Published in final edited form as:

Dev Disabil Res Rev. 2013 June ; 17(3): 260–268. doi:10.1002/ddrr.1119.

Neuropsychological Outcomes in Fatty Acid Oxidation Disorders: 85 Cases Detected by Newborn Screening

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Abstract

Mitochondrial fatty acid oxidation disorders include conditions in which the transport of activated acyl-Coenzyme A (CoA) into the mitochondria or utilization of these substrates is disrupted or blocked. This results in a deficit in the conversion of fat into energy. Most patients with fatty acid oxidation defects are now identified through newborn screening by tandem mass spectrometry. With earlier identification and preventative treatments, mortality and morbidity rates have improved. However, in the absence of severe health and neurological effects from these disorders, subtle developmental delays or neuropsychological deficits have been noted. Medical records were reviewed to identify outcomes in 85 children with FAOD's diagnosed through newborn screening and followed at one metabolic center. Overall, 54% of these children identified through newborn screening experienced developmental challenges. Speech delay or relative weakness in language was noted in 26 children (31%) and motor delays were noted in 24 children (29%). The majority of the 46 children receiving psychological evaluations performed well within the average range, with only 11% scoring <85 on developmental or intelligence tests. These results highlight the importance of screening children with fatty acid oxidation disorders to identify those with language, motor, or cognitive delay. Although expanded newborn screening dramatically changes the health and developmental outcomes in many children with fatty acid oxidation disorders, it also complicates the interpretation of biochemical and molecular findings and raises questions about the effectiveness or necessity of treatment in a large number of cases. Only by systematically evaluating developmental and neuropsychological outcomes using standardized

methods will the true implications of newborn screening, laboratory results, and treatments for neurocognitive outcome in these disorders become clear.

Keywords

fatty acid oxidation disorders; RAOD; newborn screening

Mitochondrial fatty acid oxidation is a complex process involving transport of activated acyl-Coenzyme A (CoA) moieties into the mitochondria, and sequential removal of 2 carbon acetyl-CoA units (Figs. 1 and 2). It is the main source of energy for many tissues including heart and skeletal muscle and is critically important during times of fasting or physiologic stress. Disorders of fatty acid oxidation interrupt this cycle and lead to a deficit in the conversion of fat into energy. Most patients with fatty acid oxidation defects are now identified through newborn screening by tandem mass spectrometry (MS) of carnitine esters in blood spots, and as a result, mortality, and morbidity rates have vastly improved [Wilcken, 2010]. Fasting or stress-related hypoketotic hypoglycemia, Reye-like syndrome, cardiac conduction abnormalities, cardiomyopathy, and muscle weakness or fasting- and exercise-induced rhabdomyolysis may still occur, especially in the disorders of long chain fat metabolism. Fortunately, severe neurological deficits resulting from a major hypoglycemic episode are now rare. However, newborn screening often changes the spectrum of symptoms in the diseases it identifies, and can uncover previously unrecognized developmental delays and neuropsychological impairments, despite IQ within the average range. In this report, we summarize the available literature on patients with fatty acid oxidation defects diagnosed due to clinical symptoms, as well as the few published studies on those identified through newborn screening. We next present original data on developmental and intellectual outcomes in 85 children with FAOD's diagnosed through newborn screening and treated prior to the onset of symptoms. Finally, we suggest a neuropsychological screening method designed to expose developmental delays or neuropsychological deficits to which these children may be vulnerable.

LITERATURE REVIEW

Medium Chain CoA Dehydrogenase Deficiency

Medium chain CoA dehydrogenase deficiency (MCADD; OMIM 607008), the most prevalent of the fatty acid oxidation disorders, results in a decreased ability to withstand catabolic stress [Wang et al., 1999]. Historically, it most frequently presented during the first 2–3 years of life with episodes of fasting-induced vomiting, hepatomegaly, hypoketotic hypoglycemia, and lethargy progressing to coma, seizures and in some cases, death. Diagnosis through clinical symptoms is now rare as the disorder is readily identified through newborn screening by tandem MS as is routine in many countries throughout the world [Wilcken et al., 2007; Kennedy et al., 2010].

In a retrospective study of 73 clinically presenting MCADD patients (ages 2–9 years of age) based on survey results from physicians and some direct evaluations, 44 (60%) were judged to be “normal” in terms of behavioral and learning problems [Iafolla et al., 1994]. Based on

routine developmental screening (presumably a physician's impression), speech disability was recognized in 16 subjects (22%) and attention deficit disorder was noted in 8 children (11%). Twenty-four children (40%) were judged to have "abnormal" developmental screening and received formal developmental testing. Among these children, 12 had global developmental disability, 7 had behavioral abnormalities, and 4 had both developmental and behavioral abnormalities.

In an Australian sample, 20–30% of infants not identified through newborn screening and who survived an early metabolic crisis experienced some type of developmental delay [Wilcken et al., 2007]. However, in follow-up testing of the cohort of children showing symptoms after 5 days of age, only 1 of 27 children experienced an intellectual handicap. Two required special help in school. Among the eight cases exhibiting symptoms within 5 days of age, three died [Joy et al., 2009; Wilcken et al., 2009].

In a review of published cases prior to newborn screening for MCADD, Schatz and Ensenauer [2010] noted that up to 25% of patients died, 40% required multiple hospitalizations, and up to one third exhibited severe neurologic deficits. Adult-onset MCADD was noted in seven cases in the literature, but no neuropsychological data were reported.

Newborn screening studies suggest a prevalence rate of 1 in 14,600–1/2000 infants in the United States for MCADD [Rhead, 2006; Kennedy et al., 2010], significantly higher than the number of cases identified because of clinical symptoms [Wang et al., 1999]. This suggests that newborn screening is identifying cases of MCADD that otherwise might have been benign, undiagnosed or mis-diagnosed. In a prospective follow-up study of outcomes in 20 children with MCADD detected by newborn screening, none experienced intellectual disability [Antshel and Waisbren et al., 2003], although 2 of the children later died, one at 13 months and the other at 3½ years of age [Yusupov et al., 2010]. Among 32 cases of MCADD detected by the New England Newborn Screening Program, no developmental problems were noted except for mild speech delay in one 2-year-old child [Hsu et al., 2008]. In an Australian study, outcomes in 38 children who had been diagnosed with MCADD either clinically ($n = 19$) or through newborn screening ($n = 19$) were compared [Joy et al., 2009]. Although statistically significant differences between the screened and unscreened groups were not found, the screened group registered higher scores on every subtest. There was no evidence of overall intellectual impairment in either group but there was some suggestion of poorer verbal and executive functioning (i.e., planning) abilities in the unscreened cohorts. Adaptive functioning was relatively intact with the exception of reduced Daily Living Skills in both the screened and unscreened groups.

Very-Long Chain Acyl-CoA Dehydrogenase Deficiency

Very-long chain acyl-CoA dehydrogenase deficiency (VLCADD; OMIM 201475) can present in the newborn period with arrhythmias and sudden death, or with hepatic, cardiac, or muscle symptoms later in infancy or childhood. The hepatic presentation is characterized by fasting-induced hypoketotic hypoglycemia, encephalopathy, and mild hepatomegaly, often with mild acidosis, hyperammonemia, and elevated liver transaminases. Some present with arrhythmias or dilated or hypertrophic cardiomyopathy in infancy or childhood, and

some with adolescence onset of exercise or fasting-induced muscle pain, rhabdomyolysis, elevated creatine phosphokinase, and myoglobinuria. VLCAD deficiency is now most frequently diagnosed through newborn screening and many babies thus identified have mild or minimal symptoms [Spiekerkoetter, 2010]. There are few reports of developmental outcome in this disorder. One girl diagnosed clinically with a severe hypertrophic cardiomyopathy at 5 months of life, performed in the superior intellectual range at age 4 years, and demonstrated no behavioral or emotional abnormalities [Cox et al., 1998]. Other reports on neurodevelopmental functioning in the unscreened population could not be found. Of 30 patients identified through newborn screening, 17 were deemed “asymptomatic” at follow-up through age 7 years, although neuropsychological testing was not mentioned [Spiekerkoetter et al., 2009].

Long-Chain 3-Hydroxyacyl CoA Dehydrogenase and Mitochondrial Trifunctional Protein Deficiencies

Several chain length-specific NAD-dependent 3-hydroxyacyl-CoA dehydrogenases catalyze the oxidation of 3-hydroxyacyl-CoA esters to 3-ketoacyl esters. Long-chain 3-hydroxyacyl CoA dehydrogenase (LCHAD) acts on hydroxyacyl-CoAs longer than C8. LCHAD and long-chain enoyl-CoA hydratase activities are carried on the α -subunit of the mitochondrial tri-functional protein (MTF) and long-chain α -ketothiolase is carried on the β -subunit. LCHAD deficiency can exist alone or together with deficiency of the other two enzymes. Patients with a deficiency of all three activities present primarily with symptoms of cardiomyopathy, myopathy, and hypoglycemia. Peripheral neuropathy and recurrent myoglobinuria may be present. Individuals deficient only in LCHAD activity have hepatocellular disease with hypoglycemia with or without pigmentary retinopathy. Cholestasis and fibrosis may also be present. Milder cases with adolescent onset of recurrent rhabdomyolysis have been reported [Hayes et al., 2007].

As with other fatty acid oxidation disorders, LCHAD and TFP deficiencies (OMIM 609016, OMIM 609015) are now most frequently diagnosed through newborn screening. Survey data on seven babies with LCHAD deficiency identified through newborn screening, revealed none who had died but four displayed symptoms [Spiekerkoetter et al., 2009]. In seven additional newborn screened cases, six developed symptoms including hypoglycemia, cardiomyopathy, and recurrent rhabdomyolysis [Sander et al., 2005]. No reports on neuropsychological testing could be found. Two infants with MTF deficiency and two infants with long-chain three ketothiolase deficiency detected by newborn screening were described by Sander et al. [2005] and all four died early. There were no reports of neuropsychological evaluations in any of the patients.

Short-Chain Acyl CoA Dehydrogenase Deficiency

Short-chain acyl CoA dehydrogenase deficiency (SCADD; OMIM 201470) is an autosomal recessive disorder in the final cycles of mitochondrial fatty acid oxidation. The frequency of complete SCAD deficiency based on newborn screening is ~1:33,000 [Zytkovicz et al., 2001]. There are also two common polymorphisms that are present in as high as one third of the general population that lead to increased accumulation of the characteristic metabolites but appear not to be associated with disease.

SCADD was originally described in two neonates who presented with metabolic acidosis and excretion of ethylmalonic acid. One of the babies recovered and demonstrated normal growth and development. The other baby became profoundly ill and died on day five of life [Amendt et al., 1987]. The neonatal features of SCADD reported in clinically ascertained infants have included feeding difficulties, hypotonia, lethargy, metabolic acidosis, hypoglycemia, and death [Amendt et al., 1987; Kurian et al., 2004; van Maldegem et al., 2005]. During later infancy and childhood, reported features have included failure to thrive, developmental delay, seizures, and myopathy [Coates et al., 1988; Baerlocher et al., 1997; Koeberl et al., 2003; van Maldegem et al., 2005]. The biochemical hallmarks are elevated levels of butyrylcarnitine (C4) as detected by tandem MS and urinary excretion of ethylmalonic acid [Gregersen et al., 2000]. In a study of 14 children with SCADD [Waisbren et al., 2008], 4 of the 6 clinically identified children exhibited symptoms and/or developmental delay, although alternative explanations were proposed for the medical problems and neuropsychological deficits noted. In contrast, all children identified by newborn screening were asymptomatic, except for one child with relative weakness in the motor area and another child with mild speech delay. Other infants identified through newborn screening have been largely asymptomatic [Marsden et al., 2006, Gallant et al., 2012]. In a review of the California Newborn Screening Program, 76 patients identified with SCAD deficiency were asymptomatic, although 3 of 31 patients for whom clinical data were available were noted to have isolated speech delay and 1 child presented with hypotonia [Gallant et al., 2012].

ORIGINAL DATA FROM ONE METABOLIC CENTER

In 1999, Massachusetts initiated state-wide expanded newborn screening that included detection of fatty acid oxidation disorders. In the 12^{1/2} years since this expansion, 85 children with a fatty acid oxidation disorder have been followed at one metabolic center, where developmental and neuropsychological testing are included in the clinic protocol for routine follow-up. Children with an initial out-of-range newborn screening result were excluded from this study if confirmatory laboratory or genetic testing was absent or if no follow-up information was recorded. As noted in Table 1, 47% were girls and 53% were boys, with more boys than girls identified with MCADD and VLCADD, and more girls than boys identified with SCADD and primary carnitine deficiency. Overall, 54% received developmental or neuropsychological evaluations. According to clinic protocol, children receive neuro-developmental testing at ages 6, 12, 18, and 24 months. Children receive neuropsychological testing at ages 4, 7, and 10 years. Age appropriate tests of intelligence, language, visual motor coordination, memory, and learning are administered along with parent questionnaires for ratings of adaptive behavior, executive functioning, attention deficit disorder, and emotional well-being. Results from these evaluations are placed in the child's medical record. For this study, children were described as having a language or motor deficit if they attained a test score >1 standard deviation below the normative mean on age appropriate standardized tests. In addition, if they received early intervention or special education services for motor, language or learning issues, they were rated as having "developmental concerns." The most recent developmental quotient (DQ) or intelligence quotient (IQ) was reported when multiple evaluations had taken place. This study involved a

medical record review of children evaluated at the metabolic center. Approval for the record review was received by the Committee on Clinical Investigations (Institutional Review Board).

Medium Chain CoA Dehydrogenase Deficiency

Twenty-seven children (8 girls and 19 boys) with MCADD detected by newborn screening were seen at the metabolic center (Table 2). Twelve of the children were homozygous for the common A985G mutation and 9 children had one copy of A985G and another mutation. Other mutations found in one child each included 799G>A /797A>G and c.245_246ins T/c.387G>T. Genotype was not reported in four children. Carnitine supplementation was prescribed in 14 cases. The mean age at the time of formal developmental assessment was 21 ± 9 months (range 5–33 months) and the mean age at IQ testing was 4.7 years $\pm$ 1.5 years (range 3.3–7.0 years). The mean DQ ($n = 11$) was 105 ± 25 , with two children attaining a score below 85 (1 standard deviation below the mean). Mean IQ ($n = 6$) was 109 ± 11 , with all children performing well within the average range. Thirteen of 27 children experienced speech/ language delay, significant weakness in speech compared with other abilities or a speech deficit. One of these children displayed behaviors on the autistic spectrum. Four additional children experienced developmental issues related to motor functioning (1 motor delay, 1 motor tic disorder, and 2 early feeding difficulties). Overall, 18 children (67%) experienced developmental challenges. In addition, one child died at 13 months [Yusupov et al., 2010] and one child received early intervention because of a diagnosis of MCADD. Tests measuring executive functioning abilities, attention, achievement, and visual motor performance indicated age-appropriate skills. Parents of 17 children with MCADD completed the behavioral assessment system for children, second edition (BASC-2) as part of a survey that included 9 families whose children were not followed at Children's Hospital. Elevated scores were noted on the following scales, where the normative mean is 50 and scores above 60 signify risk for problems: Anxiety (mean = 58 ± 12), Withdrawal (mean = 53 ± 17) and Internalizing Problems (mean = 56 ± 12). Overall, 44% of the children received elevated scores on the Internalizing Scale, with 44% of scores in the at-risk range on the Withdrawal index, and 33% of scores in the at-risk range on the Anxiety index. In comparison, none of the children received high scores on the Externalizing Behavior scales with Externalizing Behavior (mean = 45 ± 8) and Aggression (mean = 46 ± 7), well within the average range. For the adaptive scales, none of the children received scores in the at-risk or clinically significant range. Genotype did not predict cognitive outcome or developmental issues.

Very-Long Chain Acyl-CoA Dehydrogenase Deficiency

Fourteen children (5 girls and 9 boys) with VLCADD identified by newborn screening were followed at the metabolic clinic and 11 of these children received developmental or neuropsychological evaluations (Table 3). Mean DQ in the younger cohort ($n = 5$) was 99 ± 21 at a mean age of 22 ± 7 months. One child exhibited cognitive delay with a DQ of 75, >1 standard deviation below the population norm. Mean IQ in the older children ($n = 6$) was 115 ± 4 at a mean age of 3 years 8 months, suggesting that cognitive functioning is intact. However, 7 of 14 children (50%) exhibited motor delay or relative weakness in the motor area, 4 children (29%) experienced speech delay, 1 child had autistic spectrum behaviors

and 1 child was at risk for attention deficit disorder. Parent responses to the questionnaires provided no evidence for attention deficit disorder, executive functioning deficits, or behavioral/emotional issues in this group of children, except for the two cases described above.

Long Chain Acyl-CoA Dehydrogenase Deficiency

As noted in Table 4, two children with long chain acyl-CoA dehydrogenase deficiency (LCHADD) were identified by newborn screening (one boy and one girl). The boy was determined to be homozygous for the common LCHAD mutation, G1528C. At age 7 years, he carried a diagnosis of pervasive developmental delay, with intellectual abilities rated in the borderline range (IQ < 85). He received a gastrostomy tube for feeding and was noted to have “mild eye findings.” The little girl is heterozygous, 1528G>C (p.GLU474GLN)/c. 871C>T (p.Arg255X). At age 3 years, she was noted to have speech delay, a history of muscle pain and slight macular pigmentary changes. Electroretinogram findings suggested mild retinal function deficits. She will be attending a special preschool program for children with speech delay.

Primary Carnitine Deficiency

Overall, 15 newborns were referred to the metabolic center based on newborn screening results suggestive of primary carnitine deficiency. Of these 7 (5 girls and 2 boys) were confirmed to have a primary carnitine deficiency (Table 5). All were treated with carnitine. Three of these children received developmental evaluations with DQ or IQ above 100. Two of these children experienced mild developmental delays before age 2 years, one in the motor area and one in both motor and speech. The latter child received special education services. However, no persistent developmental delays were noted in any of the children. Newborn screening results in five additional children, with normal laboratory values on confirmatory testing, led to the identification of their mothers' primary carnitine deficiency. One mother was found to be a carrier and experienced chronic fatigue until beginning carnitine treatment. The other mothers, found to have classic disease, were asymptomatic. All were treated with carnitine and achieved near normal metabolic status.

Short Chain Acyl-CoA Dehydrogenase Deficiency

Newborn screening led to the identification of 35 infants with SCADD (21 girls and 14 boys) with diagnoses confirmed biochemically or through molecular testing (Table 6). One female, who experienced significant developmental, behavioral, and emotional problems, was diagnosed in 1988 through urine screening, which was being performed at that time. The others were all detected through recent expanded newborn screening. Fourteen children received formal developmental or neuropsychological testing at a mean age of 3.28 ± 3.31 years. The mean DQ was 106 ± 12 and the mean IQ was 113 ± 28 . One child had an IQ of 84 and all the other children tested had scores above 85. However, among the entire group of 35 children, 16 (46%) were noted to have developmental or behavioral concerns, including 4 with speech/language delay, 2 with global developmental delay, and 3 with early motor delay. Genotype, available in 25 cases, did not correspond to outcome.

SUMMARY AND DISCUSSION

As noted in Table 7, 54% of children with a fatty acid oxidation defect identified through newborn screening experienced developmental issues to some degree. Speech delay or relative weakness in language was noted in 26 children (31%) and motor delays were noted in 24 (29%). The mean DQ for the entire sample was well within the average range, with only 6% scoring <85 on developmental or intelligence tests. DQ/IQ was not different between girls and boys ($P = 0.25$).

Fatty acid oxidation disorders manifest a range of neuropsychological outcomes, even when detected early and treated prior to the occurrence of a metabolic crisis. Over half the children evaluated experienced developmental delay or significant relative weaknesses, most within a context of normal cognitive abilities. The percentage of those experiencing developmental delay might be higher, given that only 54% of children received developmental or neuropsychological testing, despite clinic protocol recommending regular evaluations. Previous reports of functional outcomes in newborn screened children relied primarily on physician and parent impressions and, in the case of MCADD, led to the belief that in the absence of a metabolic crisis, the metabolic condition conferred no risk for clinical manifestations [Schatz and Ensenuer, 2010]. And the risk of developmental, cognitive or behavioral effects from the other fatty acid oxidation disorders was generally not even considered, as evidenced by the lack of psychological follow-up. The perception that these disorders do not affect cognitive and developmental processes may deter physicians from referring patients with FAOD's for developmental or neuropsychological testing or lead to denial of coverage for testing by insurance companies. This retrospective study suggests that screening for developmental delays, neuropsychological deficits, and behavioral problems is warranted.

In MCADD, nearly 50% of cases in our series exhibited speech/language delay and 26% were delayed in the motor area. The possibility of a typical MCADD psychological profile is further reinforced by the finding that 44% showed a tendency toward anxiety and withdrawal. This personality style may place the children at risk due to a reluctance to admit they do not feel well or they need to eat or drink more frequently. In each of the other disorders, the incidence of speech/language delay was above the incidence in the general population, usually determined to be at 5–8% [Nelson et al., 2006]. Motor delays and deficits were also more common than expected, most notably in children with VLCADD. Even in SCADD, rates of developmental delay were higher than expected. Children with more severe mutations did not necessarily fare differently, although further studies with larger sample sizes are needed. On the positive side, no child had a DQ or IQ <70 (two standard deviations below the population mean). Only 11% overall attained a score more than one standard deviation below the population mean, a frequency <15% expected in the general population. Thus, expanded newborn screening prevents the most devastating cognitive effects from these disorders. LCHAD may be an exception, in that both children in our sample with this disorder experienced significant health and developmental challenges.

The reason for particular vulnerabilities in speech/language or motor development is not known. Delayed language development was found in 55% of infants fed a soy formula later

found to be deficient in thiamine [Fattal-Valevski et al., 2009], and poorer language was associated with later age at independent walking ($P = 0.005$). The investigators hypothesized that subtle insult to subcortical structures may have occurred during a critical period of development. They also speculated that the nonspecific symptoms of lethargy, restlessness and vomiting that brought them to medical attention while on the thiamine deficient formula may signify subtle but significant encephalopathy. The same could be true in these metabolic disorders, when the infant brain is subjected to abnormal metabolites or deficiencies that could have a subtle impact on later development.

This summary of the published literature and review of newborn screened cases from one large metabolic center brings to light the neuropsychological concomitants of fatty acid oxidation disorders even when DQ and IQ are within the average range. Clearly, not all of the deficits or concerns were related to the metabolic diagnosis and not all children experienced detectable deficits in a particular area. However, all children should probably be screened beyond the typical assessment of developmental milestones or parental concerns and a link with the metabolic diagnosis should be investigated. Given the cost and limited access to formal neuropsychological testing, we suggest that parents complete what we call the “Uniform Assessment Method” [Waisbren and White, 2010], comprised of three screening questionnaires. The adaptive behavior assessment system-second edition (ABAS-II) [Harrison and Oakland, 2003] measures development in a variety of areas, including communication and motor skills, and provides an index of overall functioning, general adaptive composite. The behavior rating inventory of executive function [Gioia et al., 2000], assesses aspects of higher order reasoning with scales measuring various cognitive functions, including working memory, attention, inhibition, planning, and organization. A global executive composite provides an overall measure of executive functioning. The behavior assessment system for children-second edition (BASC-2) [Reynolds and Kamphus, 2004] measures emotional well-being, and includes indices for hyperactivity, aggression, depression, anxiety, and social relationships. An “Atypicality” subscale on the BASC-2 provides a screen for autistic spectrum disorders. These questionnaires are available in multiple languages and also can be completed on-line. There are age appropriate forms across the age span, with additional self-report forms for adults. These are instruments that can be administered by nonpsychologists and are scored and interpreted electronically. Electronic reports can also be generated.

Expanded newborn screening dramatically changes the health and developmental outcomes in some children with fatty acid oxidation disorders. However, expanded newborn screening also complicates the interpretation of biochemical and molecular findings and raises questions about the effectiveness or necessity of treatment in a large number of cases. Only by systematically evaluating developmental and neuropsychological outcomes using standardized methods will the true implications of newborn screening, laboratory results, and treatments for these disorders become clear.

Acknowledgments

Grant sponsor: Maternal and Child Health; Grant sponsor: NIH; Grant number: DK54936 and DK78775; Grant sponsor: England Genetics Collaborative; Grant sponsor: Federal cooperative agreement from the United States

Department of Health and Human Services; Grant sponsor: Health Resources and Services Administration; Grant number: U22MC10980.

The authors acknowledge Rachel Loeb, Vera Anastasoie, Lydia Carr, Stephanie Petrides, and Ephraim Roberson for their help with this research study.

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Fig. 1.
Acylcarnitine transport cycle.

Fig. 2.
The fatty acid oxidation cycle.

Table 1

Fatty Acid Oxidation Disorders Detected by Newborn Screening and Followed at One Metabolic Center

Disorder	# Girls	# Boys	Total	# (%) With Developmental or Neuropsychological Evaluation
MCADD	8	19	27	17 (63%)
VLCADD	5	9	14	11 (79%)
LCHADD	1	1	2	1 (50%)
Primary Carnitine Deficiency	5	2	7	3 (43%)
SCADD	21	14	35	14 (40%)
Total	40	45	85	46 (54%)

MCADD: Medium chain acyl-CoA dehydrogenase deficiency.

VLCADD: Very long chain acyl-CoA dehydrogenase deficiency.

LCHADD: Long chain acyl-CoA dehydrogenase deficiency.

SCADD: Short chain acyl-CoA dehydrogenase deficiency.

Table 2
MCADD: Gender, Genotype and Outcome in Cases Detected by Newborn Screening

Case #	Gender	Genotype	Age at Testing or When Last Seen	DQ/IQ	Developmental Concerns
1	Male	c.985A>G (p.K329E)/c.985A>G (p.K329E)	28 mo DQ	145	Weakness in language at 10 months
2	Male	c.985A>G (p.K329E)/c.985A>G (p.K329E)	18 mo DQ	102	None noted
3	Male	c.985A>G (p.K329E)/c.985A>G (p.K329E)	6 mo	–	None noted
4	Female	c.985A>G (p.K329E)/c.985A>G (p.K329E)	33 mo DQ	140	Language score 30 points lower than cognitive score
5	Male	c.985A>G (p.K329E)/c.985A>G (p.K329E)	4 yrs 6 mo	99	Speech/language delay and motor deficits
6	Male	c.985A>G (p.K329E)/c.985A>G (p.K329E)	3 yr 6 mo	109	Speech/language delay
7	Male	c.985A>G (p.K329E)/c.985A>G (p.K329E)	24 mo	62	Speech/language delay
8	Male	c.985A>G (p.K329E)/c.985A>G (p.K329E)	14 mo	–	None noted
9	Male	c.985A>G (p.K329E)/c.985A>G (p.K329E)	5 mo DQ	117	None noted
10	Male	c.985A>G (p.K329E)/c.985A>G (p.K329E)	25 mo DQ	95	Speech/Language delay
11	Female	c.985A>G (p.K329E)/c.985A>G (p.K329E)	3 yr 3 mo	120	Speech/language and fine motor delays
12	Female	c.985A>G (p.K329E)/c.985A>G (p.K329E)	24 mo DQ	72	Speech/language delay
13	Female	c.985A>G (p.K329E)/c.1137T>G((A?)) or T137A?	7 yrs 1 mo	123	Fine motor delay and anxiety
14	Male	c.985A>G (p.K329E)/c.1137T>G((A?)) or T137A?	6 yrs 0 mo	100	None noted
15	Female	c.985A>G (p.K329E)/c.842G>C	12 mo DQ	96	Mild motor delay
16	Male	c.985A>G (p.K329E)/?	6 yr 1 mo	–	Motor tic disorder
17	Female	c.985A>G (p.K329E)/c.250C>T (p.L84F)	24 mo DQ	115	None noted
18	Male	c.985A>G (p.K329E)/c.504A>C	8 year 9 mo	–	Language and motor delay noted at 5 yr
19	Female	c.A985G (p.K329E)/c.G799A	10 mo	–	None reported
20	Male	c.985A>G (p.K329E)/c.1178A>G	9 mo DQ	104	Died at 13 mo
21	Male	c.985A>G (p.K329E)/c.C683A	24 mo DQ	106	Speech/language delay
22	Male	G799A/A797G	3 yrs 9 mo	101	Speech/language delay
23	Male	c.245_246insT/c.387G>T	4 yr 9 mo	–	Early feeding difficulties, speech deficit (stuttering)
24	Female	Not available	4 yr 0 mo	–	None noted
25	Male	Not available	7 yr 1 mo	–	Attention Deficit Hyperactivity
26	Male	Not available	5 yr 2 mo	–	Early feeding difficulties, speech deficit (nonverbal), pervasive developmental delay
27	Male	Not available	9 yrs 11 mo	–	Received early intervention

Table 3
VLCADD: Gender, Genotype, and Outcome in Cases Detected by Newborn Screening

Case #	Gender	Genotype	Age at Testing or When Last Seen	DQ/IQ	Developmental Concerns
1 ^a	Male	c.1376 G>A (R459Q)/c.1531 C>T (R511W)	3 yr 6 mo	115	None noted
2 ^a	Male	c.1376 G>A (R459Q)/c.1531 C>T (R511W)	3 yr 6 mo	115	None noted
3	Male	c.1376G>A (R459Q)/c.865G>A (G289R)/	30 mo DQ	85	Speech/language and motor delays, autistic spectrum behavior
4	Male	c848T>C (V283A)/c.1153C>T (R385W)	3 yr 5 mo	118	Mild articulation and fine motor weaknesses
5	Female	c848T>C (V283A)/c.694A (A232T)	18 mo DQ	125	Motor delay
6	Female	c848T>C (V283A)/c.1220G>C (G367A)	11 mo	–	None noted
7	Male	c848T>C (V283A)/c.865G>A (G289R)	4 yr 4 mo	120	Relative weakness in fine motor area
8	Female	c848T>C (V283A)/T848C (V283A)	13 mo	–	Speech/language delay
9	Female	c.753(–6) C>A/c.1700 G>A (R567Q)	12 mo DQ	115	None noted
10	Male	c.753-2 A>C only one: IVS8-2 A>C	34 mo	110	Relative weakness in fine motor area
11	Male	c.848T>C (Val283Ala)/c.1270G>A (Glu384Lys)	26 mo DQ	75	Speech/language and motor delays
12	Male	c.1406G>A (R469Q)	7 mo	–	None noted
13	Female	c.728T>A (L243H)/	23 mo DQ	95	None noted
14	Male	Not available	6 yr 3 mo	110	Fine motor deficits, at risk for attention deficit and emotional problems

^aTwins.

Table 4
LCHADD: Gender, Genotype, and Outcome in Cases Detected by Newborn Screening

Case #	Gender	Genotype	Age at Testing or When Last Seen	DQ/IQ	Developmental Concerns
1	Male	c.1528G>C/c.1528G>C	7 yrs 10 mo	75	Pervasive developmental delay, tics, feeding difficulties
2	Female	c.1528G>C (p.GLU474GLN)/c871C>T (p.ARG255X)	3 yrs 4 mo	–	Speech delay

Table 5

Primary Carnitine Deficiency: Gender, Genotype and Outcome in Cases Detected by Newborn Screening

Case #	Gender	Genotype	Age at Testing or When Last Seen	DQ/IQ	Developmental Concerns
1	Female	c.1193C>T (p.P398L)/c.424G>T (p.A142S) and c.1463G>A (p.R488H) (<i>cis</i>)	3 yrs 2 mo	–	None noted
2	Female	c.51C>G (p.F17L)/c.51C>G (p.F17L)	15 mo	120 (DQ)	Motor delay
3	Male	c.839C>T (p.S280F)/c.424G>T (p.A142S) and c.1463G>A (p.R488H) (<i>cis</i>)	6 mo	–	None noted
4	Male	c.641C>T (p.A214V) c.629A>G (p.N210S)	3 yrs 5 mo	105	Speech/language and motor delays
5	Female	c.424G>T (p.A142S) and c.1463G>A (p.R488H) (<i>cis</i>)/unknown second mutation	22 mo	–	None noted
6	Female	R399W/IVS3c.653-2A>C	4 yr 2 mo	113	None noted
7	Female	Not available	4 yr 2 mo	–	None noted

Table 6

SCADD: Gender, Genotype, and Outcome in Cases Detected by Newborn Screening

Case #	Gender	Genotype	Age at Testing or When Last Seen	DQ/IQ	Developmental Concerns
1	Female	c.625G>A (p.G209S) and c.1147C>T (R383C)/c.625G>A (p.G209S) and c.1147C>T (R383C)	11 mo DQ	120	None noted
2	Female	c.625G>A (p.G209S)/c.625G>A (p.G209S)	15 mo	–	None noted
3	Male	c.625G>A (p.G209S)/c.625G>A (p.G209S)	20 mo	–	Speech delay
4	Male	c.625G>A (p.G209S)/c.625G>A (p.G209S)	3 mo	–	Poor head control
5	Female	c.625G>A (p.G209S)/c.625G>A (p.G209S)	24 mo	–	None noted
6	Female	c.625G>A (p.G209S)/c.625G>A (p.G209S)	5 mo	–	Failure to thrive
7	Male	c.625G>A (p.G209S)/c.625G>A (p.G209S)	15 mo	–	Beckwith-Wiedemann syndrome, cerebral palsy
8	Male	c.625G>A (p.G209S)/c.625G>A (p.G209S)	6 mo	–	None noted
9	Female	c.625G>A (p.G209S)/c.625G>A (p.G209S)	12 mo	–	Exotropia in right eye
10	Female	c.625G>A (p.G209S)/c.625G>A (p.G209S) and heterozygous for c.157T>G (p.L53V)	7 mo	–	Motor delay
11	Female	c.625G>A (p.G209S)/c.319C>T (p.R107C)	25 mo	–	None noted
12	Male	c.625G>A (p.G209S)/c.319C>T (p.R107C)	4 mo	–	None noted
13	Male	c.625G>A (p.G209S)/c.319C>T (p.R107C)	3 mo	–	None noted
14	Female	c.625G>A (p.G209S)/c.511C>T (p.R171W)	23 mo	–	Global developmental delay
15	Female	c.625G>A (p.G209S)/c.511C>T (p.R171W)	3 yrs 4 mo	145	None noted
16	Male	c.625G>A (p.G209S)/c.529T>C (p.W177R)	13 mo	–	None noted
17	Female	c.625G>A (p.G209S)/c.529T>C (p.W177R)	12 mo	–	None noted
18	Female	c.625G>A (p.G209S)/c.529T>C (p.W177R)	28 mo DQ	100	None noted
19	Female	c.529T>C (p.W177R)/c.529T>C (p.W177R)	22 mo	–	None noted
20	Female	c.529T>C (p.W177R)/c.529T>C (p.W177R) (Probable homozygosity)	4 yrs 2 mo	96	Weakness in visual motor area
21	Male	c.529T>C (p.W177R)/c.988C>T (p.R330C)	26 mo DQ	90	Attention Deficit Hyperactivity Disorder, Aggressive behavior
22	Male	c.505A>C/505A>C and maybe also c.625G>A (p.G209S)	6 yrs 4 mo	125	Muscle pains
23	Male	c.1095G>T (p.Q365H)/c.1095G>T (p.Q365H) and heterozygous for c.625G>A (p.G209S)	14 mo ^a GAC	119	Congenital torticollis
24	Female	c.320G>A (R107H)/c.417G>C (W139C)	30 mo DQ	95	Early motor delay
25	Male	Not available	5 yr 10 mo	–	None reported
26	Female	Not available	20 mo DQ	102	None reported

Case #	Gender	Genotype	Age at Testing or When Last Seen	DQ/IQ	Developmental Concerns
27	Female	Not available	9 mo	–	None reported
28	Female	Not available	2 yr 2 mo	–	None reported
29	Female	Not available	13 yr 6 mo	84	Early speech and motor delays, later psychiatric and behavioral issues
30	Female	Not available	32 mo DQ	100	Speech delay
31	Female	Not available	9 mo DQ	111	Speech delay
32	Male	Not available	5 yr 11 mo	–	None reported
33	Male	Not available	3 mo	–	None reported
34	Male	Not available	13 mo DQ	97	None reported
35	Female	Not available	35 mo DQ	125	Speech delay

^aGAC: General adaptive composite score from the adaptive behavior assessment system, second (ABAS-II).

Table 7
Summary of developmental concerns in sample of 85 cases detected by newborn screening

Disorder (<i>n</i>)	Developmental Concerns (<i>n</i> and %)	Speech (<i>n</i> and %)	Motor (<i>n</i> and %)	DQ (mean $\pm$ SD)	IQ (mean $\pm$ SD)	Cognitive Delay (<i>n</i> and %) ^a
MCADD (27)	18 (67%)	13 (48%)	7 (26%)	105 $\pm$ 25	109 $\pm$ 11	2/17 (12%)
VLCADD (14)	8 (57%)	4 (29%)	7 (50%)	99 $\pm$ 21	115 $\pm$ 4	1/11 (9%)
LCHADD (2)	2 (100%)	2 (100%)	1 (50%)	–	75	1/1 (100%)
Primary Carnitine Deficiency (7)	2 (29%)	1 (14%)	2 (29%)	120	105, 113	0/3 (0%)
SCADD (35)	16(46%)	6 (17%)	7 (20%)	106 $\pm$ 12	113 $\pm$ 28	1/14 (7%)
TOTAL (85)	46 (54%)	26 (31%)	24 (29%)	105 $\pm$ 19	110 $\pm$ 16	5/46 (11%)

^aCognitive delay defined as DQ or IQ < 85 (1 standard deviation below the normative mean). Percents are based on total number of cases receiving developmental or intelligence testing.