UK National Screening Committee

Expanded Newborn Screening Evaluation

Policy review process summary

Purpose

This paper provides background on expanded newborn screening for homocystinuria (HCU), maple syrup urine disease (MSUD), glutaric aciduria type 1 (GA1), isovaleric acidaemia (IVA) and long chain hydroxyacyl CoA dehydrogenase deficiency (LCHADD).

Current policy

The current policy is that screening for these conditions is not recommended.

An evaluation of screening was undertaken and the report of the evaluation has been circulated for consideration. The project has been discussed at several FMCH & UK NSC meetings.

The evaluation report addresses issues relating to test performance, the epidemiology of the conditions in the UK, the practicalities and logistics of screening (for example the consent process and impact on workload) and the acceptability of screening.

In addition a systematic review of the birth prevalence rates of the five disorders is attached. This aims to pool prevalence rates in Western populations as a means of estimating UK rates and of providing a set of expectations within which the findings of the evaluation can be positioned.

An analysis of the economic impact of expanding the screening programme is also attached. This was undertaken by ScHARR and was informed by the above mentioned systematic review.

Results of the evaluation

Twelve true positive and 18 false positive cases were identified during the evaluation resulting in a mean PPV = 40% (range 22 – 100%). Condition specific test values are provided in the evaluation report.

The report suggests that early detection offered by screening is likely to have conferred benefit to the patients diagnosed with MSUD, GA1 and homocystinuria. The evaluation report's concluding comments for both LCHADD and IVA suggest that the same cannot be said for these conditions and the case made for including them in an expanded panel appears speculative in comparison to the first three.

Overall detection of these disorders by newborn screening does not appear to have resulted in a large number of false positive results nor in a marked overdiagnosis when compared with the unscreened population although data is limited. For example, for IVA there were 14 false positives, 3 mild cases and one severely affected baby which died. Though there is little evidence of disbenefit, the report is concerned to highlight that detection of the 3 mild cases may have medicalised the family.

The evaluation found that an agreed diagnostic follow-up was achievable and that clinical services have coped with the resulting referral activity. Few parents declined screening during the study and these low numbers fell progressively as the study proceeded.

The cost effectiveness study suggests that screening for these disorders is likely to be cost saving. However key uncertainties in the model are identified and these appear more significant for IVA, LCHADD and MSUD.

November 2013 FMCH and UKNSC meetings

Early drafts of the evaluation report and the cost effectiveness study were considered at the FMCH October meeting. The Subgroup considered that the case for screening for IVA and LCHADD, based on the evaluation, appeared weaker than MSUD, GA1 and HCU and that it may not be possible to recommend that all five conditions should be included in the screening panel.

On the basis of the above, and following a presentation by Prof Jim Bonham, the November 2013 meeting of the UK NSC agreed to consult on the proposal to introduce screening for MSUD, GA1 and HCU but not to introduce screening for LCHADD and IVA.

Consultation

The pilot evaluation, health economic evaluation and the systematic review of birth prevalence were circulated for consultation between 20th December 2013 to 20th March 2014. The following organisations were contacted directly:

Clinical Genetics Society, Royal College of Paediatrics and Child Health, CLIMB, PANS, UK Newborn Screening Laboratory Network, • British Inherited Metabolic Disease Group, Genetic Alliance UK, Institute of Child Health, Royal College of General Practitioners, Royal College of Midwives, Save Babies Through Screening Foundation UK

Responses were received from seven national professional organisations including one European body, a combined response was received from seven patient organisations, eight NHS organisations and five individual responses.

Clinical Genetics Society, Royal College of Paediatrics and Child Health, National Metabolic Biochemistry Network (MetBioNet), UK Newborn Screening Laboratory Network (UKNSLN), British Inherited Metabolic Disease Group (BIMDG), NHSE Clinical Reference Group for Metabolic Disorders, Screening Committee of the German Society for Paediatrics and Adolescent Medicine, PHG Foundation.

UK Patient Advocates for Newborn Screening (PANS) Group (on behalf of SBUK, Climb, MPS Society, AGSD UK, ALD Life, UK LSD Collaborative), Climb.

Paediatric Metabolic Team, University Hospital of Wales; Birmingham Children's Hospital, West Midlands Newborn Screening Laboratory; Newcastle upon Tyne Hospitals NHS Foundation Trust, Newborn Screening & Metabolic Team; Leeds Teaching Hospitals Biochemical Genetics Laboratory; Inherited Metabolic Disorders Laboratory, Birmingham Children's Hospital NHS Trust; S.E Thames Regional Newborn Screening Service; Central Manchester University Hospitals NHS Foundation Trust with North West ANNB Quality Assurance Team; Central Manchester University Hospitals NHS Foundation Trust –Newborn Screening and Willink Biochemical Genetics Unit

Dr David Sinclair (Lab Director, Portsmouth Hospitals NHS Trust), J Calvin and Sarah Hogg (Addenbroke's Hospital), Dr Kathy Jeays-Ward (Sheffield Teaching Hospitals NHS FT), Catherine Dibden, Patty and Aaron Dawson (West Linn, Oregon, USA)

Responses

One national professional organisation, the Royal College of Paediatrics and Child Health, agreed with the UKNSC proposal as circulated.

All other respondents agreed with the proposal to introduce screening for MSUD, GA1 and HCU but disagreed with the recommendation not to proceed with LCHADD and IVA screening. A response from Germany noted that HCU is not included in the national screening panel due to its rarity. However the response did not suggest that screening for HCU should not be implemented in the UK.

The difficulties relating to LCHADD and IVA were broadly acknowledged in the responses. For example the number of false positives from IVA screening was considered unacceptably high by some and the potential for unnecessary medicalisation of those identified with variants of uncertain clinical significance was also noted. In addition, respondents noted that screening had not identified an asymptomatic baby with post neonatal LCHADD and that the situation was complicated by detection of MTP cases. The reasons suggested for the continuation of screening for IVA and LCHADD clustered around a number of themes. These included:

- the five conditions included in the evaluation represented a conservative selection, screening for which was uncontroversial within the paediatric metabolic disease community both within the UK and internationally. LCHADD and IVA are no exception to this.
- the cost effectiveness study suggested that screening for all five conditions was potentially cost saving, notwithstanding the uncertainties surrounding the estimates, and that no significant cost saving could be made by the withdrawal of screening for LCHADD and IVA.
- the evaluation was not designed to evaluate clinical benefit for the five conditions. This would require a longer period of evaluation and perhaps an international approach. As such the evaluation should not be used to guide decision making in this regard. However, there was no evidence of harm or disbenefit from screening for LCHADD and IVA.
- in relation to IVA, it was noted that raising the test cut off level could reduce the false positive rate and the number of cases with milder or asymptomatic IVA. It was suggested that exploration of this option may present an alternative to immediate implementation or withdrawal.
- in relation to LCHADD, it was noted that because of the rarity of condition the evaluation may not have been of sufficient duration to identify cases of post neonatal LCHADD which may have an improved prognosis when compared to those reported during the evaluation. The options suggested for this condition by respondents were to implement on the basis of the current data or extend the evaluation.

Recommendation

- It is recommended that screening for MSUD, GA1 and HCU should be implemented nationally

- National implementation of screening for IVA should be dependent upon the outcome of further discussion on the feasibility of, and likely outcomes from, adjusting the test cut off as proposed in the consultation responses.

- LCHADD screening should not be implemented nationally:

1. No cases of asymptomatic LCHADD were identified by the screening evaluation. As such the feasibility of the test has not been demonstrated. The one case reported as screen detected was being treated at the point of screening. If clinically presenting cases were removed from the test performance calculations, the PPV would be 0% over the course of the evaluation.

2. In terms of the epidemiology and natural history, the expectation was that about 15% of cases would present in the neonatal period (ref PHG Expanded Bloodspot Screening: A Review of the Evidence, 2010) with the majority presenting after that point. But of the seven cases reported in both the screened and non screened areas the latest presentation was 31 days. In the screened areas two cases died before screening, one was a sibling of a known case, one was being treated at the point of screening, one was missed by screening.

3. The contribution of severe MTP cases has been noted in the responses. As such the condition, especially in its potentially preventable form, appears extremely rare. The prognosis for LCHADD is thought to be variable further limiting the potential for benefit. As with the response from Germany, other countries engaged in NBS expansion have acknowledged rarity and limited clinical impact as an obstacle to screening.

It is therefore difficult to make the same case for LCHADD screening as has been done for the other conditions included in the evaluation.

- More generally, concern has been raised that decision making on expanded newborn screening has been 'lax' because lacking a sound evidence base (Moyer, V et al, Expanding Newborn Screening: Process, Policy and Priorities, Hastings Center Report 38, 2008). In this context the respondents' points about the limitations of the evidence generated by the evaluation and its limited duration were well made. This concern should extend to all the conditions in the evaluation. The development of a plan to monitor test performance and outcomes should be a pre-condition of further implementation. As suggested this should aim to support a review, at 3 – 5 years, relating to the continuation of screening.