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Cognitive functioning and psychiatric disorders in children with a metabolic disease

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Abstract *Objective* To report on the intelligence scores and the psychiatric pathology of distinct groups of children with metabolic diseases. *Methods* The study population consists of 53 children between 0 and 18 years of age. Diagnostic assessment included a semi-structured interview, self-report questionnaires and a standard intelligence test. *Results* In 40% of the children older than 5 years, a child psychiatric diagnosis was made. While CBCL total and internalizing scores did not differ between metabolic disease groups, the CBCL externalizing scores for some groups did. Two fifths of the children showed a below normal intelligence, while a performal–verbal IQ discrepancy was found in half of the children. Of the school aged children almost one third attended a special needs school. *Conclusion* In spite of the small sample size, the results suggest substantial psychiatric problems in children with a metabolic disease. Further study on larger groups is warranted, which should enable further comparison of patients affected by specific metabolic diseases.

Key words cognitive – psychiatric disorder – metabolic disease

Introduction

Much research has been done on the co morbidity between somatic disorders and psychopathology [16, 25]. The link between child psychopathology and metabolic diseases in particular is, however, poorly investigated. Therefore, the objective of the current study is to describe the cognitive and psychiatric functioning of children with metabolic diseases. In addition, in order to investigate the characteristics of patients belonging to specific groups of metabolic diseases [36], groups will be compared on each of the characteristics of interest.

Although several studies describing the neuropsychological or psychiatric characteristics of children with specific metabolic diseases can be found in the literature, thorough insight is lacking because the majority of studies included small number of patients. In addition, whereas some specific reviews have been written recently on the topic [37, 43], a comprehensive review is lacking. Of the published reviews, one focused uniquely on children with PKU [37], while the other had the presence of behavioral symptoms as its main topic [43]. Because of the limitations of the existing studies, the current study will report on the intelligence scores and psychiatric pathology—both internalizing and externalizing—of distinct groups of children with a metabolic disease.

Through a Medline search on the topics "metabolic diseases" (and the different specific disease names), "psychiatry", "cognitive", "(neuro)psychological" and "behavior", mental health related articles on the following metabolic diseases were retrieved: PKU [6, 15, 20, 21, 34, 37, 39, 48, 51], hyperlysinemia [14], homocystinuria [1, 4, 8, 52], glutaric aciduria type 1 [17, 24], galactosemia [5, 29],

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methylmalonic acidiuria [18, 28, 30], Smith–Lemli–Opitz syndrome [41] and mitochondrial encephalomyopathies [31, 35, 40, 44]. The vast majority of studies have focused on neuropsychological or psychiatric problems in PKU patients, which is understandable because this group has the highest prevalence. A literature review (1961–1998) by Smith et al. [37] examining the psychopathological differences between early treated phenylketonuria (PKU) patients and normal subjects, demonstrated that the PKU group, compared to non-diseased subjects, had a greater risk for behavioral and psychological disturbance. Externalizing as well as internalizing problems were reported to occur consistently more often in the PKU group, while the findings with respect to (neuro)psychological deficits were inconsistent. Burgard [6] reported that PKU suppresses the global level of IQ without impairment of domain-specific competencies, while Huisman [21] described a significantly increased discrepancy between the intelligence sub scores in favor of the performance intelligence. In contrast of the latter Griffiths [15] reported a significantly higher verbal IQ when compared to performal IQ. Children with galactosemia constitute the second best investigated group with respect to sample size. In those subjects, lower cognitive functioning and language problems have been demonstrated in two studies [24, 29].

Except for the studies on PKU and galactosemia, most research has been conducted on small numbers of patients. In those articles, the following mental health problems have been described: schizophrenia and psychosis in homocystinuria [4], mental and physical retardation in hyperlysinemia [14], progressive mental and physical delay and coordination problems in glutaric aciduria type 1 [17] and learning difficulties and movement disorders in methylmalonic aciduria (MMA) [30]. Mitochondrial encephalomyopathies (ME), a very heterogeneous group characterized by a wide range of clinical symptoms and signs based on different defects, have been studied by Turconi et al. [44]. In 16 patients with ME, no mental deterioration but lower scores on non-verbal versus verbal tasks and selectively impaired visuo-spatial skills and short-term memory were found. Also autism spectrum disorders were found in this type of patients [33]. In addition to these studies, a number of case reports have been published [5, 8, 41, 42].

Because of the lack of insight with respect to the neuropsychological and psychiatric functioning of children with a metabolic disease, it was the aim of the current study to investigate a group of children affected by different metabolic diseases from a complete catchment's area by means of standardized neuropsychiatric instruments, and to report on the characteristics of children from specific groups of metabolic disease.

Method

Subjects

All patients attending an outpatient clinic for metabolic diseases in Antwerp were requested to participate in the study. The coverage of the area of Antwerp is almost complete because the metabolic unit CEMA (Centre for Hereditary Metabolic Diseases, CEMA) is present in the two largest children's hospitals in the city and because there is a close relationship with the metabolic lab that performs all metabolic investigations. The activities of this lab include neonatal mass screening (e.g. PKU) and all selective diagnostic metabolic investigations for the complete province of Antwerp and beyond. The coverage is supported by the prevalence of metabolic diseases, which is comparable to the numbers mentioned in the literature. The approximate prevalence in the studied age group of all these metabolic diseases taken together is 1/50,000 [9, 19]. At the time of the study, 71 patients between 0 and 18 years-old with a metabolic disease under dietary treatment were treated in this unit. A clinical and biochemical follow-up was conducted at least twice a year in all patients. Of the 71 patients, 9 (4 children of group 2, 5 children of group 3) were too severely handicapped to participate in the study and were excluded. The remaining 62 patients and their parents were invited by mail and by telephone to participate in the study. Nine eligible subjects refused to participate, resulting in a final study group of 53 children, 26 girls and 27 boys. Ten children were below the age of 4, 17 children were between 4 and 6 years-old, 19 children between 6 and 12 years and 7 children were older than 12 (no participant was older than 16).

The different metabolic diseases were classified in four groups (see Table 1). Group 4 was excluded for further data analysis as it only contained two subjects.

Instruments

Psychiatric diagnosis

A semi-structured child psychiatric interview, the K-SADS [23], was used for psychiatric assessment in children 5 years and older. This instrument is capable of generating a wide range of child psychiatric diagnoses and consists of three parts. The Introductory Interview, used to establish rapport, is followed by the 82-symptom Screen Interview, divided into 20 different diagnostic areas. The interviewer has to

Table 1 Classification of the different types of metabolic diseases

Group 1	Intoxication type	–Phenylketonuria (PKU) –Galactosemia –Lysinuric protein intolerance (LPI) –Ornithine carbamyltransferase (OCTD) –Homocystinuria –3-methylcrotonylglycinuria (3-MCG) –Glutaric aciduria
Group 2	Substrate and enzymatic disorders of the energy metabolism	–Methylmalonic aciduria (MMA) –Multiple acyl-CoA dehydrogenase deficiency (MADD) –Glycogen storage disorders –Neoglucogenosis disorders –Carnitine palmitoyl transferase-1 deficiency (CPT-1) –3-OH-3-methylglutarylCoA-lyase deficiency (HMG CoA-lyase)
Group 3	Respiratory chain defects/mitochondrial encephalomyopathies (oxidative fosforylation defects)	
Group 4	Smith–Lemli–Opitz syndrome	

administer the supplement on a disorder when a threshold score is obtained for that disorder in the Screen Interview. The instrument has shown high inter rater diagnostic reliability and was validated in extensive testing. In the current study, the interview was conducted by the first author (child psychiatrist with ample clinical experience), who determined the presence of a diagnosis according to the DSM-IV criteria [3]. A developmental interview was conducted with the parents. This interview includes developmental milestones, as well as characteristics of specific developmental disorders such as autism related disorders. Behavioral checklists included the Child Behavior Checklist (CBCL), the Teacher Report Form (TRF) and the Youth Self Report (YSR) [2]. These questionnaires are widely used instruments developed by Achenbach [2], which have been translated into Dutch and validated by Verhulst [46, 47]. The instruments obtain information on behavioral/emotional problems in a variety of areas, including the internalizing and externalizing domains. Separate versions of the instruments were used to obtain information from the children's parents, the teachers and the children themselves when they were older than 11. Based on all information, the presence of a child psychiatric disorder not included in the K-SADS was made according to DSM-IV criteria [3].

Child psychiatric disorders were classified in one of the ten following groups: autism spectrum disorder, other development disorder (including learning disabilities, disorders of motor functioning and communication disorders), disruptive behavior disorders (Attention Deficit Hyperactivity Disorder (ADHD), conduct disorders and oppositional-defiant disorders), mood disorders, psychotic disorders, anxiety disorders, delayed diagnosis and no diagnosis.

Intelligence and school functioning

Depending on the age of the participant, the following intelligence tests were used: Bayley Development Scale [45], SON-R [38], WPPSI [50] and WISC-R [49]. School functioning was investigated by means of an open question on school performance and the TRF.

Characteristics of the metabolic disease

All somatic disorders were diagnosed by means of standard and scientifically warranted tests (specific information is available on request). In addition, at each visit, the pediatrician investigated carefully whether the treatment and the eventual dietary restrictions were strictly followed. Data were collected about the age of recognition of the metabolic disease, therapy compliance and blood level of toxic metabolites during the last year before the study for each participant in the study.

Statistical analysis

For statistical analysis, the Statistical Package for Social Sciences (SPSS 10.0) was used. For all analyses, a two-tailed significance level of 0.05 was adopted. For comparison of the categorical variables between subgroups of metabolic diseased patients, χ^2-tests or Fisher exact (when $n < 5$ in one cell) tests were used. For comparison of continuous variables between subgroups, independent *t*-test was performed. Correlations between variables were analyzed by means of the bivariate Pearson correlation test.

Results

Child psychiatric evaluation

Psychiatric diagnoses (DSM-IV) were made for 30 children 5 years and older (minimum age for administration of the K-Sads). Of those children, 12 (40%) fulfilled criteria for at least one child psychiatric diagnosis, of which 5 (16.6%) carried more than one diagnosis. Results are shown in Table 2. No differences in prevalence were found by type of metabolic disease

Table 2 Psychiatric diagnosis ($N = 30$, age >5) by type of metabolic disease

	Group 1 ($n = 14$)	Group 2 ($n = 10$)	Group 3 ($n = 6$)	Total ($n = 30$)
Number of patients with childpsychiatric diagnosis	6 (43%)	4 (44%)	2 (29%)	12 (40%)
ADHD	3 (21%)	0	1 (17%)	4 (13%)
ODD	1 (7%)	0	0	1 (3%)
Mood Disorder	1 (7%)	0	1 (17%)	2 (7%)
Anxiety disord.	1 (7%)	1 (10%)	0	2 (7%)
Psychotic disord	1 (7%)	0	0	1 (3%)
Autism (related) disorder	1 (7%)	1 (10%)	0	2 (7%)
Learning disord	0	3 (30%)	1 (17%)	4 (13%)

ADHD (Attention Deficit Hyperactivity Disorder) and ODD (Oppositionel Defiant Disorder) are called together Disruptive Behavior Disorders

group. Mainly Attention Deficit Hyperactivity Disorder (ADHD) and "other development disorder" were diagnosed. Although not significantly different, Disruptive Behavior Disorders (DBD) (ADHD and Oppositional Defiant Disorder or ODD) occurred mostly in children of group 1, as well as problems in the social development were reported by the parents. Patients in group 2 showed mainly "other development disorders" who appeared to be all learning disorders. With respect to CBCL scores, significant differences were found between groups on the externalizing sub score, but not on the internalizing sub score or the total score. The externalizing sub score for both group 1 and 3 were higher than for group 2 (Table 4).

Cognitive functioning

In 21 children (39.6%), the intelligence was below normal (<85) when including the test results of all participating children. In order to further evaluate cognitive functioning and to compare metabolic disease subgroups, children tested by means of the WPPSI or WISC-R were included only, because these tests allow the evaluation of the verbal and performal intelligence separately. The mean intelligence was 93.1 (SD 22.0788). Table 3 shows intelligence scores by type of metabolic disease. In 50% of children, a statistical significant performal–verbal IQ discrepancy (IQ difference of at least 15 points) was found, for 30% in favour of the verbal intelligence and for 20% in favour of the performance intelligence. Although not significantly different, the discrepancy in intelligence occurred more often in group 1 when compared to the other groups. In group 1, a discrepancy in favour of the verbal intelligence prevailed. No correlation was found between the IQ-values, therapy compliance, blood level of toxic metabolites and the age of diagnosis of the metabolic disease.

School functioning

At the time of the study, 38 children attended school. Eleven of those children (28.9%) attended a special needs school. Eight children entered first grade 1 year later because of developmental immaturity and one child repeated a grade in primary school. Learning problems were reported by the parents for 11 children and behavioral problems at school for four children. High scores on the TRF were noticed in group 1 and group 3. Externalizing symptoms occurred significantly less in group 2 compared to group 1 (Table 4). Group 2 children manifested a high grade of absenteeism, more than 50% of these children are often absent at school because of illness. In group 1 this is 6.6% and in group 3.3%.

Table 3 IQ values prevalence based on WPPSI and Wisc-R by type of metabolic disease (age 4–16)

	Group 1	Group 2	Group 3	Total
($N = 30$)	($N = 14$)	($N = 9$)	($N = 7$)	($N = 30$)
FSIQ	86.3 (*SD: 26.0*)	99.0 (*SD: 10.9*)	99.1 (*SD: 23.0*)	93.1 (*SD: 22.1*)
VIQ	89.0 (*SD: 27.0*)	94.778 (*SD: 4.893*)	102.0 (*SD: 19.536*)	93.8 (*SD: 20.9*)
PIQ	84.3 (*SD: 22.7*)	104.7 (*SD: 16.8*)	95.1 (*SD: 24.0*)	92.9 (*SD: 22.5*)
(*N = 18*)	(*N = 5*)	(*N = 8*)	(*N = 5*)	(*N = 18*)
F1IQ	95.4 (SD: 17.658)	96.375 (SD: 7.050)	98.400 (SD: 10.359)	96.6 (SD: 11.0)
F2IQ	88.200 (SD: 13.590)	106.125 (SD: 16.164)	98.400 (SD: 6.229)	99.0 (SD: 14.8)
F3IQ	93.800 (SD: 23.900)	99.500 (SD: 13.565)	97.600 (SD: 19.616)	97.4 (SD: 17.5)
Number of patients with discrepancy in IQ	8 (57%)	4 (44%)	3 (42%)	15 (50%)
Number of patients with VIQ>PIQ	6 (42%)	1 (11%)	2 (29%)	9 (30%)

Table 4 CBCL and TRF mean scores by type of metabolic disease, age 4–16

		Group 1	Group 2	Group 3	*F*(dif, 2,24)/sig
CBCL	TOT	61.7	53.6	60.3	1.7/.196
	INT	60.1	58.8	61.7	.107/.899
	EXT	58.9[a]	46.1	54.3	8.6/.002[a,b]
TRF	TOT	54.0	48.7	58.0	2.1/.145
	INT	55.2	52.6	59.6	.8/.45
	EXT	53.9[a]	44.6	51.2	3.1/.06[a]

[a]Significant difference between group 1 and 2
[b]Significant difference between group 2 and 3

Discussion

Through psychiatric and cognitive investigation of a sample of 53 metabolically diseased children from a complete catchment's area, it was found that: (1) 40% of patients carried a child psychiatric diagnosis; (2) the mean intelligence was in the low average range and that 40% had a below average intelligence; (3) a high number of participants showed a discrepancy of the verbal versus the performal intelligence; and (4) differences between groups with regard to psychiatric problems and cognitive functioning were moderate.

Because the current study did not investigate a control group, a search was done in the literature for psychiatric and cognitive problems in another chronic disease. Chronic disease or illness refers to a disease with a protracted course that can be progressive and fatal, or associated with a relatively normal lifespan despite impaired physical or mental functioning [26]. Diabetes mellitus, type 1, was considered a relevant choice.

In 40% of the children, a child psychiatric diagnosis was found, which is higher than what may be expected in the general population [12]. Disruptive Behavior Disorders were mainly diagnosed in children of group 1 (which consists mainly of PKU patients), while both CBCL and TRF externalizing scores were the highest in this group. Previous studies reported both internalizing and externalizing problems to occur frequently in PKU patients [34, 37, 39, 51]. In our population of PKU patients internalizing problems were not found. With respect to the other metabolic disorders reported on this study, few rapports on psychiatric disorders were available in the literature, which does not allow comparison of findings. Interestingly, studies in diabetes mellitus samples have shown that nearly half of patients at a diabetes outpatient clinic met criteria for a psychiatric disorder, including ADHD, mood disorder and anxiety disorder [13]. In a review [22] on depression in diabetic adolescents two- to three-fold higher rates were found when compared with non-diabetic peers. In our study a mood disorder was found in 7% of our study population only, which is similar to the general population [10]. We think there is al clinical relevance for professionals working with children with a metabolic disease to perform a thorough child psychiatric investigation early in the development to anticipate on developing psychiatric problems, such as learning problems and frontal lobe related problems, such as ADHD.

The mean IQ (93,1) is below the mean IQ of the general population (FSIQ = 100) [49]. Forty percent of the children had an IQ below normal (<85). Between group comparisons were only performed in children who were administered the WPPSI or the WISC-R, resulting in considerably smaller comparison groups. Possible IQ differences between different types of metabolic diseases warrant further study, since average intelligence scores were found in groups 2 and 3, but (non-significantly) lower intelligence scores in group 1. Because of the low number of participants in each of the subgroups, the current study is likely to have suffered from adequate power to show differences (possible type II error).

A verbal–performal IQ discrepancy was most obvious in group 1. Our finding that this discrepancy was mainly in favor of the verbal intelligence was in line with the findings of Griffiths [15]. Yet, still a substantial part (15%) of the participants showed a higher performal than verbal intelligence. Therefore, it may be concluded that both discrepancies can be found in these children, which is in line with findings of others [6, 21]. Because of the small sample size of our and earlier studies, further investigation is needed. Since metabolic disorders have a relatively low prevalence, collaborative multi-center studies should be performed. Also, when this finding receives more broad support, the pathophysiological mechanism should be investigated.

Children of group 3 (respiratory chain defect) are already affected metabolically in utero. In the other two groups (intoxication type and substrate and enzymatic disorders of the energy metabolism), the damage is caused by accumulation of toxic metabolites, by hypoglycemia or by an energy crisis. One would expect that cognitive functioning in those two groups would be related to diet compliance and the occurrence of metabolic decompensations, an assumption that was not confirmed in our study.

Northam [32] reported that children with diabetes performed more poorly than control subjects on measures of intelligence. Severe hypoglycemia was associated with lower verbal and full-scale intelligence quotient scores. Ferguson [11] stated that the onset of the disease before the age of 7 gives poorer cognitive abilities. If our study population group 2 can be compared with diabetes because they also have periods of hypoglycemia. Indeed in this group there was more often a discrepancy in IQ in favour of the PIQ

(33%). There was no association with the age of diagnosis. It would be very interesting to investigate if this is confirmed in a larger study population. A study by McCarthy [27] showed no lower academic performance by children with diabetes compared with a control group. This in contrast to our results where almost 30% attends a special needs school. Children with diabetes did show significantly more school absences and more behavioral problems. This high grade of absenteeism was also found in group 2.

With regards to limitations of the study the most prominent one is the small sample size and the heterogeneity of the group (as well in pathology as in age). Also, only relative well functioning children were included for participation. The small number of patients make that the results must be considered descriptive and explorative. In spite of the small sample size of patients, some remarkable results were obtained that warrant further research on the topic. This study is one of the few that has shown that investigating cognitive dysfunctioning and/or psychiatric pathology in children with a metabolic disease is warranted. The question can be raised in which children with mental retardation or a childpsychiatric disorders metabolic screening should be performed. Because of the small size of the study group, it is difficult to make hard recommendations. It's seems that DBD quite often occur in group 1 and learning disorders in group 2. Inborn errors of metabolism are rare causes of isolated developmental delay and or psychiatric disorder; if associated however with a specific finding, e.g. hypotonia, regression, hepatosplenomegaly or dysmorphism, it is important to make further investigations in order to detect an underlying metabolic disorder [7].

The strength of this study includes the investigation of different groups of metabolic diseases and the inclusion of patients from a complete catchment's area. In the future we will enlarge the study population and investigate also neuropsychological characteristics.

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