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Neurodevelopmental profiles of children with very long chain acyl-CoA dehydrogenase deficiency diagnosed by newborn screening ☆

Amy Brown [a,b,*], Louise Crowe [a], Brage S. Andresen [c], Vicki Anderson [a,b,d], Avihu Boneh [b,e]

[a] Australian Centre for Child Neuropsychological Studies, Murdoch Childrens Research Institute, Royal Children's Hospital, Melbourne, Australia
[b] Department of Paediatrics, The University of Melbourne, Melbourne, Australia
[c] Department of Biochemistry and Molecular Biology, University of Southern, Denmark
[d] Department of Psychology, Royal Children's Hospital, Melbourne, Australia
[e] Metabolic Research, Murdoch Childrens Research Institute, Royal Children's Hospital, Melbourne, Australia

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ABSTRACT

Background: Very long chain acyl-CoA dehydrogenase (VLCAD) deficiency is a disorder of fatty acid oxidation with an estimated incidence of between 1:31,500 and 1:125,000. There is limited information regarding neurodevelopmental outcomes, probably because the disorder is perceived as affecting the skeletal and heart muscles, and many children are deemed asymptomatic. The aim of this study was to utilise a comprehensive neuropsychological assessment battery that assessed IQ, language, attention, memory, executive functioning, motor skills, behaviour, and social skills in children 4 to 10 years old diagnosed with VLCAD deficiency through newborn screening.

Method: Seven children completed neuropsychological assessment and one child was only involved in part of the study (2 female, 6 male). Parents completed questionnaires regarding executive functioning, behaviour and social skills.

Results: IQ scores ranged from average to the superior range. No deficits were found in fine or gross motor skills. One patient had a mild language deficit, and two patients had previously required speech therapy. Verbal memory, attention and executive functioning skills were generally average or above. Visual memory scores were mostly above average. Parents' questionnaires identified one child as having social skills deficits, and two as having behavioural problems such as hyperactivity. One child rated high on an autism spectrum subscale; another was formally diagnosed with autism spectrum disorder—both children were symptomatic at birth.

Conclusions: VLCAD deficiency does not have a significant impact on cognitive or motor skills. Some children may be vulnerable to speech, social and behavioural issues.

1. Introduction

Very long chain acyl-CoA dehydrogenase (VLCAD) deficiency is a metabolic disorder of fatty acid oxidation with an estimated incidence of between 1:31,500 and 1:125,000 [1–4]. Three phenotypes of VLCAD deficiency have been identified; an early onset, insidious type that causes a potentially lethal cardiomyopathy, a later onset type that presents with hypoketotic hypoglycaemia, and an adult onset form that mainly causes muscular symptoms [5]. Treatment of VLCAD deficiency includes a diet that is low in long chain triglycerides, prevention of fasting for long periods of time and supplementation of medium chain triglyceride (MCT) oil, particularly at times of physical activity [6]. Some centres include carnitine; however this has not been shown to benefit clinical outcome [7,8]. VLCAD deficiency is included in the newborn screening programme of many countries, allowing early diagnosis, and initiation of treatment [1].

There is limited information regarding neurodevelopmental outcomes in VLCAD deficiency, probably because the disorder is perceived as affecting the skeletal and heart muscles, and because some children are deemed asymptomatic and are less likely to be referred for a neuropsychological assessment. Positive neuropsychological outcomes were reported in a case study of a girl who had a severe onset at 5 months of age [9]. Assessed over four time points, she was found to have superior intellectual functioning at her last assessment at age 5 years. Recently a study on the neuropsychological functioning of 11 children, ranging in age from 12 months to 6 years and 3 months and diagnosed through newborn screening, reported one child as having a delay in cognitive functioning, whilst 7 of 14 displayed motor deficits or delay, and four exhibited speech delay [10]. One child was identified as being 'at

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* Corresponding author at: Department of Child Neuropsychology, Murdoch Childrens Research Institute, Flemington Road, Parkville, Melbourne, Victoria 3052, Australia.
E-mail address: amy.brown@mcri.edu.au (A. Brown).

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risk' for attention deficit hyperactivity disorder (ADHD) and another, whilst not formally diagnosed as autistic, showed behaviours associated with autism spectrum disorder (ASD).

The aim of the current study was to utilise a comprehensive neuropsychological assessment battery that assessed intelligence, language, attention, memory, executive functioning, motor skills, behaviour, and social skills in children 4 to 10 years old diagnosed through newborn screening.

2. Method

2.1. Procedure

Ethics approval was obtained from the RCH Human Research Ethics Committee (HREC #32218A). Information letters were sent to the parents of eligible participants and written informed consent was provided by parents. Assessments were conducted at the Royal Children's Hospital (RCH), Melbourne. The assessment duration was 2–3 h with breaks.

2.2. Participants

In order to administer a consistent neuropsychological test battery and enable clinical comparison we decided to include patients between 4 and 10 years of age. We identified 14 children, with a confirmed diagnosis of VLCAD deficiency. All patients are on a low fat diet, supplemented with medium chain triglyceride oil at times of increased physical activities. None of the patients are on carnitine. Seven children completed neuropsychological assessment and one child (patient 8) was only involved in part of the study as he was in the process of assessment for ASD (diagnosis later confirmed). Four children were eligible but their parents declined to participate, and two families could not be contacted. All patients, including all those who did not participate either because of refusal or because their age was outside the inclusion criteria (too young), are healthy and of normal growth and development as per common paediatric assessment. None of the patients had any episode of hypoglycaemia at any stage. The tested group consisted of two female and six male patients who were all regarded as 'physically asymptomatic' at the time of their assessment (Table 1). Patient 7 previously had an episode of rhabdomyolysis after an intensive swimming session. Parents completed questionnaires regarding executive functioning, behaviour and social skills.

2.3. Measures

Participants were assessed using a comprehensive, standardised neuropsychological assessment battery. Tests included were: *Intelligence*: Wechsler Abbreviated Scale of Intelligence (WASI) [11] and Wechsler Preschool and Primary Scale of Intelligence Third Edition (WPPSI-III) [12] for those under 6 years. *Motor function:* Movement Assessment Battery for Children (MABC-2) [13]—Manual Dexterity (fine motor), Aiming & Catching, and Balance subtests (gross motor). *Language*: Clinical Evaluation of Language Fundamentals Version 4 (CELF-4) [14]—Concepts and Following Directions (receptive), Formulating Sentences, Recalling Sentences, Word Structure/Classes (expressive), or WPPSI General language index. *Memory:* NEPSY II—Narrative Memory (verbal), Memory for Designs (visual) [15]. *Attention:* Test of Everyday Attention for Children (TEA-Ch)—Sky Search Attention (selective), Score (sustained), Sky Search DT (divided) subtests (6 years and above) [16]. *Executive Functioning:* NEPSY II—Inhibition (Naming, Inhibiting, Switching), Behaviour Rating Inventory of Executive Functioning (BRIEF) or preschool version (BRIEF-P) Parent Rating Form [17,18]. *Processing Speed:* Coding WPPSI-III (under 6 years). *Social*: NEPSY II—Affect Recognition, Social Skills Improvement System (SSIS) Parent Rating Form [19]. *Behaviour:* Strengths and Difficulties Questionnaire (SDQ) [20]. The test battery was administered according to age specifications and some tests could not be administered to the children below 6 years, or an alternate test was utilised. Parents were interviewed to obtain demographic information and a full background medical and developmental history in order to ascertain whether children required interventions or specialised allied health professionals such as speech therapy, physiotherapy or psychologists. Data on previous hospital admissions, and clinical magnetic resonance imaging (MRI) scans were obtained via medical records (Table 1).

Scores on all tests were compared with standardised age norms and a standard deviation (SD) of two or more below the mean on cognitive measures was considered to be a clinically significant deficit, whilst scores between 1 and 2 SD below the mean were considered to be below average and a mild deficit, or 'borderline' [21]. Interpretation of test scores is as follows; WASI/WPPSI-III, CELF-4 core language score,

Table 1
Diagnosis and clinical details.

ID (Sex)	Age	Genotype	Aceyl-CoA[a]	SES decile	Hospital admissions	Speech therapy	Additional information
01 (M)	4	Not available	C14:1: 2.9 C14:1/C10: 25.4	7	12	NO	
02 (F)	5	c.1117A > T (p.I333F)[b] c.1153C > T (p.R345W)[b]	C14:1: 5.27 C14:1/C10: 14.3	8	8	YES	*Food allergy, asthma*
03 (M)	5	CCT deletion 1497–1499; DelLeu460 (Homozygous)[c]	C14:1: 2.23 C14:1/C10: 11.3	5	1	NO	
04 (M)	6	c.848T > C (p.V243A) c.476A > G (p.Q119R)	C14:1: 4.86 C14:1/C10: 32.3	9	2	NO	
05 (M)	7	c.889–91delGAG (delGlu257) c.1246G > T (A376S)	C14:1: 2.64 C14:1/C10: 14.2	9	3	NO	*Bradycardia and hypoglycemia at birth*
06 (M)	8	c.1117A > T (p.I333F) c.1153C > T (p.R345W)	C14:1: 2.59 C14:1/C10: 24.4	8	6	NO	
07 (F)	9	CCT deletion 1497–1499; DelLeu460 (Homozygous)	C14:1: 2.16 C14:1/C10: 13.7	5	4	NO	
08[d] (M)	10	c.1097G > A (p.R326H) c.1322G > A (p.G401D)	C14:1: 1.69 C14:1/C10: 24.7	6	11	YES	*Prolonged bradycardia.* *Acute cardiovascular collapse at 40 h* *MRI 6 days: findings consistent with hypoxic–ischemic event.* *MRI 2 weeks: changes partially resolved* *Psychologist: Autism Spectrum Disorder*

[a] *Micromol/L.*
[b] *Inferred mutation (sibling of patient 6).*
[c] *Inferred mutation (sibling of patient 7).*
[d] *Did not complete neuropsychological assessment.*