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UK National Screening Committee

Is there evidence to alter the current UKNSC recommendation to offer a national screening programme for MCADD in all newborn babies? A pilot of the triage approach

Screening Topic: Newborn screening for medium-chain acyl-CoA dehydrogenase deficiency (MCADD)

Delivery date: December 2015

Contents

1. Background to the triage reports

This report is a rapid triage assessment of whether the existing national screening programme (NSP) for medium-chain acyl-CoA dehydrogenase deficiency (MCADD) in newborns should be continued.

For conditions for which population screening programmes are recommended by the National Screening Committee (NSC) the triage process focuses on whether there is new evidence suggesting that the NSP should be stopped.

It consists of an externally produced report on a literature search undertaken to identify whether any papers have been published:

- addressing screening programme cessation
- reporting harms from screening
- reporting balance of harms and benefits from screening

The aim of these reports is to identify any "red flags" that suggest that an NSP needs to be reviewed in greater detail. They do not aim to identify all new literature relating to screening for the condition; instead they focus specifically on evidence relating to the three areas specified above.

If no papers are identified on the above a recommendation to continue the programme is made. If papers on programme cessation or harms from screening are identified, the UK NSC will consider whether further work is necessary before making a final recommendation on the topic.

Stakeholders will be contacted for comments on the recommendation and a three month consultation will be hosted on the UK NSC website.

Based on the triage report and stakeholder comments the Committee decides whether to recommend that the issue is considered in more depth. Where further evaluation is considered appropriate, the options may include an evidence summary, primary research, systematic review, cost effectiveness assessment, modelling.

2. Executive summary

This triage assessment identified one study with potential relevance to the possible harms of MCADD screening.

This was a retrospective cohort comparing children with metabolic disorders screen-detected through newborn screening (NBS) with controls clinically detected (Landau et al. 2009). It found that all 31 of those screen-detected with MCADD were asymptomatic or had mild symptoms, compared to all 7 of those clinically diagnosed having significant symptoms.

The abstract did not report follow-up or assessment periods, or management received by two groups. Absent or minimal symptoms in screen-detected cases may be the result of appropriate management from birth, rather than an indication of "over-detected" milder disease. The abstract did not report psychological or physical harms that have resulted from screen-detection of these potentially "mild" cases.

Recommendation: This triage assessment identified a single study suggesting that milder phenotypes may be detected by screening than through clinical detection. However, this evidence was not conclusive, and did not indicate definite harms among those detected by screening. The evidence identified does not suggest that the evidence supporting the MCADD screening programme should be reviewed in more depth or that the programme should be stopped.

3. Introduction to the condition

The current NSP being assessed is newborn bloodspot screening for medium-chain acyl-CoA dehydrogenase deficiency (MCADD). MCADD is an inherited metabolic condition where the body is deficient in the enzyme needed to break down medium chain fatty acids. Untreated, fatty acid accumulation leads to metabolic crises which can lead to brain damage and increased risk of death. The child needs to avoid long periods between eating (fasting) which would cause fat stores to be broken down. The main treatment is therefore regular meals, with particular care taken when the child falls ill, by giving regular glucose drinks to prevent sugar levels from falling too low.

MCADD was a relatively recent addition to the NHS newborn blood spot (NBS) screening programme in 2009. This is offered for all newborn babies with the blood sample usually taken 5 days after birth (in exceptional cases it can be taken between Day 5 and Day 8).

This external review has searched the literature published from 2006 up to December 2015, and reviewed at title and abstract level whether there is evidence:

- Indicating that other countries have ceased MCADD screening
- reporting harms from MCADD screening
- reporting balance of harms and benefits from MCADD screening

4. Description of the evidence

Twenty-two publications were selected at the first pass sift as being potentially relevant to these three questions based on title and abstract. These were reviewed more closely at abstract level at a second pass appraisal.

One of these 22 publications met the inclusion criteria as having some relevance to these questions. Details of this study are extracted in Table 1. This study identifies a potential issue around the possibility that screening detects those who may otherwise have had a mild clinical course.

Three other studies did not meet inclusion criteria as they did not report on harms of screening or the balance of harms of benefits, but they also highlight that MCADD diagnoses made through newborn screening may be across a spectrum. Two screening programme evaluations (from New England and the Netherlands) report how fatty acid or enzyme levels and adverse outcomes among screen-detected cases varied according to genotype. Two of the screen-detected babies in one of these studies died and three more had severe hypoglycaemia, suggesting that at least some infants with severe phenotypes are detected by newborn screening. Another study presented validation of a potential strategy to differentiate between MCADD-subsets with different genotype who may have variable risk of adverse outcomes from the condition.

Any adverse outcomes in these studies appear to be from the condition, rather than from screening itself.

The remaining excluded studies included editorials generally discussing the condition and its screening, cost effectiveness evaluations in countries other than the UK, and screening programme evaluations from different countries reporting the incidence of MCADD, genotypes and outcomes for those screen-detected, and generally concluding that screening was effective.

Table 1

Publication details	Study details	Population	Intervention/test and comparator	Main findings	Comments
Screening programme cessation					
No studies identified					
Harms from screening					
No studies identified					
Balance of harms and benefits from screening					
Landau et al. 2009 Landau YE, Waisbren S, Levy HL. Expanded newborn screening and the emerging genomic era - Preliminary lessons from 13-year experience. Molecular Genetics and Metabolism. 2012;105(3):332.	Retrospective comparison cohort of those with metabolic disorders screen-detected through NBS, and controls clinically diagnosed	31 MCADD cases NBS-detected vs. 7 MCADD controls clinically diagnosed (part of the wider cohort including 180 NBS-detected cases [various disorders] vs. 115 clinically diagnosed)	Tandem mass spectrometry for NBS diagnoses	MCADD results: 26/31 NBS-detected were "essentially asymptomatic"; the remaining 5 had "transient or mild nonspecific symptoms". 7/7 clinically diagnosed controls had significant MCADD-related symptoms. Concludes: "The marked difference in frequency and symptomatology between the 2 cohorts in several disorders could reflect a prevalence of mild and potentially benign variants identified by NBS... hypothesize that most of the NBS-identified disorders have two subgroups: one that benefits from NBS, and the other with a potentially asymptomatic phenotype... crucial to delineate correlations between confirmatory lab profile and long term outcome".	The time period of the study and follow-up duration is unclear from the abstract. It is also unclear whether the absence of or minimal symptoms in the screen-detected cases could be the result of them having appropriate management from birth, rather than that they had milder disease.

5. Methodology

It is intended that the triage process for each NSP will be performed every three years. This review is the first triage review for MCADD and includes literature published in the last 10 years (depending on the date of the last evidence review).

Sifting has been carried out in two stages. The first pass sift has been conducted by an information specialist at title and abstract level, to remove clearly non-relevant material e.g. animal studies, or studies of different screening programmes. The second pass sift has been performed by a health research analyst and this sift examined the results more closely at title and abstract level to remove those studies clearly not relevant, and select those meeting inclusion criteria for summary.

The reports focus on high quality studies, i.e. systematic reviews, randomised controlled trials, non-randomised controlled trials, cohort studies or screening programme evaluations that appear at abstract level to have covered potential harms of the NSP, the balance of harms and benefits, or screening programme cessation. Lower level evidence such as case series and case reports, non-systematic reviews, editorials or opinion pieces are not included unless they clearly highlight potential harms of the NSP indicating the need for further evaluation.

Studies on any issues other than the three questions of interest are not included. For example, studies examining cost effectiveness (unless relevant to the UK and highlighting the balance of benefits and harms), or studies assessing modifications to an existing screening programme (e.g. changing age at screening, screening test used, screening interval etc.) would be excluded. Studies evaluating management of the condition are also excluded – unless they indicate that the existing treatment is ineffective or harmful, which may suggest that harms of screeningoutweigh any benefits.

These triage reports are rapid assessments to identify any “red flags” which indicate the need for further assessment of the NSP. They are complemented by consultation with stakeholders to identify any additional issues which may not be represented in the literature identified.

6. Search strategy

We searched the following bibliographic databases:

- Medline (via Embase.com)
- Embase
- The Cochrane Library: including the Cochrane Database of Systematic reviews; Cochrane Central Register of Controlled Trials (CENTRAL); Database of Abstracts of Reviews of Effects (DARE); Health Technology Assessment Database (HTA); NHS Economic Evaluation Database (EED)

The searches were limited by date to include studies published since 2006. No language limits were used. Methodological filters were not used as they would not have been appropriate given the focus of the research questions.

The search strategy was developed through testing to identify the best balance between sensitivity and specificity that was fit for purpose. The search strategy used both indexing terms and text words as relevant records could have been indexed in different ways (or not indexed at all). The Embase

search strategy was translated for the other databases and adapted to take into account the databases size, coverage and available indexing terms.

The search strategy was based on the PICO framework and combined three major concepts: the population (condition), neonatal screening, and harms from screening or screening programme cessation. (See table below)

Search strategy (Embase.com)

Concept	Search strategy
Population	1. 'medium chain acyl coenzyme a dehydrogenase'/de 2. 'medium chain acyl coenzyme a dehydrogenase deficiency'/de 3. 'medium-chain acyl-coa dehydrogenase deficiency':ab,ti 4. 'medium chain acyl-coa dehydrogenase deficiency':ab,ti 5. 'medium-chain acyl-coenzyme a dehydrogenase deficiency':ab,ti 6. 'mcad deficiency':ab,ti OR mcadd:ab,ti OR 'acadm deficiency':ab,ti OR 'mcadh deficiency':ab,ti 7. 1 or 2 or 3 or 4 or 5 or 6
Screening	1. 'newborn screening'/de 2. ((neonat* OR newborn*) NEAR/2 screen*):ab,ti 3. 'mass screening'/de 4. 'newborn'/de 5. 3 and 4 6. 1 or 2 or 5
Programme cessation	1. ceas*:ab,ti OR cessation:ab,ti OR stop:ab,ti OR stopped:ab,ti OR continu*:ab,ti OR discontinu*:ab,ti 2. appropriate*:ab,ti OR inappropriate*:ab,ti OR unnecessary:ab,ti OR question*:ab,ti 3. harmful:ab,ti OR harm*:ab,ti OR adverse:ab,ti 4. benefit*:ab,ti AND (risk*:ab,ti OR harm*:ab,ti) 5. 'side effect'/exp) 6. (side NEAR/1 effect*):ab,ti 7. overdiagnosis:ab,ti OR 'over diagnosis':ab,ti 8. 'patient safety'/exp 9. 'risk assessment'/de 10. 'risk benefit analysis'/exp 11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

Search results

Databases searched	Dates searched	Number of hits
Medline and Embase (Embase.com)	2004-11/12/2015	68
CENTRAL (Cochrane Library)	2004-11/12/2015	2
NHS EED (Cochrane Library)	2004-11/12/2015	5
Methods (Cochrane Library)	2004-11/12/2015	1
HTA (Cochrane Library)	2004-11/12/2015	3
DARE (Cochrane Library)	2004-11/12/2015	1
Total number of hits		**80**
Total number after de-duplication		**76**
Total number after first appraisal		**22**

Embase.com search strategy

#1 'newborn screening'/de 13746
#2 ((neonat* OR newborn*) NEAR/2 screen*):ab,ti 12206
#3 'mass screening'/de 49630
#4 'newborn'/de 498406

#5 #3 AND #4 2463
#6 #1 OR #2 OR #5 19026
#7 ceas*:ab,ti OR cessation:ab,ti OR stop:ab,ti OR stopped:ab,ti OR continu*:ab,ti OR discontinu*:ab,ti 1265546
#8 appropriate*:ab,ti OR inappropriate*:ab,ti OR unnecessary:ab,ti OR question*:ab,ti 1495204
#9 harmful:ab,ti OR harm*:ab,ti OR adverse:ab,ti 609591
#10 benefit*:ab,ti AND (risk*:ab,ti OR harm*:ab,ti) 166742
#11 'side effect'/exp 398996
#12 (side NEAR/1 effect*):ab,ti 268067
#13 overdiagnosis:ab,ti OR 'over diagnosis':ab,ti 3449
#14 'patient safety'/exp 68643
#15 'risk assessment'/de 369811
#16 'risk benefit analysis'/exp 43498
#17 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 3901044
#18 'medium chain acyl coenzyme a dehydrogenase'/de 809
#19 'medium chain acyl coenzyme a dehydrogenase deficiency'/de 216
#20 'medium-chain acyl-coa dehydrogenase deficiency':ab,ti 403
#21 'medium chain acyl-coa dehydrogenase deficiency':ab,ti 403
#22 'medium-chain acyl-coenzyme a dehydrogenase deficiency':ab,ti 60
#23 'mcad deficiency':ab,ti OR mcadd:ab,ti OR 'acadm deficiency':ab,ti OR 'mcadh deficiency':ab,ti 458
#24 #18 OR #19 OR #20 OR #21 OR #22 OR #23 1201
#25 #6 AND #24 381
#26 #17 AND #25 92
#27 #17 AND #25 AND [2006-2016]/py 68

Cochrane Library search strategy

#1 MeSH descriptor: [Acyl-CoA Dehydrogenase] this term only 13
#2 "Medium-chain acyl-CoA dehydrogenase deficiency":ti,ab,kw 9
#3 "medium chain acyl-CoA dehydrogenase deficiency":ti,ab,kw 9
#4 "medium-chain acyl-coenzyme A dehydrogenase deficiency":ti,ab,kw 2
#5 ("MCAD deficiency" or MCADD or "ACADM deficiency" or "MCADH deficiency"):ti,ab,kw 6
#6 #1 or #2 or #3 or #4 or #5 Publication Year from 2006 to 2015 12

7. References

Included after second pass sift

1. Landau YE, Waisbren S, Levy HL. Expanded newborn screening and the emerging genomic era - Preliminary lessons from 13-year experience. Molecular Genetics and Metabolism. 2012;105(3):332.

Included after first pass sift

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Full search results

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