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Medium chain acyl-CoA dehydrogenase deficiency: Human genome epidemiology review

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Medium chain acyl-CoA dehydrogenase (MCAD) is a tetrameric flavoprotein essential for the β-oxidation of medium chain fatty acids. MCAD deficiency (MCADD) is an inherited error of fatty acid metabolism. The gene for MCAD is located on chromosome one (1p31). One variant of the MCAD gene, G985A, a point mutation causing a change from lysine to glutamate at position 304 (K304E) in the mature MCAD protein, has been found in 90% of the alleles in MCADD patients identified retrospectively. There is a high frequency of MCADD among people of Northern European descent, which is believed to be due to a founder effect. MCADD is inherited in an autosomal recessive manner. Of patients clinically diagnosed with MCADD, 81% who have been identified retrospectively are homozygous for K304E, and 18% are compound heterozygotes for K304E. Clinical data on the probability of clinical disease indicates that MCADD patients are at risk for the following outcomes: hypoglycemia, vomiting, lethargy, encephalopathy, respiratory arrest, hepatomegaly, seizures, apnea, cardiac arrest, coma, and sudden and unexpected death. Long-term outcomes include developmental and behavioral disability, chronic muscle weakness, failure to thrive, cerebral palsy, and attention deficit disorder (ADD). Differences in clinical disease specific to allelic variants have not been documented. Factors that may increase risk for disease onset or modify disease severity are age when the first episode occurred, fasting, and presence of infection. Acute attacks must be treated immediately with appropriate intravenous doses of glucose. For those diagnosed, long-term management of the disease includes preventing stress caused by fasting and maintaining a high-carbohydrate, reduced-fat diet, and carnitine supplementation. Hospitalization costs attributable to morbidity and mortality from MCADD are unknown; MCADD is not a diagnosis in the International Classification of Disease, 10th Revision (ICD-10) codebook. Furthermore, the penetrance of the MCAD genotypes is unknown; there appears to be a substantial number of asymptomatic MCADD individuals and some uncertainty regarding which individuals will manifest symptoms and which individuals will remain asymptomatic. Several technologies are available to detect MCADD. Diagnostic technologies include DNA-based tests for K304E mutations using the polymerase chain reaction (PCR), and the detection of abnormal metabolites in urine. Screening technologies include tandem mass spectrometry (MS/MS), which detects abnormal metabolites mostly in blood. State programs are beginning to offer screening in newborns for MCADD using MS/MS. In addition, a private company currently offers voluntary supplemental newborn screening for MCADD to birthing centers. ***Genetics in Medicine*, 1999:1(7):332–339.**

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GENE

The medium chain acyl-CoA dehydrogenase (MCAD) gene is located at chromosome 1p31. The protein formed, MCAD, is a homotetramer and an oxidoreductase enzyme that catalyzes the first step of the medium-chain fatty acid oxidation cycle, a two-electron oxidation of fatty acyl-CoA thiolesters. MCAD is part of the acyl-CoA dehydrogenase (flavoprotein) family and is one of five acyl-CoA dehydrogenases that catalyze the β-oxidation of fatty acids.

GENE VARIANTS

Twenty six MCAD gene variants have been reported,[1] with nine alleles of special interest listed in OMIM.[2] This review will focus on K304E, the MCAD mutation reportedly found in 90% of all retrospectively identified MCAD deficient patients' alleles, and for whom 81% of all MCAD patients are homozy-

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gous; 18% of MCAD patients are compound heterozygous for K304E. Caucasian individuals of Northern European descent exhibit the highest frequency of MCADD genotypes. The carrier frequency of K304E among this group is estimated to be 1:40 to 1:100 and the homozygote frequency is 1/6,500–20,000.[3] Haplotype analyses have suggested that the K304E MCAD mutation is a founder effect from a single person in a Germanic tribe.[4]

Table 1 lists the frequencies of the K304E mutation for the MCAD gene by country. Only two studies have been conducted on a population-based prospective cohort of newborns; most others are retrospective studies. Although heterozygotes have been identified with this method, few homozygotes have been identified; the frequencies of homozygosity shown in Table 1 are therefore mostly estimates based on the frequency of heterozygosity and using Hardy-Weinberg equilibrium. Despite this limitation, Ziadeh and colleagues' 1995 population-based study of U.S. newborns demonstrated a frequency of homozygosity (1/20,408) that is similar to those estimated in some northern European countries.[5] Ziadeh and colleagues studied the first 80,371 newborns from a supplemental newborn screening program in Pennsylvania and eastern Ohio for more than 35 metabolic disorders.[5] Despite the heterogeneity of the population, which included high proportions of Eastern

Table 1
Frequency by country of homozygosity and heterozygosity for K304E MCAD mutation

Country of origin	Frequency of homozygosity*	Frequency of heterozygosity	Homozygotes	Heterozygotes	Population total	Sample source	Reference No.
Australia	1/20,000	1/71	0	5	353	Anonymous spare Guthrie cards	7
Belgium	1/24,000	1/77	0	13	998	Surveyed newborn blood samples	8
Bulgaria	1/33,000	1/91	1	9	1005	Surveyed newborn blood samples	8
Czech Republic	1/231,000	1/240	0	5	1201	Surveyed newborn blood samples	8
Denmark	1/42,000	1/102	0	9	921	PKU cards	9
Finland	1/10,000	1/50	0	4	200	Blood donors	10
France							
Lyon		1/532	0	2	1064	Unselected newborn blood spots	11
Aquitaine	1/44,000	1/105	0	20	2090	Unselected newborn blood spots	12
Normandy		1/118	0	17	2000	Random newborn blood spots	13
Paris	1/19,000	1/140	0	6	414	Caucasian blood donors	14
Germany	1/53,000	1/116	0	26	3015	Surveyed newborn blood spots	8
Hungary	1/192,000	1/168	0	6	1008	Surveyed newborn blood spots	8
Italy	1/442,000	1/333	0	3	997	Newborn PKU cards	15
Japan	0	0	0	0	1000	Anonymous spare Guthrie cards	7, 8
Netherlands	1/16,000	1/63	0	99	6195	Anonymous spare Guthrie cards	16
Poland	1/38,000	1/98	0	10	980	Surveyed newborn blood spots	8
Russia	1/27,000	1/83	0	5	413	Unselected newborn blood spots	17
Scotland	1/304,000	1/276	0	2	552	Women AFP lab clotted blood	18
Spain	1/82,000	1/141	1	5	1000	Unspecified newborn blood spots	8
Switzerland	1/11,000	1/52	0	22	1142	Guthrie cards from healthy babies	19
Turkey	1/186,000	1/216	0	5	1079	Surveyed newborn blood spots	8
UK	1/17,000	1/64	0	158	10,171	Surplus dried blood samples	20
Trent	1/18,500	1/68	0	6	410	Neonatal population	21
Birmingham	1/6,400	1/40	0	12	479	Anonymous Guthrie cards	22
US							
North Carolina	1/28,000	1/84	0	31	2611	Caucasian PKU cards	4
Texas		1/107	0	5	536	Anonymous spare Guthrie cards	7
Pennsylvania**	1/20,408	†	4	5‡	80,371	Supple. newborn screening program	5

*Estimated from frequency of heterozygosity; †, cannot be calculated—entire population not genotyped; ‡, compound heterozygotes, not including carriers.
**Prospective population–based study.

Europeans and Blacks, nine MCADD newborns were diagnosed from the first 80,371 newborns screened between November 1, 1992 and September 30, 1994 by tandem mass spectrometry. However, upon DNA sequencing of the nine MCADD newborns, 44% (4 of 9) were homozygous for K304E and 56% (5 of 9) were compound heterozygotes, versus the 81% homozygous and 18% compound heterozygotes previously calculated based on retrospective data. In the U.K., however, Pollitt and Leonard's 1998 prospective study of MCADD through the British Pediatric Surveillance Unit identified 57 people in England with MCADD, for an MCADD incidence of 4.5/100,000. Of the 45 people with MCADD whose DNA has been analyzed thus far, 36 of 45 (80%) were homozygous for K304E, and 9 of 45 (20%) were heterozygous for K304E,[6] which is consistent with data from retrospective studies (because data are still pending, this study is not listed in Table 1). It is important to note that most of the retrospective studies are conducted using spare blood samples and their results are not necessarily representative of the population, nor can they accurately assess incidence of the disorder. Only from population-based prospective cohort studies can incidence of a disorder be accurately assessed.

Research on MCADD is in its infancy, with most of the published articles having concentrated on the biochemical and molecular aspects of the disease. The natural history and long-term outcomes of patients with the disorder are still not clearly defined, nor is determining who will present with disease and who will remain asymptomatic. Population and epidemiologic information gathered from pilot and supplemental testing programs currently being conducted will begin to provide much needed information about the long-term clinical spectrum of the disorder.

MCAD DEFICIENCY

The first MCADD patients were identified in 1982, and between 1982 and 1994, more than 200 MCADD patients were identified.[23] MCADD is an autosomal recessive genetic disorder that leads to an abnormal protein product and subsequent inefficient enzymatic activity to metabolize medium chain fatty acids. The K304E MCAD mutation occurs when glutamate is substituted for lysine at position 304 in the mature MCAD protein. Individuals who are homozygous or compound heterozygous for an MCAD mutation may exhibit some clinical manifestations of MCADD. Differences in clinical manifestations specific to allelic variants have not yet been documented.

The incidence of MCADD can only be calculated from prospective population-based studies. Updated data from Ziadeh and colleagues' study in Pennsylvania and Eastern Ohio population have identified 16 newborns with MCADD out of 211,067 tested, for an incidence rate of 1/13,192.[24] These rates are higher than the MCADD incidence rate found in Pollitt and Leonard's 1998 prospective study (1/22,222) in the U.K.[6]

Although the frequency of the allele is rather high in Caucasian populations, based on rates of heterozygosity and under Hardy-Weinberg conditions, there is a greater number of expected MCADD cases than are currently diagnosed. On the basis of the heterozygote frequency in New South Wales, Wilcken and colleagues (1994) estimated that the MCADD incidence rate should be 1/15,000 to 1/20,000 or 42 cases in their 1975–1984 study.[25] However, only 9 MCADD individuals (21% of expected) were identified, and only 7 of an expected 31 from 1985–1991 were identified. Similarly, Fromenty and colleagues (1996) found that of 414 French blood donors, the mutant gene frequency of 1/138 produces a homozygote frequency of 1/19,000 according to Hardy-Weinberg, for an expected 42 MCADD individuals.[14] However, only six cases of MCADD were reported.

The numbers of MCADD cases observed have been consistently lower than the number expected. Two hypotheses have been offered to explain this lower than expected number of cases. First, symptomatic newborns may be misdiagnosed as having SIDS or Reye's syndrome or may die before MCADD is detected. Second, a substantial number of people with MCADD may be asymptomatic and unidentified, suggesting a penetrance of $< 100\%$. Although misdiagnosis and early deaths may account for some unidentified cases, they are not likely to account for all of them.

There is a wide spectrum of disease severity ranging from no symptoms to sudden death. The following two sections summarize the disease outcomes associated with MCADD, and the risk factors for presenting with the various outcomes. Genotypic-phenotypic correlations have not been documented. Clinical manifestations presented in the following sections are therefore general outcomes of the disorder and not specific to any allelic variant.

DISEASE ASSOCIATIONS

Clinical symptoms and outcomes

Clinical signs and symptoms usually first occur during a child's first 3 years of life (average is 1 year). Neonatal onset is possible, but presentation rarely occurs in adults.[26] MCADD is an episodic disorder. Children suddenly present with a constellation of features; the most common features include vomiting and lethargy. Hypoglycemia, encephalopathy, respiratory arrest, hepatomegaly, seizures, coma, apnea, cardiac arrest, and sudden death have also been documented. Long-term outcomes may include developmental and/or behavioral disabilities including mental retardation, cerebral palsy, and ADD. Table 2 displays results from three studies that have documented symptoms observed in clinically diagnosed MCADD patients. In summary, although the signs and symptoms of MCADD are variable, they are similar to those seen in other encephalopathies: vomiting, lethargy, seizures, and progressive coma. Routine clinical laboratory findings include hypoketotic hypoglycemia, with hyperammonemia and abnormal liver function. Although these features are presented in this review individually, clinical presentation consists of any combination of these features.

Table 2
Presenting symptoms observed in MCADD patients

Clinical symptoms	120 cases (27)	65 cases (28)	First 23 cases (29)
Hypoglycemia	n.r.	96%	91%
Probable infection	85%	74%	n.r.
Lethargy	84%	100%	26%
Vomiting	66%	60%	52%
Coma/encephalopathy	49%	n.r.	78%
Respiratory arrest	48%	n.r.	4%
Hepatomegaly	44%	59%	30%
Seizures	43%	29%	17%
Apnea	37%	n.r.	n.r.
Cardiac arrest	36%	n.r.	n.r.
Sudden death	18%	26%	17%

n.r., not reported.

Numerous case reports and case series have documented clinical outcomes for people with MCADD who were untreated prior to presentation. Few studies, however, have reviewed the outcomes of MCADD individuals beyond the scope of the case reports. Systematic evaluations of morbidity and mortality in population-based studies have not been conducted. Furthermore, because MCADD is not listed in the ICD-10 or previous codebooks, estimates of morbidity, hospitalization burden, and annual costs of the disease cannot be calculated. Two studies that did attempt to quantify the number of people affected or presenting with various clinical outcomes are summarized in Table 2. To date, Iafolla and colleagues (1994) have reviewed the largest number of MCADD cases. All 120 patients in the study were of European descent: 112 from the United States, and the remaining 8 from the United Kingdom, Australia, Canada, or Ireland.[27] These cases were clinically identified through physicians and subsequently analyzed and confirmed by at least two methods of MS. Touma and Charpentier (1992) reviewed outcomes for 65 MCADD patients identified upon acute onset of the disease at hospitals who had their MCADD diagnosis confirmed by GC/MS.[28] A third study summarized the outcomes of the first 23 reported cases of MCADD in the world (mostly from Europe), which were compiled from published case reports of each individual.[29] The prevalence of clinical symptoms reported for patients in all three studies are summarized in Table 2. It is important to note that there is overlap between the studies referenced in Table 2. For example, some of the patients reported by Roe and Coates (1989)[23] contribute to Iafolla and colleagues'[27] patient population, which also includes some patients reported by Touma and Charpentier,[28] which in turn includes some patients from Vianey Liaud and colleagues[29] 1987 study. However, because it is unknown how many or which patients are reported in duplicate among these studies, the studies are presented separately for the purposes of this review. Therefore, differences and similarities between the outcomes reported for each of these studies should be compared with the knowledge that there is some duplicate reporting among the studies.

As shown in Table 2, hypoglycemia is the most common finding, present in over 90% of MCADD patients, followed by lethargy and vomiting. Most children with MCADD present with lethargy after a period of fasting, and more than one-half of MCADD patients exhibited vomiting. The study of Iafolla and colleagues was the only study to report encephalopathy. These findings are supported by the most recent prospective study on MCADD[6] in the U.K., in which 37 of 46 MCADD patients (80%) suffered from acute hypoglycemia, and 23 of 46 (50%) experienced encephalopathy.

The presence of seizures ranges from 17–43% among the three studies. Despite the overwhelming incidence of coma in the first 23 MCADD patients reported (78%), coma was not assessed in the later studies; reasons for this include the possible reclassification as encephalopathy in later studies, or a possible decrease in coma due to interventions preventing coma associated with the increased awareness of MCADD.

Sudden death

Two of nine (22%) MCADD patients identified through newborn screening in Pennsylvania died suddenly and unexpectedly.[5] In a study by the British Pediatric Association Surveillance System, 10 of 46 (21%) MCADD patients who presented acutely, died.[6]

Case studies have often documented sudden deaths among MCADD patients. The mean age of death among children with MCADD was 18.5 months. Among MCADD cases documented to date, patients have a 20–25% mortality rate at first presentation.[27,30] However, these percentages may be lower if a number of MCADD patients remain undiagnosed during their lifetime. Furthermore, increased clinical awareness of fatty acid oxidation disorders in general may have significantly changed the observed outcomes over recent years.

Although various studies have investigated the relationship between sudden death and MCADD, few have strictly investigated SIDS (defined as sudden and unexpected death among infants less than 1 year of age) and MCADD. These studies have varied in quality, and the results have been inconsistent. Furthermore, MCADD cases reported to date involve patients who are symptomatic even though many people with MCADD will be asymptomatic. Because the prevalence of symptoms is a risk factor for death, the relatively high incidence of death in clinically reported MCADD patients is not unexpected.

Table 3 lists the estimated K304E carrier frequency in SIDS populations. These studies demonstrate that the frequency of this mutation in SIDS populations is similar to that in general newborn populations. These results indicate that this most common MCADD mutation has not accounted for much of the SIDS incidence in populations studied to date.[12,13] Thus, universal newborn screening would not be expected to significantly lower rates of SIDS. However, given the use of convenient samples (not population-based) and small sample sizes, a large variance in allelic frequencies is seen. Nevertheless, al-

Table 3
Frequency of the K304E MCAD allelic variant among SIDS patients

No. of SIDS	Population	K304E homozygotes	K304E heterozygotes	Heterozygote frequency	Reference No.
309	US–Maryland	1	1	1/309	31
100	France–Aquitaine	0	1	1/100	12
1224	US–California	0	3	1/375	32
120	Denmark–Copenhagen	0	1	1/120	33
233	W. Scotland	0	3	1/78	16
262	US–Maryland	0	3	1/88	34
67	US–New York	0	3	1/22	35
119	US–North Carolina	0	4	1/30	36
153	Germany	0	0		37
708	Australia	0	7	1/101	38

though MCADD may not account for much of SIDS, it is still clearly a cause of sudden death in young children.

Long-term outcomes

Iafolla and colleagues have conducted the only long-term outcome evaluation of MCADD patients; their results are summarized in Table 4.[27] Developmental, behavioral, and neurological disabilities are beginning to be documented. Iafolla and colleagues[27] followed 73 MCADD survivors older than 2 years of age; they found that 32% had abnormal results on formal psychodevelopmental tests, including speech and language delay and behavioral problems. Clinical onset between 12 and 18 months of age, which included seizures or encephalopathy, correlated strongly with the development of speech disability.[27] A smaller study with longer follow-up reported handicaps and failure in school in MCADD patients.[25]

Table 4
Long–term consequences in 97 surviving MCADD patients 6 months to 9 years old*

Long–term outcome	% of MCADD patients
Developmental disability**	16%
Speech and language delay**	22%
Behavioral problems**	15%
At least one of the above outcomes	32%
Attention deficit disorder**	12%
Proximal muscle weakness	16%
Chronic seizure disorder	14%
Cerebral palsy	9%
Failure to thrive	10%
Aphasia following illness	5%

*See reference 27.
**Out of 73 patients for whom psychodevelopmental information was available.

In Pollit and Leonard's 1998 study, conducted with the British Pediatric Association Surveillance System, 6 of 36 surviving MCADD patients suffered neurological damage. Because follow-up has not been conducted past childhood or past the immediate post-illness period, it is unknown whether this number would increase if follow-up were performed through adulthood.[39] Neurological defects among MCADD patients have also been documented in Denmark.[40]

Other long-term outcomes of MCADD include episodic hypoglycemia and muscle weakness. Hypoglycemia can be induced by several measures such as illness or immunization. Treatment for hypoglycemia has been required for MCADD patients receiving the diphtheria-pertussis-tetanus vaccine, and for children with chicken-pox and otitis media. Risk factors for muscle weakness include an older age at diagnosis (>3 years of age), increased number of clinical events and hospitalizations before diagnosis, and time between clinical onset and diagnosis with longer delays increasing risk.[27]

Failure to thrive, seizure disorders, cerebral palsy, and ADD have also been reported as long-term outcomes among MCADD patients. A strong correlation existed between seizure at onset and cerebral palsy. Patients with ADD were more likely to have had seizures, encephalopathy, and hyperammonemia at the time of onset, as well as more episodes of clinical illness before and after diagnosis. MCADD patients diagnosed with ADD were also older at diagnosis of MCADD than patients who did not have ADD. The percentage of ADD cases attributable to MCADD is not known at present but is probably small.

INTERACTIONS WITH RISK FACTORS

MCADD results in only partial blockage of fatty acid oxidation; patients are therefore still able to metabolize short-chained fatty acids. As a result, a stimulus is needed for clinical symptoms to present. It is often in times of metabolic stress induced by fasting or infection when the demands on fatty acid

oxidation are particularly high, that an MCADD patient may present with symptoms.

Factors that affect clinical outcomes include prolonged fasting, infections or recent immunization, the patient's age when the first episode occurred, and a family history of SIDS or a sibling diagnosed with MCADD. In other words, the phenotype of MCADD is dependent on the degree of metabolic stress and a combination of other factors such as fever, infections, etc.[1]

Fasting

Episodes of hypoketotic hypoglycemia, vomiting, lethargy, seizures, and coma often are precipitated by fasting. Procedures such as anesthesia and surgery, which are preceded by fasting, can therefore also precipitate episodic events. Fasting leads to hypoglycemia, then vomiting or lethargy. Seizures and coma occur in fewer but more severe cases. The specific magnitude of risk associated with fasting has not yet been assessed or calculated.

Infection/intercurrent illness

Hypoglycemia requiring hospitalization is the most common outcome resulting from infection. This is often due to the vomiting and/or diarrhea brought on by the illness. Therefore, episodes of hypoketotic hypoglycemia, vomiting, lethargy, seizures, and coma all occur in association with infection. If these episodes are severe, death can result. Three of 22 MCADD patients with chicken pox required treatment for hypoglycemia during an illness.[27] One of two MCADD newborns who died in the supplemental testing program in Pennsylvania died during intercurrent illness.[5] Furthermore, physiologic stresses due to intercurrent infections frequently lead to the loss of appetite in children who are ill, resulting in a period of fasting and subsequent metabolic imbalance and induction of episodes.

Immunizations

Four percent of MCADD patients suffered from hypoglycemia requiring hospitalization after being immunized.[27] One of the two MCADD patients who died after being identified through the supplemental newborn testing program provided in Pennsylvania, died after a metabolic crisis stimulated by immunization.[5]

Age of first episode

Disease severity varies with a patient's age of first presentation. Episodes usually occur when children are between 3 months and 3 years of age, with an average of 12 months. The risk of dying from MCADD is higher among patients whose first episode occurs after the age of 1 year. If the first episode occurs when the child is less than 1 year of age, the outcome usually consists of hypoglycemia and is not fatal. However, if the first episode doesn't occur until the child is older than 1 year of age, significant mortality can result. The highest risk for death occurs among children whose symptoms first appear when they are 15 to 26 months old.[26] Roe and Coates[23] reported that clinical onset between 12 and 18 months was usually marked by seizures or encephalopathy, and correlated strongly with the development of a speech disability. Twelve of 63 (19%) infants less than 1 year old died during their first MCADD episode. Nine of 41 (22%) children older than 1 year died during their first episode.[26]

Age of diagnosis

The older a child is when the MCADD diagnosis is made, the higher the child's risk for muscle weakness and ADD.[27] Risk for muscle weakness also increases as the time between clinical onset and diagnosis increases and the number of clinical events before diagnosis increases. Whether age is a true risk factor or simply a surrogate for delay in diagnosis needs to be explored.

Seizures

MCADD patients who present with seizures are at an increased risk for death, recurrent seizures, or cerebral palsy in the future.[27]

Family history

Family history of MCADD is technically not a risk factor for having clinical symptoms; however, the association between the two is consistent with the autosomal recessive inheritance of the disease. A proportion of MCADD patients in all studies have siblings who are affected with MCADD or have siblings who died unexpectedly and suddenly, with some deaths diagnosed as SIDS. In one-half of the families studied by Touma and Charpentier,[28] patients had one or more siblings who died prior to the proband's presentation. Of 43 families identified by Roe and Coates,[26] one-third had one or more unexplained sibling death.[26] Iafolla and colleagues' 1994 study[27] of 120 MCADD patients reported that 32% of patients had siblings who were either known to have MCADD or had died of SIDS. Of 57 cases collected prospectively by the British Pediatric Association Surveillance System between 1994 and 1996, five had siblings who died. Iafolla and colleagues reported that 20% of families (19 of 94) had one or more unexplained sibling death.[41] Similarly, of 109 siblings of MCADD children, eight had died from MCADD.[23]

To date an average of 30% (10–50%) of MCADD patients have affected siblings. The presence of an affected sibling may thus be a risk factor for MCADD; it is also possible for the association to be due to ascertainment bias. Roe and Coates[23] concluded that younger siblings of children with MCADD were the ones most at risk for a fatal first episode. However, the percentage of specific clinical outcomes among MCADD patients with affected siblings has not been determined. Studies comparing MCADD patients with family history of MCADD to MCADD patients identified in the population have not been conducted. Therefore, whether MCADD patients with affected siblings have a higher incidence of clinical symptoms than patients identified in the population is unknown. In other words, we do not know whether the penetrance of MCADD for clinical outcomes is higher among patients with a family history of

the disorder than among patients identified in the general population.

LABORATORY TESTS

The main technologies available for detecting individuals with MCADD involve the detection of abnormal biochemical markers in the blood or urine. Tandem mass spectrometry (MS/MS) detects abnormal metabolites mainly in blood samples. Although MS/MS is used as an initial screening modality, confirmation of MCADD diagnosis is conducted with urine organic acid profile and/or DNA mutation analysis. Dicarboxylic aciduria is an important diagnostic element and detection of urinary acylglycines (hexanoylglycine, phenylpropionylglycine, and suberylglycine) are traditional and accurate diagnostic methods for MCADD. Confirmation of MCADD through blood samples and dried-blood spots can be conducted with DNA/PCR technology.[42]

MS/MS is the most recent technology developed and the most suitable for large-scale population screening for MCADD. MS/MS detects octanoylcarnitine and other acylcarnitines in blood and is currently the method used in a supplemental screening program offered by a private company that screens most newborns in Pennsylvania and eastern Ohio.[43] MS/MS is also the method of choice for North Carolina, California, and Massachusetts in their expanded newborn screening programs that will include screening for MCADD. MS/MS screening is being piloted in the U.K. and Australia.

POPULATION TESTING

North Carolina and Massachusetts are currently testing for MCADD as part of their newborn screening program. Soon, California will offer optional testing for MCADD to parents. In addition, Neo Gen Screening (Pittsburgh, PA) offers voluntary MCADD testing to newborns born at birthing centers in the Northeast; 75% of Pennsylvania's newborns receive this test in addition to the testing provided by the Pennsylvania state screening program.[21] In Europe, the Institute of Child Health in London is planning a population-based pilot study of MS/MS screening on newborns, which includes screening for MCADD.

According to the 1997 British Health Technology Assessment report, MCADD satisfies most criteria for universal newborn screening: its incidence in relevant populations is known, it is associated with significant morbidity or mortality, effective treatment is available, there is a period before onset of symptoms during which intervention improves outcome, and MS/MS allows safe and simple testing for the disease on the routine newborn screening blood spots. Data from population studies and screening programs currently being conducted will be useful in assessing the long-term outcomes and effectiveness of screening for MCADD.

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Appendix

Internet sites

General resources

National Organization for Rare Disorders, Inc.: (http. //www.stepstn.com/nord/rdb sum/585.htm)

Fatty Acid Oxidation Disorder Network: (http. //www.cinternet.net/FOD/mcad3.html) and (http://www.cinternet.net/FOD/mcad2.html)

Genetic databases

Gene Cards; (http. //bioinfo.weizmann.ac.il/cards-bin/carddisp?ACADM&search=mcad&suff=txt)

The Genome Database: (http. //gdbwww.gdb.org/gdb-bin/genera/accno?GDB:118958)

Human Gene Mutation Database: (http.//www.uwcm.ac.uk/uwcm/mg/search/118958.html)

Online Mendelian Inheritance in Man: (http. //www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?201450)

Educational resources

University of California, San Diego: (http. //chem-faculty.ucsd.edu/harvey/MCAD/index.html)

Wittenberg University: (http. //blackbox1.wittenberg.edu/academics/chem/faculty staff/aanderson/chem100 Sum98/ssato/s01 ssato.htm)

University College London (http. //www.biochem.ucl.ac.uk/bsm/pdbsum/3mdd/main.html)

Support groups

Fatty Oxidation Disorder Family Support Group (FOD): (http. //www.familyvillage.wisc.edu/lib mcad.htm)

United Mitochondrial Disease Foundation, Southern CA Support Group: (http. //biochemgen.ucsd.edu/umdf)