Neuropsychological Development in Patients with Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase (LCHAD) Deficiency

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Abstract *Background:* Reports on cognitive outcomes in long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency

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(LCHADD) are scarce. We present results from neuropsychological assessments of eight patients diagnosed with LCHADD prior to newborn screening with regard to clinical disease severity.

Methods: Intellectual ability and adaptive and executive functions were assessed using age-appropriate Wechsler Scales, Adaptive Behavior Assessment Scales (ABAS), and Behavior Rating Inventory of Executive Function (BRIEF).

Results: Five patients performed in the normal range on IQ tests but with lower scores on verbal working memory. In addition, they had lower parent-rated adaptive and executive functions.

Three patients had intellectual disabilities with IQs below normal and/or autism spectrum disorders. In addition, they had low results on parent-rated adaptive functions. (Two of these patients had epilepsy.)

Conclusions: Patients with LCHADD seem to have a specific cognitive pattern, with presentation as intellectual disability and specific autistic deficiencies or a normal IQ with weaknesses in auditive verbal memory and adaptive and executive functions. Future studies are warranted to investigate whether newborn screening programs and early treatment may promote improved neuropsychological development and outcomes.

Abbreviations

ABAS	Adaptive Behavior Assessment System [®]
ASD	Autism spectrum disorder
BRIEF	Behavior Rating Inventory of Executive Function [®]
DHA	Docosahexaenoic acid
FAOD	Fatty acid oxidation defect
GAC	General Adaptive Composite
GEF	Global executive function

LCHADD	Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency
LCT	Long-chain triglyceride
MCT	Medium-chain triglyceride
MTP	Mitochondrial trifunctional protein

Introduction

Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHADD) is an inborn error of fatty acid metabolism, characterized by an impaired ability to sequentially metabolize long-chain fatty acids to acetyl-CoA units by mitochondrial beta-oxidation. The deficiency results in insufficient energy production, as well as accumulation of fatty acid intermediates.

The LCHAD enzyme is part of the mitochondrial trifunctional protein (MTP) and catalyzes the third of the four mitochondrial beta-oxidation reactions with its highest specificity for fatty acids with 12–16 carbons. LCHADD (OMIM 609016) is a rare autosomal recessively inherited disorder with an estimated incidence of 1:60,000 (Swedish screening of 500,000 neonates). The most common mutation is [c.1528G>C], which affects the alpha subunit of the MTP.

Newborn screening for fatty acid oxidation defects (FAODs) identifies most of the patients and was introduced in Sweden in 2010. Prior to screening, the patients presented with hypoketotic hypoglycemia, rhabdomyolysis, and metabolic acidosis. Mortality rates were high (Saudubray et al. 1999; Den Boer et al. 2002; Olpin et al. 2005). These symptoms may still occur mostly in association with prolonged fasting, exercise, infections, or other catabolic situations. Dietary treatment is started at the time of diagnosis and involves avoidance of fasting, low intake of long-chain triglycerides (LCTs), and supplementation with medium-chain triglycerides (MCTs) and essential fatty acids. Despite dietary treatment, LCHADD patients develop progressive and irreversible retinal changes. The cause of the specific chorioretinopathy, leading to visual impairment, is unknown. Several theories have been proposed, including toxic effects of accumulating long-chain hydroxy-acylcarnitines, energy deficiency, or deficiency of docosahexaenoic acid (DHA) (Bakermans et al. 2011; Fletcher et al. 2012; Gillingham et al. 2005). Recent research has demonstrated language, motor, and/or developmental delays in patients with FAODs (Brown et al. 2014; Hsu et al. 2008; Iaifolla et al. 1994; Joy et al. 2009; Waisbren et al. 2013), although information on neuropsychological development in LCHADD is very limited. In this report, we present data on neuropsychological outcomes and developments in eight LCHADD patients

diagnosed at our centers prior to newborn screening and relate the results to the clinical severity of the disease.

Patients and Methods

Patients

At our clinics, ten patients were diagnosed with LCHADD before newborn screening for FAODs was introduced in Sweden. As previously reported, all patients had developed, to different degrees, the characteristic chorioretinopathy found in patients with LCHAD/MTP deficiency (Fahnehjelm et al. 2008). Two of the patients declined to participate due to difficulties connected with traveling to our center. The remaining eight patients (6 females and 2 males) participated in the neuropsychological assessments. Five patients were homozygous for the [c.1528G>C] mutation, while three were compound heterozygous (patients 3, 6, and 7), the second mutations constituting two novel mutations and a deletion (manuscript in preparation). The acyl-CoA-hydrolase and keto-acyl-CoA-dehydrogenase activities have not been investigated in detail in these patients. The patterns of urinary organic acids and plasma acylcarnitines were the same as in the patients who were homozygous for the 1528G>C mutation. We have therefore chosen to denote the whole group as having an LCHAD deficiency rather than an MTP deficiency. Patient characteristics are shown in Table 1. Dietary treatment was started at diagnosis and included restriction of LCT and supplementation with essential fatty acids, DHA, and MCT fat. The fat intake was adjusted to a maximum intake of grams/day for different ages, but carbohydrate and protein intakes were not adjusted in detail. Fasting periods were limited to 3–4 h and all patients had overnight intragastric feedings. One patient received carnitine supplementation.

Procedure

The patients were investigated using cognitive tests and age-appropriate assessment scales in a clinical setting. Parents completed questionnaires regarding adaptive and executive functions. The tests used to assess cognitive outcome were chosen based on the best available translations to the Swedish language and norms. Our clinical experience is that patients with other metabolic diseases have affected executive functions. Therefore parents of the LCHADD children were asked to complete questionnaires, addressing executive function parallel to the patients' cognitive tests. Birth data, clinical symptoms, and laboratory data were retrieved from the medical records. The Ethics Committee at Uppsala University, Sweden, approved the study, and all families gave their informed consent.

Table 1 Clinical data and mutations

Patients	Age at diagnosis (months)	Symptoms at diagnosis	Gestation weeks	Caesarian section	Birth weight (g)	Epilepsy	Mutations
1 ♀	5	Vomiting, seizures, lethargy, acidosis, liver enlargement, hypotonia, cardiomyopathy	37	Yes	2,165		Homozygous c.1528G>C
2 ♂ [†]	8	Hypoglycemia, seizures, elevated liver enzymes	38		3,070	Yes	Homozygous c.1528G>C
3 ♀	8	Neonatal hypothermia, elevated liver enzymes, and 3OH-FA. Treated from birth due to suspected metabolic disease	35		1,910		Compound heterozygous c.1528G>C
4 ♀	0.25	Vomiting, diarrhea, apnea, lethargy, hypoglycemia, and renal-, liver-, and heart-failure. Seizures	40		3,260		Homozygous c.1528G>C
5 ♀	0.25	No symptoms. Treated from birth due to family history	38		3,510		Homozygous c.1528G>C
6 ♂ [†]	7	Hypoglycemia, hypotonia	40		3,165		Compound heterozygous c.1528G>C
7 ♀	10	Neonatal hypoglycemia, intraventricular/intraparenchymal hemorrhage grades III–IV, periventricular leukomalacia. Failure to thrive, liver enlargement	31	Yes	1,309	Yes	Compound heterozygous c.1528G>C
8 ♀	8	Lethargy, hypotonia	29	Yes	1,101		Homozygous c.1528G>C

Measures

Intelligence quotients (IQs) were evaluated using the age-appropriate Wechsler Scales WPPSI-III, WISC-IV, and WAIS-III and IV (Wechsler 1997, 2002, 2004, 2008). The results were analyzed as wholesale IQ and as four-factor index scores: verbal and perceptual ability, working memory, and processing speed. To evaluate visual working memory, spatial span board (Wechsler and Naglieri 2006) was added. IQ was defined as being within or below the normal range (IQ 70–130 and $\text{IQ} \leq 69$, respectively). In addition, adaptive and executive functions were assessed using parental questionnaires. Adaptive skills, which are important in everyday life, were assessed using the Adaptive Behavior Assessment System® ABAS (mean 100, SD 15) (Harrison and Oakland 2003). Executive function and self-regulation in children and teens were evaluated using the Behavior Rating Inventory of Executive Function® (BRIEF) (Gioia et al. 2000). The results were reported on a t-scale (mean 50, SD 10). Lower scores on BRIEF indicated a better outcome, and scores above 65 were considered clinically significant.

Statistical Analysis

The results were presented as the mean, median, and range for the group.

Results

Five patients underwent cognitive testing twice, while three patients had one cognitive assessment. The median age for the first evaluation was 10 years (min 6 years, max 21 years) and, for the second assessment, 14 years (min 8 years, max 21 years). Three patients displayed autistic-like behavior, and two of them were given an autism spectrum disorder (ASD) diagnosis. Two patients were diagnosed with mental retardation and also had epilepsy. All patients were treated according to our recommendations (Haglund et al. 2013) and had DHA levels, in mole percentage, within reference values.

Intellectual Abilities

Wholesale IQ scores, based on the latest assessment, ranged from 46 to 112 (mean 82, median 88) for the whole group (Table 2). Two subgroups, groups I and II, were identified (Table 2). In the first group, the IQ scores were in the normal range, whereas the patients in the second group had greater cognitive difficulties and IQ scores below

normal. The two different subgroups are described separately:

Group I

Five patients (4 females, 1 male) had an IQ score of 87 or above (mean 95, median 92, min 87, max 112); see Table 2. On a four-factor index level, the mean verbal ability score was 101 (median 102, min 87, max 112), the mean perceptual score 97 (median 98, min 80, max 106), and the mean processing speed 102 (median 101, min 85, max 128). The scores for working memory were lower and ranged from 73 to 91 (mean 81, median 80). The visual working memory, assessed by the spatial span board, was normal for all patients (t-scale values: mean 52, median 56, range 43 to 68). The patients in this group were tested twice. There was no statistical difference in IQ for the group over time, although individual differences were noted, and none of the patients were given a neuropsychiatric diagnosis.

The mean age for an LCHADD diagnosis was 5 months (median 7, range 0.25 to 8 months). One patient had acute symptoms at diagnosis, while the others had more unspecific symptoms, e.g., hypoglycemia, elevated liver enzymes, and hypotonia preceding the LCHADD diagnosis. Two children, presenting with unspecific symptoms at diagnosis, were compound heterozygous for [c.1528G>C]; the others were homozygous. Ocular examinations showed that all patients had moderate retinal changes (Fahnehjelm et al. 2008). All children attended regular schools and managed the age-appropriate curriculum, some with individual adjustments regarding the homework load, number of school hours, and participation in physical education. Three patients had assistance in handling the dietary regimen during school days.

Group II

Three patients (2 females, 1 male) had a full-scale IQ score of 77 or below (mean 60, median 56, min 46, max 77) (Table 2). Mean verbal ability ranged from 57 to 70 (mean 65, median 68), perceptual reasoning from 55 to 90 (mean 67, median 56), and processing speed from 49 to 63 (mean 57, median 60). Only two patients completed the test for working memory, and their scores were 65 and 68, respectively (mean 67). All three patients displayed autistic-like symptoms; however, only two were diagnosed with autism spectrum disorder (ASD).

Two of the three patients were delivered by acute Caesarian section. One child, compound heterozygous for the common mutation, was born preterm (GW 31) and

Table 2 Results of IQs and parental reports of adaptive (ABAS mean 100, SD 15) and executive functions (BRIEF t-scale mean 50, SD 10) for the whole group and the subgroups

	All patients, latest assessment (<i>n</i> = 8)			Patients without ASD (<i>n</i> = 5)			Patients with ASD (<i>n</i> = 3)		
	Mean	Median	Range	Mean	Median	Range	Mean	Median	Range
<i>Intelligence (WPPSI-III/WISC-IV/ WAIS-III/WNV)</i>									
Full-scale IQ	82	88	46–112	95	92	87–112	60	56	46–77
Verbal	87	92	57–112	101	102	87–112	65	68	57–70
Perceptual	85	93	55–106	97	98	80–106	67	56	55–90
Working memory	77 (<i>n</i> = 7)	77	65–91	81	80	73–91	67 (<i>n</i> = 2)		65–68
Processing speed	85	90	49–128	102	101	85–128	57	60	49–63
Visual working memory				53	56	43–68			
<i>Adaptive functioning (ABAS)</i>									
GAC	69 (<i>n</i> = 7)	80	28–102	83	89	52–102	34 (<i>n</i> = 2)		28–42
Cognitive	68 (<i>n</i> = 7)	78	12–97	85	92	59–97	26 (<i>n</i> = 2)		12–40
Social	70 (<i>n</i> = 7)	75	4–109	87	83	72–109	27 (<i>n</i> = 2)		4–50
Practical	77 (<i>n</i> = 7)	92	12–114	97	94	83–114	28 (<i>n</i> = 2)		12–44
<i>Executive functioning (BRIEF)</i>									
Inhibit				48	50	39–55			
Shift				66	67	57–77			
Emotional control				53	51	47–61			
Behavioral regulation index				55	58	47–63			
Initiate				57	56	50–68			
Working memory				64	64	43–79			
Plan/organize				65	61	51–84			
Organization of materials				55	59	46–62			
Monitor				57	57	47–67			
Metacognition index				62	60	51–75			
Global executive function				60	61	50–69			

Higher scores on IQs and ABAS indicate a better outcome, whereas better outcome on BRIEF is indicated by lower scores. A score above 65 on BRIEF is considered to be clinically significant

suffered a complicated neonatal period along with stage III–IV cerebral hemorrhage. The other two patients were homozygous for [c.1528G>C].

All three patients were diagnosed with LCHADD after the neonatal period, with a mean and median age at diagnosis of 8 months (min 5, max 10 months). One patient had acute symptoms, with elevated liver enzymes, acidosis, and seizures. Two of the patients had epilepsy. One of the patients had poor seizure control despite treatment. MRI showed normal results in one patient and status post cerebral hemorrhage in the other. Examination of the ocular fundi demonstrated severe chorioretinopathy (Fahnehjelm et al. 2008). The patients in this group underwent one cognitive assessment. Their cognitive dis-

abilities mandated specific special education needs and daily support.

Adaptive and Executive Functions

The parent-reported adaptive functions, summarized as the General Adaptive Composite (GAC) score, ranged from 28 to 102 (mean 69, median 80) for the whole group (Table 2). The patients with IQs in the normal range and no autistic behavior had a GAC score ranging from 52 to 102 (mean 83, median 89). As expected, parents of children with ASD and intellectual disabilities reported lower scores (mean 34, range 28 to 42).

Parents of children/adults without ASD completed the BRIEF inventory. The results showed that parents to some

patients reported that their child had significant problems with working memory, flexibility, and planning or in several of these domains (Table 2). One person had a Global Executive Function (GEF) score above 65, indicating clinically significant difficulties with overall executive function. Patients requiring assistance with the dietary treatment during school hours were rated to have more problems with executive functions than the others (BRIEF GEF mean 64 vs. 54 and ABAS GAC mean 74 vs. 97).

Discussion

In this study, we assessed neuropsychological development in LCHADD patients diagnosed before newborn screening. The mean IQ for the entire group was within the normal range, with the majority scoring ≥ 88 on intelligence tests. Nevertheless, as many as 37.5% had considerable cognitive disabilities and IQ scores in the range of mental retardation and an ASD diagnosis or autistic behavior at assessment.

The five individuals with IQs in the normal range displayed resources in intellectual abilities and a normal processing speed, but had a lower index for working memory. Since the Wechsler scales rely mostly on auditive tests, a specific test of visual working memory was added. This test showed that the visuospatial working memory was within the normal range for most patients, indicating a specific deficit in verbal/auditory working memory, which can generate problems in learning new auditory material, such as a new language (Baddeley 1992). Generally speaking, deficits in working memory are associated with executive dysfunction, and we therefore assessed parent-reported executive dysfunctions using BRIEF scales. The parental questionnaires confirmed the presence of problems in the domains of working memory, shifting (flexibility), and planning for some, but not all, patients. The presence of some executive dysfunctions does not normally impair everyday life for children and adults, and many outgrow these difficulties or adjust their behavior to the deficiency. However, as children with LCHADD become young adults and have to manage their own treatment, skills such as planning, monitoring, multitasking and being flexible are required. Hence, executive dysfunctions may pose risks for the individual's ability to become autonomous in the care of his/her own disorder. This is an area that calls for further research and development of technical solutions in order to facilitate the daily management of this disorder.

Three individuals had intellectual disabilities in addition to significant communication and social difficulties, resulting in an autism diagnosis (ASD) or autistic behavior.

Hence, the neuropsychiatric disabilities in LCHADD seem to present as autistic rather than as general intellectual deficits alone.

The reasons for the specific vulnerabilities in executive function/auditory working memory and high prevalence of ASD in this group are not known. Furthermore, the same mechanisms that have been discussed for the development of retinopathy and other LCHADD-related complications are also of interest for the cognitive outcome. Energy deficiencies, unmetabolized intermediates (Bakermans et al. 2011), and/or a DHA deficiency (Harding et al. 1999) may have a negative impact on the developing brain. DHA (22:6n-3), the most abundant omega-3 fatty acid in membrane phospholipids in the retina and in the cerebral gray matter (Fliesler and Anderson 1983; Carver et al. 2001; Svennerholm 1968), is involved in neurogenesis, memory formation, and neuronal signaling and plays a major role in visual development (De Urquiza et al. 2000; German et al. 2013). In developing animal brains, decreased DHA levels causes deficits in neurogenesis, neurotransmitter metabolism, and altered learning and visual function although the relationships in humans are still not clear (Heaton et al. 2013). Since patients detected before screening have also suffered secondary complications during metabolic decompensations and due to seizures, the etiology of autistic problems in this group can be difficult to disentangle.

Autism is a syndrome characterized by deficits in social interaction, communication, and restricted repetitive behavior (APA DSM IV 2000). It is multifactorial in background with high heritability (Sandin et al. 2014) and the underlying neurobiological mechanisms have yet to be determined. Current research is looking at gene-environment interaction models to explain the etiology and also the variations in phenotypic expression (Chaste and Leboyer 2012). Inborn errors of metabolism are recognized as the underlying cause of several neuropsychiatric conditions (Kayser 2008; Manzi et al. 2008; Walterfang et al. 2013). LCHADD and other FAODs seem to elicit an increased incidence of autistic behavior (Brown et al. 2014). This gives relevance to theories of mitochondrial dysfunction (Rossignol and Frye 2012) and disorders of fatty acid oxidation (Clark-Taylor and Clark-Taylor 2004) as possible neurobiological mechanisms behind autistic dysfunction. In addition, perinatal stress and brain inflammation have been discussed as risk factors (Angelidou et al. 2012). Lately, a connection with gut microbiota has been demonstrated (Cryan and Dinan 2012).

The patients with IQs within the normal range were diagnosed at a mean age of 5 months, and one-fifth had

acute onset symptoms. In comparison, the patients with cognitive disabilities were slightly older at diagnosis (mean age, 8 months) and one-third had critical symptoms at presentation, and they also had more severe ocular changes. In both groups, the majority were homozygous for the common mutation. It may be argued that patients with a low LCHAD activity develop energy deficiency and high levels of long-chain acylcarnitines and dramatic symptoms at an early age and subsequently receive an earlier diagnosis and treatment. Patients with nonspecific symptoms may be diagnosed later when fatty acid intermediates build up and/or an energy deficiency has caused pathological developments. Hence, both the severity of symptoms and the age at diagnosis may be associated with cognitive disability. An early diagnosis and absence of dramatic symptoms at diagnosis may also be associated with a better cognitive outcome. One of the patients had an early diagnosis due to dramatic symptoms with cardiac arrest and wholesale IQ scores within the normal range. Two of the patients in the group with low IQs and ASD had epilepsy. It is possible that the epilepsy per se has contributed negatively to the cognitive outcome, but it is also possible that the seizures reflect the severity of the disease and that other consequences of the disease have contributed to the negative cognitive outcome. Further studies are needed to clarify the pathophysiology. Identification of resilience factors are not within the scope of this study, but an overall good metabolic control may possibly have a positive impact.

The patients in this study with no neuropsychiatric diagnoses had symptoms of executive dysfunction from an early age, which were detectable by neuropsychological testing at around 9 years of age, or younger. However, these symptoms do not appear to have caused considerable problems on a daily basis, or at school, until at higher educational levels when tougher requirements associated with planning and flexibility have become important. With adequate treatment and support, all of the children with an IQ in the normal range attended regular schools. Moreover, they were engaged in a wide variety of activities. Screening for neuropsychological deficits is important and should be included in the routine checkup for this patient group, which has also been suggested by others (Waisbren et al. 2013). The psychological follow-up should preferably be done at transition stages within the school system, so as to ensure psychological or educational support if needed. In addition, quality-of-life measurements are important to capture the subjective experience of living with LCHADD and to further investigate if and how the specific executive dysfunctions impact the ability to live an independent life and manage the treatment.

Information on neuropsychological function and development in children and young adults with LCHADD is very limited. Recent research has demonstrated language and motor/developmental delays in patients with other FAODs and individual patients have been reported to have autistic symptoms (Table 3). To date, neuropsychological testing to evaluate the cognitive outcome in LCHADD patients has been performed in only one study. Waisbren and coworkers found one LCHADD patient with developmental delay and one with speech delay, but no formal IQ test (Waisbren et al. 2013) (Table 3). Patients with an LCHAD deficiency seem to have a different neuropsychological profile than patients with other FAODs, which is important to consider in the clinical management and follow-up.

In this descriptive study, the number of patients included is small; however, due to the rarity of the disease, this study is the most comprehensive summary of intellectual outcomes in LCHADD. All patients followed at our center did not participate, which may have created a selection bias toward the more normally functioning patients. It is not possible to draw definite conclusions about resilience factors from this small cohort, but one can hypothesize about the role of exercise, adherence to diet, and, possibly, the role of DHA substitution. Future studies are needed to show whether the cognitive and ocular findings have a common underlying pathophysiology.

The first LCHADD patients were reported in the early 1990s and the oldest patients are now young adults or high school aged. They were diagnosed clinically, often due to dramatic symptoms of the disease. Today a growing number of patients are being diagnosed in newborn screening programs and are treated before any symptoms occur. Future studies are necessary to investigate whether early diagnosis and treatment can improve the neurological outcome in these patients.

Conclusions

Patients with an LCHAD deficiency appear to have a specific cognitive pattern, presenting as intellectual disability and specific autistic deficiencies or a normal IQ with weaknesses in auditive verbal memory and adaptive and executive functions. Many countries have newborn screening programs for fatty acid oxidation defects and thus initiate early treatment which may benefit neurological developments and outcomes. Clinical screening and future studies are needed, however, to delineate the neuropsychological profiles in the screened cohorts.

Table 3 Cognitive assessments in FAOD

Defect	Diagnosed before NBS		Diagnosed by NBS		Authors (year of publication)
	IQ	Disabilities	IQ	Disabilities	
MCADD	60% Normal (<i>n</i> = 73)	16% global developmental disability, 10% isolated behavioral abnormalities, 5% developmental and behavioral disabilities, 22% speech disabilities, 11% attention deficit disorder (<i>n</i> = 73)			Iafolla et al. (1994)
	105 (<i>n</i> = 13)	Lower scores on executive abilities than in the NBS group (<i>n</i> = 13)	104 (<i>n</i> = 12)		Joy et al. (2009)
VLCADD			109 (<i>n</i> = 6)	48% speech disabilities, one patient ASD (<i>n</i> = 27)	Waisbren et al. (2013)
			Normal	One patient mild speech delay (<i>n</i> = 32)	Hsu et al. (2008)
			111 (<i>n</i> = 32)		Brown et al. (2014)
			111 (<i>n</i> = 7)	No significant deficits, two patients autistic behaviors (<i>n</i> = 8)	Waisbren et al. (2013)
			115 (<i>n</i> = 6)	50% motor delay, 29% speech delay, one patient autistic behavior (<i>n</i> = 11)	Cox et al. (1998)
LCHADD	Normal to superior range (<i>n</i> = 1)				Den Boer et al. (2002)
		27% psychomotor delay (<i>n</i> = 11)			Waisbren et al. (2013)

Information was extracted from studies on patients diagnosed prior to and after the introduction of newborn screening for FAOD

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Synopsis

Patients with LCHADD seem to have a specific cognitive pattern, with presentation as intellectual disability and specific autistic deficiencies or a normal IQ with weaknesses in auditive verbal memory and adaptive and executive functions.

Compliance with Ethics Guidelines

Conflict of Interest

Anna Bengtsson Strandqvist, Charlotte Bieneck Haglind, Rolf H. Zetterström, Antal Nemeth, Ulrika von Döbeln, Maria Halldin Stenlid, and Anna Nordenström declare that they have no conflict of interest. The study was supported by research grants. *Anna Bengtsson Strandqvist, Charlotte Bieneck Haglind, Rolf H. Zetterström, Antal Nemeth, Ulrika von Döbeln, Maria Halldin Stenlid, and Anna Nordenström* confirm that the content of the article has not been influenced by the grants.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Ethics Committee of Uppsala University, Sweden, decision number 2006/005, 2009-09-30) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all families for being included in the study. This article does not contain any studies with animal subjects.

Anna Bengtsson Strandqvist, Charlotte Bieneck Haglind, Rolf H. Zetterström, Antal Nemeth, Ulrika von Döbeln, Maria Halldin Stenlid, and Anna Nordenström have seen the final version of the manuscript and confirm that the data has not been published elsewhere. An abstract for a poster presentation, based on the same data, has been submitted to SSIEM 2015. All authors agree with submission.

Anna Bengtsson Strandqvist performed and analyzed all cognitive tests and contributed to the conception, design, analysis and interpretation of data, and drafting the article and is the guarantor for the cognitive tests.

Charlotte Bieneck Haglind contributed to the conception and design, analysis and interpretation of data, and drafting the article and is the guarantor for the work.

Anna Bengtsson Strandqvist and Charlotte Bieneck Haglind share the first authorship as *Anna Bengtsson Strandqvist* has been responsible for performing neuro-cognitive tests and *Charlotte Bieneck Haglind* has been responsible for writing and editing the manuscript. They have equally contributed to the design, analysis, and interpretation of data.

Rolf H Zetterström has been involved in analysis and interpretation of data, as well as drafting and critically revising the manuscript for intellectual content.

Antal Nemeth has been involved in critical revision.

Ulrika von Döbeln contributed to the analysis and interpretation of data and has been critically revising the article for intellectual content. She has also been responsible for many of the laboratory analyses.

Maria Halldin Stenlid has been involved in design and interpretation of data and critically revising the article for intellectual content.

Anna Nordenström has been involved in conception and design, analysis, and interpretation of data, drafting the article, and critically revising it for intellectual content.

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