill: scientific review and recommendations. Biol Psychiatry 58:175–189

Freeze HH (2006) Genetic defects in the human glycome. Nat Rev Genet 7:537–551

Grünewald S (2009) The clinical spectrum of phosphomannomutase 2 deficiency (CDG-Ia). Biochim Biophys Acta 1792:827–834

Jaeken J (2010) Congenital disorders of glycosylation. Ann N Y Acad Sci 1214:190–198

Jaeken J, Hennet T, Matthijs G, Freeze HH (2009) CDG nomenclature: time for a change! Biochim Biophys Acta 1792:825–826

Koene S, Kozicz TL, Rodenburg RJ et al (2009) Major depression in adolescent children consecutively diagnosed with mitochondrial disorder. J Affect Disord 114:327–332

Koskentausta T, Iivanainen M, Almqvist F (2004) CBCL in the assessment of psychopathology in Finnish children with intellectual disability. Res Devel Disabil 25:341–354

Liem YS, Bode L, Freeze HH, Leebeek FW, Zandbergen AA, Paul Wilson J (2008) Using heparin therapy to reverse protein-losing enteropathy in a patient with CDG-Ib. Nat Clin Pract Gastroenterol Hepatol 5:220–224

Masi G, Brovedani P, Mucci M, Favilla L (2002) Assessment of anxiety and depression in adolescents with mental retardation. Child Psychiatry Hum Deve 32:227–237

Masi G, Favilla L, Mucci M (2000) Generalized anxiety disorder in adolescents and young adults with mild mental retardation. Psychiatry 63:54–64

Masi G, Mucci M, Favilla L, Poli P (1999) Dysthymic disorder in adolescents with intellectual disability. J Intellect Disabil Res 43:80–87

Mohamed M, Guillard M, Wortmann SB et al (2011) Clinical and diagnostic approach in unsolved CDG patients with a type 2 transferrin pattern. Biochim Biophys Acta 1812:691–698

Mokkink LB, van der Lee JH, Grootenhuis MA, Offringa M, van Praag BMS, Heymans HSA (2007) Omvang en gevolgen

van chronische aandoeningen bij kinderen. Tijdschr Kindergeneeskd 75:154–158

Morava E, Gardeitchik T, Kozicz T et al (2010) Depressive behaviour in children diagnosed with a mitochondrial disorder. Mitochondrion 10:528–533

Morava E, Guillard M, Lefeber DJ, Wevers RA (2009a) Autosomal recessive cutis laxa syndrome revisited. Eur J Hum Genet 17:1099–1110

Morava E, Wevers RA, Willemsen MA, Lefeber D (2009b) Cobblestone-like brain dysgenesis and altered glycosylation in congenital cutis laxa Debré type. Neurology 73:1164

Morava E, Zeevaert R, Korsch E et al (2007) A common mutation in the COG7 gene with a consistent phenotype including microcephaly, adducted thumbs, growth retardation, VSD and episodes of hyperthermia. Eur J Hum Genet 15:638–645

Mueller SC, Ng P, Sinaii N et al (2010) Psychiatric characterization of children with genetic causes of hyperandrogenism. Eur J Endocrinol 163:801–810

Northam EA, Rankins D, Cameron FJ (2006) Therapy insight: the impact of type 1 diabetes on brain development and function. Nat Clin Pract Neurol 2:78–86

Phoenix C, Schaefer AM, Elson JL et al (2006) A scale to monitor progression and treatment of mitochondrial disease in children. Neuromuscul Disord 16:814–820

Sparks SE, Krasnewich DM (2005) Congenital disorders of glycosylation overview. In: Pagon RA, Bird TD, Dolan CR, Stephens K (eds) GeneReviews [Internet]. University of Washington, Seattle (WA)

Theodore M, Morava E (2011) Congenital disorders of glycosylation: sweet news. Curr Opin Pediatr 23:581–587

Waisbren S, White DA (2010) Screening for cognitive and social-emotional problems in individuals with PKU: tools for use in the metabolic clinic. Mol Genet Metab 99:96–99