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Newborn screening for homocystinuria (Review)

Walter JH, Jahnke N, Remmington T

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TABLE OF CONTENTS

[Intervention Review]

Newborn screening for homocystinuria

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ABSTRACT

Background

Homocystinuria is a rare inherited disorder due to a deficiency in cystathionine beta synthase. Individuals with this condition appear normal at birth but develop serious complications in childhood. Diagnosis and treatment started sufficiently early in life can effectively prevent or reduce the severity of these complications. This is an update of a previously published review.

Objectives

To determine if newborn population screening for the diagnosis of homocystinuria due to cystathionine beta synthase deficiency leads to clinical benefit compared to later clinical diagnosis.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Inborn Errors of Metabolism Trials Register.

Date of the most recent search of the Inborn Errors of Metabolism Register: 08 June 2015.

Selection criteria

Randomised controlled trials and controlled clinical trials assessing the use of any neonatal screening test to diagnose infants with homocystinuria before the condition becomes clinically evident. Eligible studies compare a screened population versus a non-screened population.

Data collection and analysis

No studies were identified for inclusion in the review.

Main results

No studies were identified for inclusion in the review.

Authors' conclusions

We were unable to identify eligible studies for inclusion in this review and hence it is not possible to draw any conclusions based on controlled studies; however, we are aware of uncontrolled case-series which support the efficacy of newborn screening for homocystinuria and its early treatment. Any future randomised controlled trial would need to be both multicentre and long term in order to provide robust evidence for or against screening and to allow a cost effectiveness analysis to be undertaken.

PLAIN LANGUAGE SUMMARY

Newborn screening for homocystinuria

Review question

We reviewed the evidence to determine if newborn population screening for the diagnosis of homocystinuria due to cystathionine beta synthase deficiency leads to clinical improvement compared to later clinical diagnosis and to determine the psychological effects on parents or carers of newborn population screening for homocystinuria. This is an update of a previously published review.

Background

Homocystinuria is a rare condition caused by mistakes in a gene that is responsible for making an enzyme called cystathionine beta synthase. People with homocystinuria have a deficiency of this enzyme and as a result have high levels of a substance called homocysteine in their bodies. Although such individuals appear normal at birth, over a period of months and years, they develop serious problems that effect eyesight, lead to delayed mental development, cause unhealthy bones, and have a high risk of having blood clots. Treatment with a special diet and medicines can prevent the development of these complications, but must be started very early in life to be truly effective. In some parts of the world homocystinuria has been tested for in newborn babies.

Search date

The evidence is current to: 08 June 2015.

Key results

No trials were found. We know of some uncontrolled studies which suggest that newborn screening for homocystinuria and its early treatment are effective. Future long-term research is needed to provide strong evidence for or against screening. This research may also show whether screening is cost effective.

BACKGROUND

Description of the condition

Homocystinuria is a rare genetic disorder caused by a deficiency in the enzyme cystathionine beta synthase (CBS) associated with raised levels of the amino acids homocysteine and methionine in blood and tissue. The incidence in the UK is between 1 in 60,000 to 1 in 100,000 and highest in ethnic groups with high consanguinity and in those of Irish decent (Mudd 2001). Children with this condition appear normal in early infancy, but subsequently develop a number of severe health problems including learning difficulties, skeletal abnormalities, myopia (short-sightedness) followed by lens dislocation (detected in most untreated children from 5 to 10 years of age) and thrombotic episodes. Death in childhood may occur (Mudd 1985). Those with less severe forms can present later in childhood to adulthood. Treatment options include oral pyridoxine (for those who are vitamin B6 responsive), betaine, and a strict low-methionine diet with amino acid, mineral and vitamin supplements. These interventions can lower blood homocysteine levels and, if started sufficiently early in life, prevent the development of complications. However, the clinical diagnosis is usually made only after irreversible damage has occurred. The severity and age of presentation of untreated disease depends primarily on the severity of the enzyme deficiency and whether affected individuals are responsive to pyridoxine (vitamin B6), the co-factor for CBS. Over 150 mutations in the CBS gene have been described. Of the two most prevalent, the G307S mutation accounts for approximately 21% of mutant alleles in the UK and is associated with B6 non-responsive disease whereas the I278T mutation, accounting for 29% of mutant alleles in the UK, usually predicts B6 responsiveness. The heterozygote frequency of I287T in certain European populations exceeds that predicted from those presenting clinically and identified to have this mutation, suggesting that there may be a number of individuals who remain asymptomatic (Skovby 2010). The pathophysiology of homocystinuria is not fully understood, but it is believed that the accumulation of homocysteine is likely to be the primary agent causing disease. If not detected early and treated effectively, the condition is associated with significant long-term morbidity and mortality.

Description of the intervention

The intervention to be assessed in the review is the early detection of homocystinuria by population screening in the newborn period.

Population screening for disease aims to detect specific disorders that may benefit from early intervention, but are otherwise unlikely to be detected until after serious irreversible harm may have occurred. Wilson and Junger have published criteria for considering a disorder for screening and which are also relevant for screening in the newborn period (Wilson 1968). These criteria include that the condition being screened for should be an important health problem; that the natural history of the condition should be understood; that there should be an early detectable stage; and that there should be an effective treatment that is of more benefit if started at an early stage rather than later. In addition, there must be a suitable and acceptable test available; the process of screening should cause more benefit than harm; and finally, the process should be cost effective. A good example of this is phenylketonuria (PKU), an inherited metabolic disorder, that has been judged to meet these criteria for screening. In the majority of developed countries PKU is tested for within the first week of life by collection of heel prick blood specimen.

Various biochemical methods have been, and are still being, used for newborn screening for homocystinuria. Generally, these have been based on measuring blood levels of methionine (Naughten 1998). However, levels may not be sufficiently raised in all cases of homocystinuria in the first few days of life and this limits the sensitivity of methodology based on measuring methionine. This fact is more relevant now that the age of screening in many countries has been reduced to between two and three days. Recent data suggests improved sensitivity may be possible with measurement of total homocysteine in the blood, rather than methionine (Gan-Schreier 2010). Tandem mass spectrometry (TMS) is now used for newborn screening by many laboratories. This method is able to detect a number of inherited metabolic disorders from the analysis of a single heel prick blood spot at little extra cost, so that the addition of disorders for screening by this methodology may now be more acceptable as regards cost-benefit basis providing other criteria are met.

How the intervention might work

Early detection by newborn screening allows treatment, as described above, to be commenced in early infancy. Maintaining blood homocysteine at a lower level from this age may prevent the development of complications and consequently improve clinical outcome both in terms of mortality and morbidity. The prevention of thromboembolic disease may: increase survival; increase the prevention of eye disease and skeletal abnormalities; improve quality of life; and have beneficial effects on the brain to allow normal development and school function. Over the last few decades newborn screening has been undertaken in a number of centres throughout the world, who have reported good cognitive outcomes and prevention of skeletal, vascular and ophthalmological complications for those children treated from early infancy (Naughten 1998; Walter 1998).

Why it is important to do this review

Newborn screening for a number of metabolic disorders is now becoming accepted practice in many countries. However, often disorders are selected without proof of benefit.

Newborn screening for homocystinuria is undertaken in a number of countries including those in Western Europe, Australia, the United States of America and Japan (Aoki 2003; Bodamer 2007; Kaye 2006; Wilcken 2009).

It is important to assess the evidence to support the efficacy of screening programs regarding the number of false negatives and the number of false positives. Homocystinuria fulfils a number of criteria for inclusion in a newborn screening programme: the natural history of the disorder is described; the incidence is known; it causes significant morbidity and mortality; there is a long presymptomatic phase; there is effective treatment; screening may be cost-effective (if diagnosis is made by using TMS, the addition of a test for homocystinuria is of minimal additional cost) (Wilson 1968). However, the disorder is rare and there are shortcomings with current screening methods. The aim of this review is to address the evidence for the efficacy of treatment and current screening methodology.

This is an updated of a previously published Cochrane review (Walter 2011; Walter 2013).

OBJECTIVES

To determine:

1. if newborn population screening for the diagnosis of homocystinuria due to CBS deficiency leads to clinical benefit compared to later clinical diagnosis;
2. the psychological effects on parents or carers of newborn population screening for homocystinuria.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and controlled clinical trials (CCTs) such as trials using quasi-randomisation methods (e.g. alternation) will be included if there is sufficient evidence that the treatment and comparison groups are comparable at baseline.

Types of participants

All individuals diagnosed with CBS deficiency either following clinical manifestations or by newborn screening.

Types of interventions

Any neonatal screening test, which enables infants with homocystinuria to be diagnosed in most cases before the diagnosis becomes evident clinically, compared to a later clinical diagnosis. We will include studies which compare a screened population versus a non-screened population.

Types of outcome measures

Entire Population

Primary Outcomes

1. Number of infants recognised with condition
2. Psychological effects of the diagnosis in parents or carers (e.g. a validated questionnaire)

Secondary Outcomes

1. Direct medical costs of screening

Diagnosed Population

Primary Outcomes

1. Survival
2. Quality of life

Secondary Outcomes

1. Thromboembolic events
2. Eye events (reduction of visual acuity, lens dislocation)
3. Cognitive function (reduction in IQ)
4. Skeletal changes (there are many scoliosis, pathological fractures, vertebral collapse, dolichostenomelia, arachnodactyly, etc)
5. Blood homocysteine and methionine levels
6. Time to diagnosis

Search methods for identification of studies

Electronic searches

We searched the Cystic Fibrosis and Genetic Disorders Group's Inborn Errors of Metabolism Trials Register using the term: homocystinuria.

The Inborn Errors of Metabolism Trials Register was compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of *The Cochrane Library*), weekly searches of MEDLINE and the prospective handsearching of the *Journal of Inherited Metabolic Disease*. Unpublished work were identified by searching through the abstract books of the Society for the Study of Inborn Errors of Metabolism conference and the SHS Inborn Error Review Series. For full details of all searching activities for the register, please see the relevant section of the Cystic Fibrosis and Genetic Disorders Group Module.

Date of the most recent search of the Inborn Errors of Metabolism Register: 08 June 2015.

Searching other resources

If future searches identify any references to studies, we plan to search the reference lists of these papers for any additional studies.

Data collection and analysis

We did not identify any eligible trials for inclusion in this review. If, for future updates, we identify any eligible trials, we will undertake the methods detailed below.

Selection of studies

Two authors will independently select studies for inclusion in the review according to the criteria stated above. If there are any disagreements regarding eligibility, they will resolve these by consensus or by consulting with the third author.

Data extraction and management

Two authors will independently extract data from eligible studies using a customised data extraction form designed for this review. They will record information about study and participant characteristics, the intervention and the outcomes. If there are any uncertainties, they will contact the primary investigators of the study in question for clarification. They will check the data for accuracy and consistency, and resolve any disagreements by consensus or by consulting the third author. They will enter the data into Review Manager software for analysis (RevMan 2014).

The authors plan to accept data from all reported time-points and to categorise these into up to one month and annually thereafter.

We plan to assess outcomes for two separate comparisons:

1. entire population (regardless of diagnosis);
2. diagnosed population (screening diagnosis versus clinical diagnosis at a later date).

Assessment of risk of bias in included studies

Two authors will independently assess the risk of bias according to the method described in *The Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). In particular we will consider the generation of allocation sequence and its

concealment (we are aware of the possibility of selection bias), the degree of blinding within a study, if any data are incomplete, if any outcomes have been selectively reported (for further details see below 'Assessment of reporting biases') or if there are any other potential sources of bias.

Measures of treatment effect

For dichotomous outcomes, we will calculate the risk ratios (RR) and their associated 95% confidence intervals (CI) for each treatment group.

For continuous outcomes, we will report the mean relative change from baseline or the mean post-intervention value as well as the difference in means between treatment groups and their associated 95% CIs. We will also report the standard deviations (SD); where standard errors (SE) are provided, we will use these to calculate the SD.

Unit of analysis issues

Studies of cross-over design are not appropriate for this intervention. If we include cluster-randomised trials in this review, we will analyse these using the effective sample size approach as described in Chapter 16 of *The Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

Dealing with missing data

We plan to contact the primary investigators of the studies to obtain any data missing from the published study reports.

Assessment of heterogeneity

If we are able to include a sufficient number of trials in the review, we will assess heterogeneity between studies estimates using the I^2 statistic (Higgins 2003). This statistic describes the percentage of total variation across studies that are due to heterogeneity rather than by chance. The values of I^2 lie between 0% and 100%, and a simplified categorisation of heterogeneity that we plan to use is:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

If sufficient trials are included in the review (at least 10), we will assess reporting bias using funnel plots.

To identify outcome reporting bias, we will compare the study's protocol to the final published paper. If the study protocol is not available, we plan to compare the methods section of the paper with the results section to ensure that all the outcomes measured and at all time-points are reported. We will also consider if an outcome which we would expect to be measured, is not reported.

Data synthesis

We plan to analyse the data using a fixed-effect model. If we identify moderate, substantial or considerable heterogeneity between studies, we will analyse the data using a random-effects model.

Subgroup analysis and investigation of heterogeneity

If we establish a moderate, substantial or considerable degree of heterogeneity, we will investigate this by means of the following subgroup analyses:

- different trial designs;
- different biochemical methods of screening;
- B6-responsive versus non-responsive variants.

Sensitivity analysis

If we are able to include a sufficient number of studies, we plan to undertake sensitivity analyses to determine the effect of a high risk of bias for generation of sequence, for concealment of sequence and blinding.

RESULTS

Description of studies

No studies were identified for inclusion in the review.

Risk of bias in included studies

No studies were identified for inclusion in the review.

Effects of interventions

No studies were identified for inclusion in the review.

DISCUSSION

Summary of main results

Given there are no studies identified for inclusion there are no results to summarise.

Agreements and disagreements with other studies or reviews

Uncontrolled studies have supported the efficacy of newborn screening for homocystinuria (Naughten 1998). The evidence for expanded screening, including that of homocystinuria, has recently been reviewed (Burton 2010).

AUTHORS' CONCLUSIONS

Implications for practice

Given no studies were found for inclusion in the review, it is not possible to comment on the evidence for or against the efficacy of newborn screening for homocystinuria. However, uncontrolled studies do suggest benefit both for newborn screening and early treatment for homocystinuria.

Implications for research

No controlled studies of the effectiveness of newborn screening appear to have been undertaken. In view of the rarity of homocystinuria and the time taken to develop complications, any such study would need to include a number of screening centres and to monitor outcomes over a period of many years. However, it would provide more robust evidence for or against screening and allow a cost-effectiveness analysis to be undertaken.

ACKNOWLEDGEMENTS

We thank the peer reviewers for their comments on this review.

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APPENDICES

Appendix 1. Glossary of terms

Term	Explanation
Allele	One of two or more forms of the DNA sequence of a particular gene. Each gene can have different alleles and sometimes different alleles can result in different traits, such as colour.
Amino acid	Molecules containing an amine group, a carboxylic acid group and a side chain that varies between different amino acids. Amino acids are used in every cell of the body and are used to build the proteins needed to survive.
Arachnodactyly	A condition in which the fingers are abnormally long and slender in comparison to the palm of the hand.
Co-factor	A substance that must be associated with an enzyme for the enzyme to function.
Consanguinity	Relationship by blood or by a common ancestor.
Dolichostenomelia	A condition in which the limbs are unusually long.
Enzyme	An enzyme is a protein formed by the body that acts as a catalyst to cause a certain desired reaction. Enzymes are very specific. Each enzyme is designed to initiate a specific response with a specific result.
False-negative result	When an individual is found to have a negative test result, but in actual fact has the condition being tested for.
False-positive result	When an individual is found to have a positive test result, but in actual fact does not have the condition being tested for.
Gene	A hereditary unit consisting of a sequence of DNA that occupies a specific location on a chromosome and determines a particular characteristic in an organism.
Phenotype	The expression of a specific trait, such as stature or blood type, based on genetic and environmental influences and the interaction between the two.
Scoliosis	A medical condition in which a person's spine is curved from side to side.
Thromboembolic disease	When a blood clot breaks off from where it has formed and travels through the bloodstream. Eventually, the blood clot will get trapped inside a blood vessel that is too small to let it pass.
Thrombotic episodes	The formation, presence, or development of a blood clot.

WHAT'S NEW

Date	Event	Description
8 April 2021	Review declared as stable	Due to a lack of research in this area the Editorial Board of the Cystic Fibrosis and Genetic Disorders Review Group have decided to no longer update this review.

HISTORY

Protocol first published: Issue 11, 2010
Review first published: Issue 8, 2011

Date	Event	Description
3 September 2015	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Inborn Errors of Metabolism Trials Regsiter did not identify any potentially eligible trials for inclusion in the review.
3 September 2015	New citation required but conclusions have not changed	Minor changes have been made throughout the review. The 'Plain language summary' has been updated.
24 July 2013	New citation required but conclusions have not changed	Minor changes have been made throughout the review.
24 July 2013	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Inborn Errors of Metabolism Trials Register did not identify any potentially eligible trials.
17 October 2012	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

Roles and responsibilities	
Task	**Author**
Protocol stage: draft the protocol	JW, NJ, TR
Review stage: select which trials to include (2 + 1 arbiter)	JW, NJ, TR
Review stage: extract data from trials (2 people)	NJ, TR
Review stage: enter data into RevMan	NJ, TR
Review stage: carry out the analysis	NJ, TR
Review stage: interpret the analysis	JW
Review stage: draft the final review	JW, NJ, TR
Update stage: update the review	JW, NJ, TR

DECLARATIONS OF INTEREST

John Walter: received honorariums for educational work for Recordarti Rare Diseases Foundation.

Nikki Jahnke: none known.

Tracey Remmington: none known.

SOURCES OF SUPPORT

Internal sources

- University of Liverpool, UK

External sources

- National Institute for Health Research, UK

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INDEX TERMS

Medical Subject Headings (MeSH)

Cystathionine beta-Synthase [*deficiency]; Early Diagnosis; Homocystinuria [*diagnosis]; Neonatal Screening

MeSH check words

Humans; Infant, Newborn