

THE UK COLLABORATIVE STUDY OF NEWBORN SCREENING FOR MEDIUM CHAIN ACYL Co-A DEHYDROGENASE DEFICIENCY (UKCSNS- MCADD): OVERVIEW AND EARLY FINDINGS

OVERVIEW

- The UKCSNS-MCADD is a research evaluation of a pilot newborn screening service for MCADD. This evaluation was commissioned by the Department of Health to inform a review of newborn screening policy in the UK.
- It is co-ordinated by the MRC Centre of Epidemiology for Child Health at the UCL Institute of Child Health, London.
- The study involves six newborn screening laboratories in England that tested babies for MCADD between 1.3.2004 to 28.2.2006.
- The evaluation is ongoing and will continue until the end of 2008. An interim report was provided to the National Screening Committee in May 2006.
- The study involves an extensive collaborative network of laboratory and clinical scientists, metabolic paediatricians and research teams at the Institute of Child Health and University of Oxford, the British Inherited Metabolic Disease Group (BIMDG) and the parent support group - Climb. See list below for more detail.
- The aim of the evaluation was to report on
 1. how accurately children with and without MCADD are identified by newborn screening
 2. the experiences of families of children diagnosed through screening
 3. the early childhood outcomes for children with MCADD diagnosed by screening
 4. the cost effectiveness of newborn screening for MCADD

Interim data from the UKCSNS are available addressing 1 and 2 above, and work on 3 and 4 is ongoing.

STUDY DESIGN

- Over a 24 month period, babies were screened for MCADD in the six participating pilot laboratories using the dried bloodspot screening sample taken routinely at 5-8 days of age and which is currently tested for phenylketonuria (PKU), congenital hypothyroidism, sickle cell disorders and cystic fibrosis. No extra blood was required as the test is carried out on the same blood spot used for PKU testing.

- The MCADD screening test was carried out to an agreed protocol with electrospray tandem mass spectrometry of underivatised blood spot samples using multiple reaction monitoring (MRM) mode acquisitions to quantitate octanoyl carnitine (C8) which is raised in those with MCADD.
- Babies with a positive screening test were seen as soon as possible by a paediatric team specialising in metabolic diseases so that follow-up diagnostic tests could be carried out. While awaiting results of tests, parents were given advice and written information about feeding and what to do if their child became ill. They were seen at regular intervals to confirm the diagnosis and so that their child's progress could be followed.
- A Quality Assurance (QA) group was established to support the work of the participating pilot screening laboratories (see list below for membership) and the DNA analysis for diagnostic confirmation: two schemes for specimen circulation were established.
- An independent Diagnostic Review Panel was convened to review anonymised data on all children with a possible MCADD diagnosis (see list below for membership).
- Dietary guidelines were prepared and have been published by the BIMDG in collaboration with the UKCSNS-MCADD.
- As part of the evaluation, the co-ordinating centre set up a surveillance study across the UK to identify all MCADD diagnoses over a four year period: this allows all screened children with MCADD to be followed through a paediatrician. It also allows all children presenting clinically in areas where screening was not offered to be identified and followed. This was carried out through the British Paediatric Surveillance Unit and through an additional biochemical surveillance scheme (BioSS) set up especially for this study. This allows the clinical outcome of MCADD in early childhood to be monitored through clinician report.
- Families of children diagnosed through screening have, with their GP's permission, been invited to take part in a special follow up study to explore their feelings and responses to a diagnosis made by screening.
- Health economists from Oxford have been collecting data to compare the costs and effects of screening and follow up with costs of not screening.

EARLY FINDINGS

- Nearly three quarters of a million babies were screened over 24 months. A total of 105 babies had 'positive' screening tests, around 1.4 of 10,000 babies born. Of these, 87 were confirmed as having MCADD.
- Results from the pilot indicate that screening for MCADD at 5-8 days shows good screening test performance. 84% of those with a positive screening test were confirmed as having MCADD: a higher positive predictive value than reported from other studies worldwide where screening is offered at a younger age. This is

important as it means that very few families of either carrier or unaffected infants have had to undergo investigations due to false positive tests.

- Over half of the children diagnosed with MCADD through screening carry two copies of the most common mutation associated with MCADD. This is consistent with recent international reviews.
- To date there has been no association with adverse clinical outcomes following screening, however further follow up is required to determine longer-term clinical outcome.
- The QA scheme for octanoyl carnitine has shown good agreement between the six laboratories. The DNA scheme has also demonstrated good performance.

POLICY IMPLICATIONS

- A report of the findings together with updated information from programmes in Australia, the USA and Germany was presented to the National Screening Committee as part of a fast track policy review in May/June 2006.
- Subsequently, in February 2007, the Department of Health announced that screening for MCADD is to be added to newborn bloodspot screening in England in a phased roll out during 2007/8 and 2008/9 with continuation of screening in existing pilot sites (Gateway reference number:7801).

FURTHER WORK

- Follow up of the children diagnosed through screening continues until 2008.
- Surveillance through the BPSU and BioSS will also continue until July 2008.
- The cost-effectiveness analysis is being concluded.
- Ongoing support to the Quality Assurance schemes until transition to an integrated bloodspot scheme is achieved.
- Protocols and data from different elements of the study are being used to support detailed planning of the implementation, allowing rapid rollout .

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