

Medium Chain Acyl CoA Dehydrogenase Deficiency (MCADD)

- Principal Investigators** Professor Carol Dezateux and Juliet Oerton in collaboration with
The British Inherited Metabolic Disease Group
Centre for Paediatric Epidemiology and Biostatistics
Institute of Child Health
30 Guilford Street
London WC1N 1EH
Tel: 020 7905 2241 Fax: 020 7905 2381
Email: J.Oerton@ich.ucl.ac.uk
- Duration** June 2004 for 25 months (in the first instance)
- Coverage** United Kingdom (not including Republic of Ireland)
- Objective** To ascertain all cases of MCADD diagnosed during the study period in order to determine clinical outcome to 2 years of age with the aim of informing future national screening policy.
- Secondary Objectives** To determine the detection rate of screening for MCADD in a UK setting.
- Background** MCADD is a recessively inherited metabolic disorder which has been identified through two systematic reviews commissioned by the Health Technology Assessment Programme as a strong candidate for newborn screening. The authors of these reviews concluded that more UK based data were required to inform screening policies based on tandem mass spectrometry. Subsequently, the Department of Health and National Screening Committee have funded a pilot newborn screening service for MCADD which started in March 2004 in certain areas of England. They have also commissioned a concurrent research study to evaluate this pilot service.
- Although the findings of a number of primary studies of MCADD screening in other countries have been reported, important questions relevant to screening policy remain unanswered, including clinical outcome following detection through newborn screening and screening programme performance in a UK setting. Furthermore, the generalisability of findings from these studies is uncertain, as screening is carried out several days later in the UK. It is therefore vital to ensure that performance and longer term clinical outcomes of screening are carefully evaluated in a UK setting.
- The research study will obtain estimates of the false negative rates of screening for MCADD. Importantly it will determine clinical outcomes in affected children identified through screening and compare these with similar outcomes in clinically diagnosed children. Surveillance through the BPSU is critical to both these endeavours. Screening is being carried out over two years in six laboratories covering at least half of all UK births each year. All screen positive infants are being followed to ascertain final diagnosis and outcome to two years following detection. This information will be used to estimate the prevalence and genotype distribution of MCADD ascertained through screening. Concurrently, clinically diagnosed cases of MCADD will be ascertained and followed through the BPSU so that detection rates can be estimated and clinical outcomes compared amongst screened and unscreened populations. The primary clinical outcome for the study is encephalopathy-free survival to 2 years of age. This outcome reflects the fact that median age at death in clinical case series is 14 months, that most acute events will have occurred by 2 years of age and that the majority of clinical diagnoses will have been made by this age.

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Case Definition

MCADD is one of the most common of the fatty acid oxidation defects. These are disorders of intermediary metabolism that may cause hypoglycaemia, acute encephalopathy and sudden death. During an intercurrent illness, particularly gastroenteritis, there may be progressive encephalopathy with drowsiness, hypoglycaemia, lethargy and hypotonia progressing to coma. Children with MCADD usually present clinically before the age of two. Treatment entails avoidance of fasting, use of an emergency dietary regime during intercurrent illness and admission to hospital for intravenous glucose if this is not tolerated.

MCADD is recessively inherited and between 1 in 40 and 1 in 80 of the UK population are unaffected carriers. Approximately 80-90% of affected individuals have the same genetic mutation (G985A), with the majority of the remainder being heterozygous for this mutation. From this it is predicted that the birth prevalence is about 1 in 10,000 (1 in 6500 to 1 in 20,000).

The diagnosis of MCADD can be made following clinical presentation, investigation of a sudden unexpected death, diagnosis in an affected family member or through newborn screening. A child will be considered to have a diagnosis of MCADD if one or more of the following criteria are met:

- Elevated octanoyl carnitine in blood test using tandem mass spectrometry (or in other body fluids if a post-mortem diagnosis)
- Characteristic urine profile of organic acids with hexanoyl, suberyl and phenylpropionyl glycine
- Molecular genetic studies confirming presence of a mutation characteristic of MCADD
- Enzyme studies based on skin fibroblasts showing reduced activity of medium chain fat oxidation

Reporting Instructions

Please report any cases seen for the first time since July 2004 in the first instance, and in the past month thereafter, that meet the surveillance case definition, including those where the child may have died. If the paediatrician is not certain or awaiting confirmation, the case should be reported anyway.

Methods

Paediatricians are asked to notify cases on the orange card through the BPSU in the usual way. These notifications will be forwarded to study investigators at the Institute of Child Health who will send a case notification questionnaire to the notifying paediatrician. This will be followed approximately 4 months later by a brief questionnaire to confirm diagnosis. Follow-up questionnaires will be sent to establish clinical outcome at one and two years following diagnosis.

No specimens will be required.

Returned questionnaires will be kept in a locked filing cabinet in an office which is locked out of hours. Demographic details will not be stored with clinical data. Data will be entered into a database on a PC with password protection. All the requirements of the Data Protection Act and Caldicott arrangements will be followed.

Ethical Approval

This study has been approved by the London GOS MREC (no local investigator status)

Funding

Department of Health

References

Available from the BPSU office.