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Review

Executive summary

Newborn screening for inborn errors of metabolism: a systematic review

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Health Technology Assessment
NHS R&D HTA Programme

Executive summary

Objectives

• To establish a database of literature and other evidence on neonatal screening programmes and technologies for inborn errors of metabolism.
• To undertake a systematic review of the data as a basis for evaluation of newborn screening for inborn errors of metabolism.
• To prepare an objective summary of the evidence on the appropriateness and need for various existing and possible neonatal screening programmes for inborn errors of metabolism in relation to the natural history of these diseases.
• To identify gaps in existing knowledge and make recommendations for required primary research.
• To make recommendations for the future development and organisation of neonatal screening for inborn errors of metabolism in the UK.

How the research was conducted

There were three parts to the research.

• A systematic review of the literature on inborn errors of metabolism, neonatal screening programmes, new technologies for screening and economic factors. Inclusion and exclusion criteria were applied, and a working database of relevant papers was established. All selected papers were read by two or three experts and were critically appraised using a standard format. Seven criteria for a screening programme, based on the principles formulated by Wilson and Jungner (WHO, 1968), were used to summarise the evidence. These were as follows.
– Clinically and biochemically well-defined disorder
– Known incidence in populations relevant to the UK
– Disorder associated with significant morbidity or mortality
– Effective treatment available
– Period before onset during which intervention improves outcome
– Ethical, safe, simple and robust screening test
– Cost-effectiveness of screening
• A questionnaire which was sent to all newborn screening laboratories in the UK.
• Site visits to assess new methodologies for newborn screening.

The classical definition of an inborn error of metabolism was used (i.e. a monogenic disease resulting in deficient activity in a single enzyme in a pathway of intermediary metabolism).

Research findings

Inborn errors of metabolism

• Phenylketonuria (PKU) (incidence 1:12,000) fulfilled all the screening criteria and could be used as the 'gold standard' against which to review other disorders despite significant variation in methodologies, sample collection and timing of screening and inadequacies in the infrastructure for notification and continued care of identified patients.
• Of the many disorders of organic acid and fatty acid metabolism, a case can only be made for the introduction of newborn screening for glutaric aciduria type 1 (GA1; estimated incidence 1:40,000) and medium-chain acyl CoA dehydrogenase (MCAD) deficiency (estimated incidence 1:8000–1:15,000). Therapeutic advances for GA1 offer prevention of neurological damage but further investigation is required into the costs and benefits of screening for this disorder. MCAD deficiency is simply and cheaply treatable, preventing possible early death and neurological handicap. Neonatal screening for these diseases is dependent upon the introduction of tandem mass spectrometry (tandem MS). This screening could however also simultaneously detect some other commonly-encountered disorders of organic acid metabolism with a collective incidence of 1:15,000.
• Neonatal screening for congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (incidence 1:17,000) has been shown to be beneficial in other countries and similar benefits should accrue in the UK. A national programme of neonatal screening for CAH would be justified, with reassessment after an agreed period.
• Biotinidase deficiency is of low incidence in the UK (estimated 1:100,000), but this may be outweighed by the simplicity of the screening methodology and the benefits in prevention of serious neurological disease in patients with profound biotinidase deficiency. This question requires further investigation and a national neonatal screening programme would be justified, with reassessment after an agreed period.
• Neonatal screening for galactosaemia (incidence 1:44,000) has been based upon prevention of neonatal mortality. However, evidence suggests that, despite early treatment, long-term outcome is poor with neurological dysfunction and a high incidence of ovarian failure in females. The accepted criteria are not currently met by galactosaemia and newborn screening is not justified.
• The accepted criteria for a neonatal screening programme are not currently met by non-PKU amino acidopathies (including tyrosinaemia type 1, homocystinuria and maple syrup urine disease), familial hypercholesterolaemia, peroxisomal disorders, urea cycle defects, trace metal disorders, purine or pyrimidine disorders, or lysosomal disorders.

Screening technologies

• Automation of all or parts of the screening process is technically possible but some current methodologies

are not amenable to automation. Fully automated neonatal screening utilising time-resolved fluorescence is currently being developed.
• Current molecular (DNA) techniques do not permit the simultaneous screening of large numbers of mutations and can be very expensive. At present there is no indication for newborn screening for inborn errors of metabolism using these techniques.
• Tandem MS can be considered as the most important of the new technologies for newborn screening for inborn errors of metabolism. It has the potential for simultaneous multi-disease screening for selected disorders of amino acid and organic acid metabolism using a single analytical technique and is complementary to immunoassay-based methods for congenital hypothyroidism (CH) and CAH screening. The technology has been demonstrated to be robust (accurate, sensitive, lack of false-positives) and suitable for the reliable detection of PKU and some other inborn errors of metabolism. However, introduction of new technologies for neonatal screening must be determined by the perception and evidence for the need for screening for each disorder or group of related disorders and by the need for the new technology in existing programmes. Of those disorders detectable by tandem MS in addition to PKU, evidence has identified only GA1 and MCAD deficiency as disorders for which a case for newborn screening can be made. Further, evidence for the utility of tandem MS in prospective neonatal screening for inborn errors of metabolism has come from only one source, based on relatively small numbers screened. Thus this technology requires further evaluation through primary research in the UK with prospective screening of more than 1,000,000 neonatal infants for PKU, GA1, MCAD deficiency (and possibly other selected disorders) in order to validate fully the utility of tandem MS for newborn screening for inborn errors of metabolism.

Economic evidence

• PKU screening provides a positive net monetary benefit to society and justifies the collection of blood samples from neonatal infants. There is insufficient economic evidence to support a change from current methodology to tandem MS-based screening solely for PKU. More information is needed on the cost-effectiveness of extending screening to other disorders. There is insufficient evidence to assess the economic value of screening for any other inborn errors of metabolism.

Conclusions and recommendations

• Universal neonatal screening for PKU is worthwhile and should be continued. Cost–benefit analyses show that screening for PKU by itself justifies the collection and testing of neonatal blood spots.
• If the neonatal screening programme is to be expanded a clinical and supportive infrastructure for paediatric metabolism urgently needs to be established to provide adequate treatment and care for identified patients and their families.
• National programmes for neonatal screening for profound biotinidase deficiency and CAH would be justified on the evidence. If they were introduced, there would need to be structured, coordinated, on-going evaluation to ensure that they are cost-effective, with review after 5 years.
• Screening for MCAD deficiency should be seriously considered for inclusion in newborn screening programmes. Similarly, a case can be made for the introduction of newborn screening for GA1. The clinical effectiveness and cost-effectiveness of such screening would need to be carefully monitored, with review after 10 years. Such screening is dependent upon the introduction of tandem MS technology into newborn screening programmes. Tandem MS could simultaneously detect other selected disorders.
• There is however insufficient evidence at present for the widespread introduction of tandem MS technology into newborn screening programmes in the UK. Tandem MS for newborn screening for PKU, MCAD deficiency and GA1 should be further evaluated by primary research conducted over 5 years with a defined timetable and external and independent statistical, health economic and scientific monitoring and evaluation of the technology and programmes. This research should be conducted at four selected centres that have been identified as having the required infrastructure and appropriate expertise. During this primary research, and until reports are presented and decisions made, there should be an embargo on the introduction of tandem MS technology into newborn screening laboratories in the UK.
• There is no evidence to support a newborn screening programme for galactosaemia and any current newborn screening for galactosaemia should be discontinued.
• Screening for other inborn errors of metabolism is not warranted at this time.
• Technologies for fully automated immunoassay-based screening are not yet sufficiently developed. The benefits from a fully automated neonatal screening system remain to be demonstrated. These benefits will probably only be achieved if the range of tests is expanded from CH (and PKU) alone and this will in turn depend upon decisions about other diseases to which newborn screening should be extended.
• At present there is no indication for newborn screening using molecular techniques.

Publication

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NHS R&D HTA Programme

The overall aim of the NHS R&D Health Technology Assessment (HTA) programme is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and work in the NHS. Research is undertaken in those areas where the evidence will lead to the greatest benefits to patients, either through improved patient outcomes or the most efficient use of NHS resources.

The Standing Group on Health Technology advises on national priorities for health technology assessment. Six advisory panels assist the Standing Group in identifying and prioritising projects. These priorities are then considered by the HTA Commissioning Board supported by the National Coordinating Centre for HTA (NCCHTA).

This report is one of a series covering acute care, diagnostics and imaging, methodology, pharmaceuticals, population screening, and primary and community care.

The views expressed in this publication are those of the authors and not necessarily those of the Standing Group, the Commissioning Board, the Panel members or the Department of Health.

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