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Inborn errors of metabolism causing Sudden Infant Death: a systematic review with implications for population neonatal screening programs

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Abbreviations: DBS, dried blood spot; IEMs, inborn errors of metabolism; MeSH, Medical Subject Headings; NBS, neonatal bloodspot screening; RS, Reye syndrome; SID, sudden infant death; TMS, tandem mass spectrometry.

Key words: neonatal screening; inborn error of metabolism; mitochondrial fatty acid oxidation; Reye syndrome; sudden infant death; tandem mass spectrometry; treatment; metabolic autopsy.

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Abstract:

Background: Many inborn errors of metabolism (IEM) may present as sudden infant death (SID). Nowadays increasing numbers of patients with an IEM are identified presymptomatically by population neonatal screening (NBS) programs. However, some patients escape early detection because their symptoms and signs start before NBS test results become available, die even before the sample for NBS has been drawn, or due to IEMs which are not included in the NBS programs.

Objectives & methods: A comprehensive systematic literature review to identify all IEMs associated with SID, including their treatability and detectability by NBS technologies. Reye syndrome (RS) was included in the search strategy because this condition can be considered as a possible pre-stage of SID in a continuum of aggravating symptoms.

Results: 43 IEMs were identified that were associated with SID and/or RS. Of these IEMs (a) 26 can already present during the neonatal period, (b) treatment is available for at least 32, and (c) 26 can currently be identified by analysis of acylcarnitines and amino acids in dried bloodspots.

Conclusion: We advocate extensive analysis of amino acids and acylcarnitines in blood/plasma/dried bloodspots and urine for all children who died suddenly and/or unexpectedly, including neonates in whom a blood spot for the routine NBS program has not yet been drawn. The application of combined metabolite screening and DNA sequencing techniques would facilitate fast identification and maximal diagnostic yield. This is important information for both clinicians who need to maintain clinical awareness, and for decision-makers to improve population NBS programs.

Introduction:

Many inborn errors of metabolism (IEM) that cause cellular energy deficiency and/or intoxication are associated with sudden infant death (SID). Based on retrospective studies, approximately 0.9-6% of all SID cases represent IEMs.[1-3] Although these studies were subject to several forms of selection bias, they form the rationale behind metabolic autopsy protocols for young children, which include analyses of amino acid and acylcarnitine profiles in plasma/urine.[4]

Since the 1990s, tandem mass spectrometry (TMS) in dried blood spots (DBS) has been developed to perform high-throughput simultaneous quantitative analysis of different diagnostic metabolites in small amounts in biological samples.[5] As a consequence, in the last two decades population neonatal bloodspot screening (NBS) programs have been expanded with many IEMs. Patients with treatable IEMs can remain undetected by population NBS programs for several reasons. In some IEMs, symptoms and signs including death already occur prior to the NBS test results becoming available or even before the blood spot has been drawn, annulling the benefits of NBS.[6-10] This is especially relevant in areas where neonatal blood is collected relatively late, for instance in the Netherlands (i.e. 72-168 hours after birth).[11, 12] Between different areas worldwide, population NBS programs differ with respect to methodological aspects and disorders to screen for.

Systematic studies on the percentage of IEMs among SID cases are required as, although rare, preventable SID cases due to treatable IEMs still occur. Therefore, we performed this comprehensive systematic literature review to identify IEMs (1) that are associated with SID, (2) have clinical ascertainment during the neonatal period, (3) are treatable and (4) are detectable by TMS.

Methods:

Search strategy

A literature search for relevant references was performed according to the Cochrane Collaboration methodology. CINAHL, Cochrane, Pubmed and Embase public databases were searched using both Medical Subject Headings (MeSH) terms and free text. A detailed presentation and assessment of the search strategy, including the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist, is presented in Supplemental Data 1. Figure 1 presents the flowchart of the detailed search strategy together with the steps of the systematic review.

The following search terms were included to further optimize our search strategy. The term "mitochondrial fatty acid oxidation" was included because, based on previous studies and our personal expertise, this disease group has the highest incidence among IEMs associated with both SID [1-3] and NBS programs.[6, 7, 10] SID is historically defined to occur in the first year of life. We therefore expanded our search strategy with "sudden unexpected death of infant". Originally, Reye syndrome (RS) has been described as a non-inflammatory encephalopathy in childhood, associated with hepatic dysfunction.[13] Since the 1980s it has been recognized as a presenting symptom of IEMs rather than being an etiologic diagnosis.[14] We considered RS as a potential pre-stage of SID in a continuum of aggravating symptoms. Therefore we also included the term "Reye syndrome" in our search strategy.

All reports published since 1990 were included, corresponding with the first publications about the availability of TMS and general progressions made in the field of molecular and enzymatic confirmatory testing in the field of IEMs. References published before 1990 were only included when available upon request. Two independent reviewers (GK and TD) performed title and abstract screenings. Consensus on inclusion was reached

during regular meetings. Subsequently, three independent (WvR, GK and TD) screened the full text articles of all selected references. The inclusion of a diagnosis as a cause of SID and/or RS was based on the presence of detailed patient data and a confirmed diagnosis in the full text articles. Specific exclusion criteria were (1) no detailed patient data reported; (2) lack of accessibility of the articles; (3) confirmatory metabolite, molecular or enzymatic studies were inconclusive; (4) when there had been a (possible) additionally contributing cause of death; (5) patients suffering from SID and/or RS aged above 18 years and/or (6) abstract and/or article not available in English or Dutch language.

Data analysis

All IEMs were classified according to the Society for the Study of Inborn Errors of Metabolism classification of IEMs.[15] Based on the included references, associations between confirmed diagnoses and SID and/or RS were documented. For example, a plus sign in the SID column in Table 1 indicates that the particular IEM has been associated with SID in at least one of the corresponding references presented in Supplemental Table 1. Neonatal clinical presentation was reported based on detailed patient data of the included references. Based on recent textbooks and literature, treatability [16] and detectability by TMS in a DBS [17-19] were documented, respectively.

Results:

This systematic review included a total of 136 references. Table 1 presents the 43 IEMs associated with either SID and/or RS, concerning mostly disorders of mitochondrial fatty acid oxidation, the urea cycle and organic acidurias. References of all included articles are presented in Supplemental Table 1. Out of these 43 IEMs, minimally 26 already presented during the neonatal period of which 15 are both treatable and detectable by TMS methodologies. In at least 32 out of the 43 IEMs, a specific dietary and/or pharmacological treatment is available in order to prevent clinical presentation. Identification by population NBS programs by TMS analysis of amino acids and/or acylcarnitines in DBS is possible in 26 out of the 43 IEMs.

Discussion:

This unique systematic literature review identified at least 43 IEMs that are associated with SID and/or RS, of which 26 can already present during the neonatal period. At least 32 out of 43 are considered as treatable disorders and 26 out of 43 are currently detectable by TMS analysis of amino acids and/or acylcarnitines in DBS. The remaining 17 IEMs will not be detected by current *metabolite* screening methods, but require additional testing either by expanding the metabolic testing options or by *genetic* and/or *enzymatic* laboratory methods. Out of the 26 IEMs in which clinical ascertainment within the neonatal period has been reported, at least 15 are both treatable and detectable by TMS analysis. This is important information to improve population NBS programs as early detection and subsequent treatment may prevent clinical presentation and even death (Table 1). Moreover, with the results of our study, diagnostic (laboratory) protocols can be improved for children (including neonates) presenting with sudden/unexpected death.

There is no doubt that expanded population NBS programs have significantly improved the outcomes of many patients, but there remains a subset of patients that unfortunately escapes early identification.[20] First, one group escapes early identification because limited numbers of IEMs are included in the NBS programs. It is important to realize that population NBS programs differ worldwide, and may even differ within countries. Second, another group escapes early identification because symptoms and signs present before NBS test results become available or even before the blood spot has been drawn. This is aggravated by relative late NBS blood obtainment and/or follow-up after positive test results in some areas/countries. In the Netherlands neonatal blood for the NBS test is collected between 72-168 hours after birth.[11, 12] In 2013, the response rate for the NBS program was 99.35%. Referral to a metabolic physician was initiated before day 8 in 62% of the positive neonates, whereas 441 out of 173,118 newborns died (etiology not specified) before the NBS

blood spot could be drawn.[11] Reports from population NBS programs from Australia, the USA and Germany present patients with clinical ascertainment and sometimes even neonatal death before NBS test results have become available (indicated with ** in table 1).[6, 7, 10] In line with these reports, in our country since the expansion of the NBS program (Table 1), clinical symptoms and signs preceded the NBS test results, sometimes even leading to early death, in cases of very long-chain acyl-CoA dehydrogenase deficiency, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency/mitochondrial trifunctional protein deficiency, medium-chain acyl-CoA dehydrogenase deficiency, maple syrup urine disease and galactosemia (data unpublished). Last, patients may escape early identification due to false-negative NBS results, (for example patients with carnitine transporter deficiency or very long-chain acyl-CoA dehydrogenase deficiency [21, 22]) or (pre-)analytical reasons, which is of concern for patients with carnitine palmitoyltransferase 2 deficiency [23]. These examples stir the debate on whether the NBS test should be performed earlier in life and/or twice at two different timings.

The general view on 'the metabolic autopsy' has originated from case studies and small retrospective cohort studies that introduced bias.[4] It is generally recognized that low incidences and aspecific symptoms and signs cause underdiagnosis of IEMs.[9] The current study strengthens the rationale why – despite low incidences of the individual IEMs – neonates who died deserve at least a TMS analysis of amino acids and acylcarnitines in a DBS, when feasible. For most of the disorders listed in Table 1, the associated recurrence rate for affected families is at least 25%.

Several methodological issues of this study should be mentioned. First, the retrospective study designs of many included cohort studies and case studies could have introduced both a publication bias and a data availability bias as 1) reports do not always describe detailed patient data and 2) obviously not all SID cases due to IEMs have been

reported in literature. Second, there are many factors, including aspecific symptoms, causing underdiagnosis of IEMs in neonates.[9] Third, despite our extensive and detailed search strategy, we cannot exclude that few references have been missed. The fact that after including the full text articles in the first round (n=91) new references still emerged via the reference lists of excluded and included full text articles emphasizes this once more. In order to optimize the search strategy, we conducted the second (n=44) and third (n=1) screening rounds. Fourth, in medical literature the definition of SID is not always applied consistently with regard to age ranges and clinical symptoms and signs. In an attempt to overcome this issue, we added the term "sudden unexpected death of infant" to our search strategy. Last, some included IEMs exemplify one protein deficiency in a large metabolic pathway involving many enzymes and transporters that potentially could cause a similar clinical picture. Therefore, we believe, based on our systematic review, that the IEMs included in Table 1 should be considered as the minimal number of IEMs associated with SID and/or RS. Despite expanding NBS programs, clinical awareness needs to remain high amongst neonatologists and pediatricians as many IEMs have not been implemented in NBS programs. Early recognition of clinical presentations and subsequent diagnostic testing can possibly prevent fatal outcomes.[24]

In summary, our systematic review identified the IEMs that are associated with RS and SID, a significant proportion of them being treatable disorders. Therefore in our opinion analysis of amino acids and acylcarnitines in blood/plasma/DBS and urine should be part of post-mortem diagnostic protocols, next to isolation of DNA and preferentially, material for functional tests such as analysis of cultured skin fibroblasts. To date, the combination of metabolite screening and DNA sequencing techniques would harbor the best of both methods, i.e. fast identification and a high diagnostic yield.

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Legends to tables and figures:

Figure 1. Flowchart of detailed search strategy.

Legend: CINAHL, Cochrane, Pubmed and Embase were searched using both MeSH terms and free text ("Metabolism, Inborn Errors"[Mesh] OR "inborn errors of metabolism" OR "mitochondrial fatty acid oxidation") AND ("Sudden Infant Death"[Mesh] OR "sudden infant of death" OR "sudden infant death syndrome" OR "unexpected death" OR "sudden unexpected death of infant" OR "Reye Syndrome"[Mesh]) AND (Humans[Mesh]) AND ("Infant, Newborn, Child, Adolescent"[Mesh] OR newborn OR infant OR child). Search strategy was conducted on February, 15th 2013. Due to the elapsed time between the execution of the search strategy and the completion of the manuscript, the search strategy was repeated on August, 28th 2015, to screen for possible extra IEMs. This lead to the inclusion of only one additional IEM associated with either SIDS and/or RS: dihydrolipoamide dehydrogenase deficiency (DLD deficiency; MIM #246900).

Table 1. The IEMs associated with either SID and/or RS.

Legend: [*]Dihydrolipoamide dehydrogenase deficiency (DLD deficiency; MIM #246900), [#]Medium chain 3-ketoacyl-CoA thiolase deficiency (MCKAT deficiency; MIM #602199): these IEMs were not included in the list of the Society for the Study of Inborn Errors of Metabolism, but were found via the search strategy and therefore included as IEMs associated with either SID and/or RS. [†]According to McHugh et al [17]; [‡]according to Kishnani et al [18]; [§]according to Gonzalez et al.[19] [**]Reported to have caused clinical ascertainment and/or neonatal death before NBS test results were available.[6, 7, 10] [‖]Included in the expanded Dutch population NBS program since 2007.[25] [¶]Recommended in 2015 for expansion of the Dutch population NBS program.[25]