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Original Article

Cystic Fibrosis Screen Positive, Inconclusive Diagnosis (CFSPID): A new designation and management recommendations for infants with an inconclusive diagnosis following newborn screening

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Abstract

Background: Newborn screening (NBS) for cystic fibrosis (CF) results in the recognition of a number of infants with a positive NBS result, but an inconclusive diagnosis. Varied practice exists with respect to the management of these infants.
Methods: A Delphi consensus approach was used to determine agreement on statements generated by a core group of specialists. A designation (naming) exercise was required after Round 1 and further expert opinion was sought to guide that process. After Round 2, a sensitivity analysis was undertaken to assess the impact of attrition on subsequent agreement levels.
Results: Infants were divided into group A (normal sweat chloride and two CFTR mutations, at least one of which has unclear phenotypic consequences) and group B (intermediate sweat chloride and one or no CFTR mutations). 32 statements were produced for Round 1 and 24 achieved consensus. After Round 1, a designation exercise was undertaken and the term "CF Screen Positive, Inconclusive Diagnosis (CFSPID)" was suggested for Round 2. Agreement was achieved for this statement and for all other statements aside from the need for routine respiratory culture, on which there was divided opinion. The core group advocated local practice for this issue. A sensitivity analysis demonstrated that consensus for Round 2 was achieved by change in opinion rather than attrition.
Conclusion: We have generated a new designation and statements to guide the management of infants with CFSPID through a robust international Delphi process. These statements will be a valuable tool for CF teams and will improve the consistency of management of these infants.
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Keywords: Cystic fibrosis; Newborn screening; CRMS; CFSPID

1. Introduction

Newborn screening (NBS) for cystic fibrosis (CF) is a valid public health strategy for a population with a high incidence of the condition [1]. There has been rapid and considerable global

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expansion of this strategy over the past ten years with a wide variety of protocols employed [2]. All programmes rely on measurement of immuno-reactive trypsinogen (IRT) from a dried blood sample taken during the first week of life [2]. This is a sensitive screening test for CF, but a second tier test is needed to improve the specificity of the protocol. Second tier tests vary from programme to programme, and often include DNA analysis [3]. The diagnosis is confirmed by clinical assessment, DNA testing and measurement of chloride concentration in sweat (the sweat test).

In some cases the sweat chloride result may be intermediate or CFTR gene changes may be recognised, the phenotypic consequences of which are unclear. Previous work by this group produced a consensus guideline for the evaluation and early management of infants with an inconclusive or equivocal diagnosis following screening [4]. This work provided an algorithm for the investigation of these infants with a particular focus on communication with the families.

At the same time a consensus group in the US also considered this issue and developed guidelines with similar themes to the European guidelines [5]. The US group proposed a term for designation of these infants, cystic fibrosis transmembrane conductance regulator (CFTR)-related metabolic syndrome (CRMS). This designation reflects the nomenclature stream under which CF is categorised in the US and the need for a diagnostic designation to comply with the US funding arrangements. The European guidelines did not propose a designation, advocating clear communication of this interim situation to the family.

Despite these two guidelines, it has become apparent through published commentaries and surveys of European programmes that diverse practice exists with respect to the management of these infants, ranging from early discharge with little information to the family to full CF care in a CF centre [6,7]. There is limited data on the long-term outcomes, but it is clear from epidemiological studies that a significant number will have minimal or no phenotypic consequence [8,9]. We also know from case reports that a small number will develop significant CFTR related airway disease that has an impact on their well-being and potentially their survival [10].

In view of this lack of consensus and the limited evidence base on which to guide treatment, the ECFS Neonatal Screening Working Group (NSWG) organised a further Delphi process to determine consensus on the management of these infants. This paper describes the method employed and the recommendations.

2. Methods

A core group (AM, AS, JB, KWS and SM) produced preliminary statements through a series of face-to-face meetings, teleconferences and email discussions. The level of evidence to support each statement was recorded. Once finalised by the core group, the statements were circulated by email to all members of two ECFS working groups (the Diagnostic Network and the Neonatal Screening Working Group). Additional invitations were made to increase multidisciplinary input. In total, 391 invitations were sent. It was determined, a priori, that an agreement level of 80% would constitute consensus, consistent with previous exercises by this group and work in other fields [4,11].

For Round 1, participants were asked to rate the statements by either agreeing or disagreeing. Participants in disagreement were asked to provide an alternative statement. Participants were encouraged to include comments, which were all assessed by the core group and influenced the altered statements for Round 2.

Following Round 1, the core group revised statements not achieving consensus taking into account comments and suggestions. When the meaning of a statement was changed these statements were called rewritten. Some statements that achieved consensus were modified, if the comments were felt to improve or clarify a statement. Modified and rewritten Round 2 statements were circulated to all respondents to Round 1, together with the original statements and comments.

During the consensus process it became apparent that most participants considered there was a requirement for a diagnostic label to classify infants with inconclusive diagnosis. A separate designation exercise (described more fully in Section 3) was therefore undertaken to determine consensus on a diagnostic term for these infants.

After Round 2, a sensitivity analysis was undertaken to determine if the result of Round 2 was a reflection of changing opinion or rather a consequence of attrition in the number of respondents. For participants that contributed to Round 2, we reassessed their responses to Round 1 to assess the impact on agreement. This analysis was to retrospectively assess the Delphi process and had no bearing on the final statements.

3. Results

The first outcome of the core group discussion was the decision that two sets of statements were necessary to reflect different degrees of clinical concern for infants with a normal sweat chloride value (<30 mmol L^{-1}) compared to infants with an intermediate sweat chloride value (30–59 mmol L^{-1}) [12].

- Group A, normal sweat chloride value (<30 mmol L^{-1})
- Group B, intermediate sweat chloride value (30–59 mmol L^{-1}).

Infants in Group A have two *CFTR* mutations, at least one of which has unclear phenotypic consequence. Infants in Group B have one or no *CFTR* mutations. Infants with two *CFTR* mutations and an intermediate sweat chloride should be referred to a CF clinic, as per previous consensus agreement [4].

Statements for Group B were associated with more active interventions. The decision to establish this grouping was subjective, after much discussion, and not based on any current evidence that infants in Group A have a better course than infants in Group B.

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