Inconclusive diagnosis after a positive newborn bloodspot screening result for cystic fibrosis; clarification of the harmonised international definition

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HIGHLIGHTS

• Newborn bloodspot screening (NBS) for cystic fibrosis (CF) has been a successful public health strategy.

• Occasionally a positive NBS result is associated with an inconclusive diagnosis.

• Infants in this situation may be mislabelled.

• Accurate designation of infants after NBS for CF is important to ensure appropriate management.

• In some cases, the diagnosis remains inconclusive and the international designation, Cystic Fibrosis Transmembrane Conductance Regulator-Related Metabolic Syndrome/CF Screen Positive, Inconclusive Diagnosis (CRMS/CFSPID), should be used.
Newborn bloodspot screening (NBS) for cystic fibrosis (CF) is a successful public health strategy with a considerable impact on the well-being of young people with CF [1]. Most infants with a positive NBS result for CF will have either a clear diagnosis of CF (true positive NBS result) or CF excluded (false positive NBS result), however a small but significant number will have an inconclusive diagnosis. This is a challenging situation for families and for healthcare professionals [2].

There has been progress over the past ten years with respect to the evaluation, designation and management of these infants. This includes a global harmonisation process undertaken in 2016, with a publication in 2017, which provided a consistent international approach and definition [3,4]. A recent survey undertaken by the European CF Society (ECFS) with support from the Cystic Fibrosis Foundation (CFF) NBS Quality Improvement Group revealed significant confusion with respect to the designation of infants with inconclusive results after a positive NBS test (Online appendix for summary). The survey, which will be presented at the 2019 European CF Conference, demonstrated that doctors who classified themselves as CF specialists were as likely to be wrong with diagnostic options as those who classified themselves as respiratory pediatric consultants. In light of these results, we felt it important to highlight and clarify the published harmonised definition [3].

1. BACKGROUND

Newborn bloodspot screening for CF results in the recognition of a small number of infants with a positive screening result but an inconclusive diagnosis, irrespective of the screening protocol used. The proportion of inconclusive diagnosis increases when NBS protocols use larger DNA panels and extended gene sequencing to identify cystic fibrosis transmembrane conductance regulator (CFTR) gene variants [5]. A number of bodies have considered the evaluation and management of infants with these findings. An expert group convened by the CFF produced the diagnostic designation CFTR-related metabolic syndrome (CRMS) to describe these infants [6]. This term is consistent with the World Health Organisation International Disease Classification system (aligned with CF) and is a designation that enables access to insurance funds for healthcare in the US. In Europe, a panel of experts embarked on a Delphi consensus exercise to determine
guidance on the evaluation of infants in this situation [7]. At this time, the consensus group did not provide a designation for these infants as it was considered that a “name” might increase the risk of over medicalisation. A subsequent ECFS consensus determined agreement that a designation would be useful and, after wide stakeholder engagement, the term CF Screen Positive, Inconclusive Diagnosis (CFSPID) was adopted [8].

2. GLOBAL HARMONISATION EXERCISE

There was cross Atlantic acknowledgement that having two terms to describe these infants was unsatisfactory and at a large international meeting supported by the CFF, there was consensus that the terms should be amalgamated to a joint CRMS/CFSPID designation with a consistent definition (Fig. 1) [3]. The harmonised definition reflected the increased capacity of the cftr2 website (https://www.cftr2.org/) to characterise CFTR variants as “CF causing”, “non-CF causing”, “varying clinical significance” or “unknown significance” [9]. The key difference between previous definitions of CFSPID and CRMS and the new harmonised definition was the inclusion of “CF causing variant” for the infants with an intermediate sweat chloride (30–59 mmol/L). Consequently an infant with two CFTR variants and an intermediate sweat chloride will now be designated as CRMS/CFSPID if only one variant is characterised as CF causing (Fig. 2). This is in contrast to the previous ECFS definition of CFSPID, in which infants with two CFTR variants and an intermediate sweat chloride would be referred for CF care.
3. WHAT DOES THIS HARMONISED DESIGNATION MEAN FOR HEALTHCARE PROFESSIONALS?

There is guidance for the early evaluation of infants with an inconclusive diagnosis after a positive NBS result for CF [6,7]. Key points include the organisation of a second sweat test to measure sweat chloride in a centre with a high level of experience. Infants with only one CFTR variant recognised and a normal repeat sweat chloride (<30 mmol/L) should be reported as carriers and no further testing undertaken. Infants with a CRMS/CFSPID designation are well and have no clinical features consistent with a diagnosis of CF. A positive outcome from the consensus exercises has been a move away from over-medicalising this situation and improved communication with families. It is important, however, that these infants continue to have regular clinical review by physicians with an interest in CF, as they have a risk to develop significant clinical features consistent with CF.
4. WHAT DOES THIS MEAN FOR FAMILIES?

This is an extremely unsettling situation for families; the traditional framework of health and disease is undermined [2]. Delivery of the initial positive NBS result and the subsequent inconclusive result places the family in a psychologically vulnerable position with oscillating emotions. It is essential that families have clear and precise information at all stages of this process, including the longer term risks that a child with CRMS/CFSPID faces, especially the development of a CFTR related disorder (CFTR-RD); a monosymptomatic clinical entity (for example, CBAVD/pancreatitis/bronchiectasis) associated with CFTR dysfunction that does not fulfill the diagnostic criteria for CF [3,10].

5. THE OUTLOOK FOR THESE CHILDREN

A number of infants with CRMS/CFSPID will develop clinical features consistent with a diagnosis of CF, and will be transitioned to a CF diagnosis (albeit a less typical form in most cases). This is more likely to occur for infants with an initial intermediate sweat chloride value [4]. In other CRMS/CFSPID infants, a diagnosis of CF may be established because of a subsequent positive sweat test result or from new knowledge reclassifying a CFTR variant as CF causing (https://www.cftr2.org/mutations_history). All infants with CRMS/CFSPID have a risk of developing a CFTR-RD, but the extent of this is not currently quantifiable and likely relates to individual CFTR variants [[11], [12], [13], [14]]. The accurate designation of infants with CRMS/CFSPID is vital and facilitates the establishment of appropriate databases to monitor longterm outcomes. This information will provide a clearer assessment of risk for children with CRMS/CFSPID as they grow into adults.

Conflicts of interest

There are no conflicts of interest.

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REFERENCES


