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What is MCADD?

Medium chain acyl-CoA dehydrogenase deficiency (MCADD), a fatty acid oxidation disorder, is an **autosomal recessive** enzyme deficiency. This condition prevents the normal use of fat as an alternative source of energy during times of fasting or increased metabolic demands. People with MCADD cannot burn fat for energy when their bodies run out of glucose, and as a result they may be affected by low blood sugar, altered central nervous system function, coma, or sudden death.[1, 2] If treatment is initiated before the onset of metabolic crisis, however, morbidity and mortality can be prevented.[1] With an early diagnosis, MCADD can be managed successfully by eating regularly and avoiding fasting.[2]

Autosomal Recessive
Inheritance of two copies of a mutant gene, one from each parent, on one of the 22 autosomes (chromosomes other than X or Y).

Why Test Newborns for MCADD?

Plasma concentrations of MCADD markers in the blood decline significantly after the first few days of life.[3] Because MCADD can be identified more easily during the newborn period, and pre-symptomatic treatment is reported to prevent morbidity and mortality, advocacy groups such as the March of Dimes[2] have recommended universal newborn screening for MCADD.

Tandem Mass Spectrometry Screening Test

Tandem mass spectrometry (MS/MS) is currently used to screen for MCADD as well as for other metabolic diseases.[4] This method detects elevated levels of certain intermediate metabolites of medium-chain fatty acids that are associated with MCADD. Octanoylcarnitine (C8) is the primary MCADD marker; additional markers include hexanoylcarnitine (C6), decanoylcarnitine (C10), and decenoylcarnitine (C10:1).[3,5]

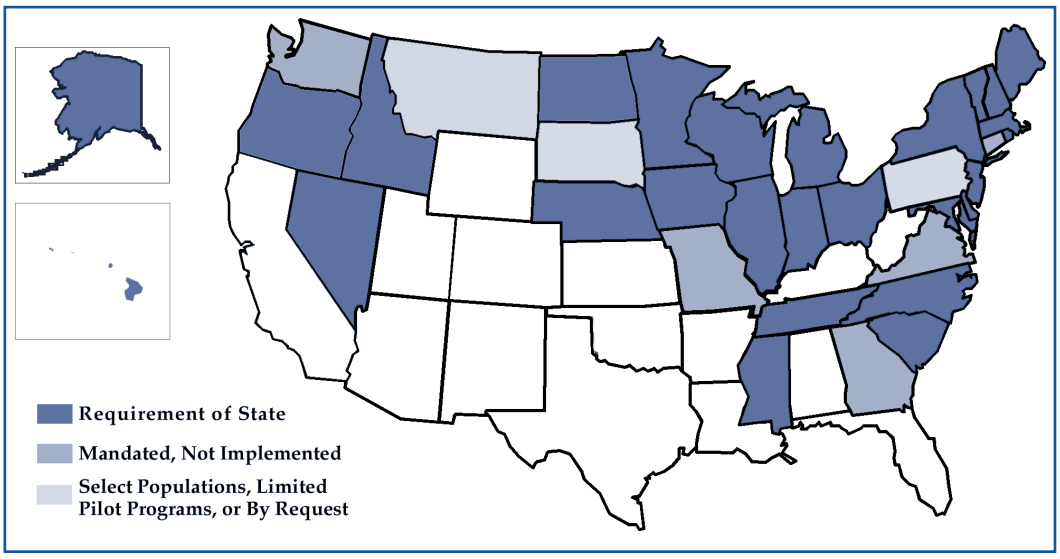
The high specificity and sensitivity of MS/MS to identify MCADD have been verified by reported results of newborn screening tests and retrospective MS/MS analyses of specimens from individuals who have been diagnosed clinically. Combined results[5-10] from 1.9 million newborn screening tests contained approximately equal numbers of true-positive (n=112) and false-positive (n=110) MS/MS test results and no known false-negative results.

Retrospective MS/MS analyses[6,11-12] of 56 specimens from unscreened, clinically diagnosed MCADD patients produced only one false-negative result, obtained from a stored newborn screening blood spot sample that had been collected from a newborn in metabolic crisis.

Adding MCADD Screening to Existing Newborn Screening Programs

Professional groups, including the American Society of Human Genetics (ASHG) and American College of Medical Genetics (ACMG),[13] have decided that the use of MS/MS in newborn screening programs might benefit patients. Many states[14] (Figure 1) have added screening for MCADD to their newborn screening programs and other states are currently considering adding screening for this disorder. The process by which states evaluate diseases as candidates for their screening programs varies. Massachusetts has documented the importance of an advisory committee in deciding to screen for MCADD.[15]

Figure 1. State Newborn Screening Programs Performing MS/MS Testing for MCADD, as of January 2004[14]



Is Universal Screening for MCADD Justified?

Reviews of MCADD as a candidate for newborn screening found that it fulfills either most[16] or all[17] of the criteria conventionally used to justify universal screening. MCADD is the most common fatty acid oxidation disorder. Newborn screening programs report prevalence between 1 in 12,500 and 1 in 25,000;[5-10] this is similar to the frequency of phenylketonuria (PKU) in the same populations.

The natural history of MCADD is still not well understood.[18] It is unknown what proportion of people identified with MCADD through MS/MS screening would

become symptomatic without this screening and subsequent interventions. Identifying affected people who would otherwise remain asymptomatic could subject them to unnecessary medical therapies, psychological stress, and difficulty in obtaining health insurance. Population-based studies to demonstrate the usefulness of MCADD screening have been recommended.[18] CDC and the Health Resources and Services Administration (HRSA) are funding follow-up studies of identified children to increase understanding of the impact of newborn screening for MCADD and other disorders identified by MS/MS.

The potential impact of early identification and intervention for MCADD on mortality is not well understood. Estimated mortality among children clinically diagnosed with MCADD ranges from 8% to 25%.[1,19-21] One study estimated mortality in an unscreened cohort of children with MCADD.[4] This study found eight children with MCADD among 100,600 British children whose stored newborn blood spots were analyzed using MS/MS; one (12.5%) of the eight children with MCADD died. Larger studies of this type or prospective data from screening programs could provide more precise mortality estimates.

The potential impact of newborn screening for MCADD on morbidity is unknown. Long-term neurological impairment has been reported in 16% to 33% of survivors of metabolic crises, about half of whom are seriously impaired.[1,19-21] No cases of neurological impairment in children with MCADD identified by screening programs have been reported.[22-24] Systematic long-term assessment of neurological outcomes is needed; although preliminary data from an assessment of infants born in New England and Pennsylvania indicate normal cognitive development.[24]

Cost-Effectiveness of Newborn MCADD Screening

The two published studies that analyzed cost-effectiveness of adding MS/MS to newborn screening concluded that it is probably cost-effective, either for MCADD alone[9] or because of the added benefits from early detection of disorders in addition to MCADD.[25] A study published in 2003 concluded that, for jurisdictions already using MS/MS to screen for PKU, it would be cost-effective to screen for MCADD as well.[26]

The cost-effectiveness of screening (from the perspective of the screener) using MS/MS depends on the technology chosen and on assumptions about the numbers of lives saved and cases of disability prevented. According to the Wisconsin Public Health Laboratory,[9] the laboratory cost of MS/MS screening for MCADD is about $4 per infant. The additional costs of confirmatory testing and specialist services for children with MCADD are estimated to add $1.25 per infant

Quality-Adjusted Life Years (QALYs)
Outcome of a treatment measured as the number of years of life saved, adjusted for quality.

screened. The Wisconsin study estimated a cost-effectiveness ratio of $42,000 per **quality-adjusted life years (QALYs)** in the base-case analysis, and $6,000 in the best-estimates analysis. The authors concluded that the true cost-effectiveness ratio is probably below the normal cutoff of $50,000 per QALY most commonly used to justify healthcare interventions.

Challenges for Implementing MCADD Screening

The addition of new disorders to newborn screening programs presents many challenges. For MCADD, these may include implementing new technology in the laboratory and assuring appropriate follow-up to confirm the diagnosis of MCADD and begin effective interventions promptly. Legal and ethical issues are also present at every stage of developing and conducting newborn screening programs.

Laboratory Implementation Issues: The use of MS/MS has proven to be a reliable method to screen for MCADD. Because plasma concentrations of MCADD markers decline significantly after the first few days of life,[3] it is important to establish age-appropriate cutoff levels for newborn screening tests. CDC's Newborn Screening Quality Assurance Program[27] conducts proficiency testing surveys that have allowed U.S. newborn screening laboratories to meet Clinical Laboratory Improvement Amendments (CLIA) quality assurance (QA) requirements.[28] The surveys include specimens enriched with three MCADD markers—C8, C6, and C10 (no synthetic standard is available for C10:1).

Follow-Up Implementation Issues: Short- and long-term follow-up protocols are essential components of newborn screening programs.[29] Several states have developed pilot short- and long-term follow-up studies. For example, Oregon and Iowa are part of a cooperative agreement with CDC to develop a long-term follow-up protocol for MS/MS screening.

Legal and Ethical Issues: MS/MS technology used for MCADD screening is able to detect more disorders than those mandated by newborn screening policy, although for many of these disorders, information about the clinical validity or utility of testing is not available. This presents an ethical dilemma that states have approached in various ways. In some states, parents are given the option to consent to receive results of non-mandated tests; other states do not make non-mandated test results available.

Conclusion

Laboratory testing is only one element of an effective newborn screening program. Clinical follow-up is essential for optimizing outcomes for children and their families. Some states are conducting research that will help fill knowledge gaps related to MS/MS screening for MCADD and other disorders. For example, the

California Department of Health Services instituted a pilot program that lets parents volunteer to have their child undergo supplemental testing for MCADD and other disorders detectable by MS/MS technology. This project aims to generate epidemiological data that will be used to inform policy decisions about which disorders to add to the list of routine screening tests, as well as to evaluate protocols and develop guidelines for follow-up.

Resources

General

National Newborn Screening and Genetics Resource Center (NNSGRC)
1912 W. Anderson Lane, Ste. 210
Austin, TX 78757
Phone: (512) 454-6419
http://genes-r-us.uthscsa.edu/index.htm

March of Dimes (MOD)
1275 Mamaroneck Avenue
White Plains, NY 10605
http://www.modimes.org/

Morbidity and Mortality Weekly Report (MMWR)
April 13, 2001; Vol. 50; No. RR-3
Using Tandem Mass Spectrometry for Metabolic Disease Screening Among Newborns: A Report of a Work Group
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5003a1.htm

Newborn Screening Quality Assurance
In Genetics and Public Health in the 21st Century, Khoury MJ et al., editors. Oxford University Press, 2000.
http://www.cdc.gov/genomics/info/books/21stcent3.htm

Tandem Mass Spectrometry

Newborn Screening Quality Assurance Program (NSQAP)
http://www.cdc.gov/nceh/dls/newborn_screening.htm

Policy/Legal Issues

National Conference of State Legislators (NCSL)
Denver Office:
7700 East First Place
Denver, CO 80230
Tel: 303-364-7700
Fax: 303-364-7800

Washington Office:
444 North Capitol Street, N.W., Suite 515
Washington, D.C. 20001
Tel: 202-624-5400
Fax: 202-737-1069
For information re: genetics laws and legislative activity go to:
http://www.ncsl.org/programs/health/screen.htm

Ethics

Hastings Center
Route 9-D / 21 Malcolm Gordon Road
Garrison, NY 10524-5555
Phone: (845) 424-4040
For information re: ethics and newborn screening project go to:
http://www.thehastingscenter.org/research/prog2/healthcarepolicy_4.htm

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