Stratifying Cystic Fibrosis Risk for Newborn Screen Infants With Equivocal Sweat Chloride Levels

We read with interest the recent study by Ooi et al,[1] which adds significantly to the recent literature guiding physicians on how to manage infants with equivocal sweat chloride (30–59 mmol/L, termed cystic fibrosis [CF] screen positive, inconclusive diagnosis [CFSPID]) identified through newborn screening. Nine (11%) of 82 subjects with CFSPID were subsequently diagnosed with CF during the 3-year follow-up period. The findings are in agreement with our recent publication that analyzed a similar retrospective cohort, in which 48% (14 of 29) were later diagnosed with CF over a longer follow-up period.[2]

In the current study by Ooi et al,[1] 4 (44%) of the 9 CFSPID infants presented with initial sweat chloride levels between 30 and 39 mmol/L; the remainder had levels between 40 and 59 mmol/L. The risk of later CF diagnosis, based on the initial sweat chloride level, would be of great interest but was not presented.

We considered this information within our cohort of 29 patients with an elevated newborn screening immunoreactive trypsinogen level, heterozygous for the p.F508del mutation, and an intermediate initial sweat chloride level between 30 and 59 mmol/L. Comparing 2 cohorts based on initial sweat chloride level (30–39 mmol/L vs 40–59 mmol/L), the incidence of a later CF diagnosis was less in patients from the 30- to 39-mmol/L cohort versus the 40- to 59-mmol/L cohort (3 of 14 [21%] vs 11 of 15 [73%]; $P = .009$). The mean age of CF diagnosis was older in patients from the 30- to 39-mmol/L cohort compared with the 40- to 59-mmol/L cohort (2.9 vs 0.26 year; $P = .0001$). Among the patients in the 30- to 39-mmol/L cohort, 2 were diagnosed based on proven pancreatic insufficiency at 1.5 and 2.5 years, with initial sweat chloride levels of 38 and 32 mmol/L at 1.5 and 2 months, respectively. Identification of the second gene mutation (p.Val470Met) confirmed the diagnosis in the former patient at 2.5 years. The latter patient had follow-up sweat chloride levels of 33 and 55 mmol/L at 9 months and 2.5 years, respectively. One patient was diagnosed based on a respiratory clinical course consistent with CF at 4.5 years. This patient had follow-up sweat chloride levels of 45, 29, and 35 mmol/L at 3 months, 4 years, and 14 years, respectively, along with significant bronchiectasis confirmed on computed tomography scanning from 6 years of age, with resistant nonmucoid *Pseudomonas aeruginosa* from repeated subsequent sputum samples.

Our data, with the data from the CFSPID infants of Ooi et al,[1] illustrate potential relative risk stratification between initial sweat chloride values and later CF diagnosis. In fact, the current North American guidelines,[3] which use a cutoff of 40 mmol/L over 6 months of age to assess indeterminate sweat chloride values, would have missed a CF diagnosis in 2 patients (14%) within our cohort. This finding is higher than the estimated 5% discordance between diagnosis in such infants comparing North American and European lower sweat chloride cutoff limits in infancy reported in the earlier study by Ooi et al.[4] We support the consistent use of the lower cutoff of 30 mmol/L as outlined in the European guidelines.[5] It would be of great interest to know if the data of Ooi et al[1] also support this stance.

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Conflict of Interest:
None declared

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Authors' Response

Re: Stratifying Cystic Fibrosis Risk for Newborn Screen Infants With Equivocal Sweat Chloride Levels

We thank Groves et al[1] for their interest in our study in infants diagnosed as having "cystic fibrosis (CF) screen positive, inconclusive diagnosis" (CFSPID).[2] In our study, both repeat sweat testing and extensive genotyping helped clarify the diagnosis of CF (CFSPID→CF). At the initial cross-sectional evaluation, the sweat chloride levels were significantly higher in CFSPID→CF subjects than in CFSPID→CFSPID subjects (mean ± SD: 43.1 ± 8.3 vs. 28.7 ± 11.5 mmol/L; $P = .0005$). However, unlike the cohort by Groves et al,[3] our CFSPID cohort included children with 2 CF transmembrane conductance regulator mutations and

normal sweat chloride levels ($n = 39$). When we only compared CFSPID→CF and CFSPID→CFSPID subjects with intermediate sweat chloride values, there were no differences in levels between the 2 groups (43.1 ± 8.3 vs 39.0 ± 6.6 mmol/L; $P = .13$). Furthermore, there was no significant increased risk of developing CF among CFSPID subjects, with initial intermediate sweat chloride values based on initial sweat chloride concentrations of 30 to 39 mmol/L versus 40 to 59 mmol/L (odds ratio: 0.62 [95% confidence interval: 0.14–2.8]; $P = .71$). These findings highlight the importance of repeat sweat testing rather than predicting the risk of future CF, on an individual basis, according to an initial or single sweat test result.

In our study, 11% (9 of 82) of subjects with CFSPID were subsequently diagnosed with CF,[2] whereas Groves et al[3] reported 48% (14 of 29) of their subjects who were later diagnosed with CF. There may be several reasons for this large discrepancy. The study by Groves et al extended over at least 15 years while ours followed up subjects for only 3 years. Furthermore, we conducted a prospective study because a retrospective study can be associated with the risk of ascertainment and differential selection biases. Finally, because the diagnosis of CF can be challenging,[4,5] we adhered strictly to the diagnostic criteria to allow comparisons between different studies and centers. Only 6 (20.1%) of 29 patients had a CF diagnosis based on elevated sweat chloride levels ($n = 3$) and 2 CF-causing mutations ($n = 3$) in the cohort described by Groves et al, which more closely matches our finding in our CFSPID cohort.[2]

Groves et al[4] also commented on our previous publication in older children and adults with a CF-like phenotype. Both our prospective studies[2,4] highlight 2 different populations of individuals who pose diagnostic challenges in CF; the former being asymptomatic infants with positive newborn screening but inconclusive diagnosis of CF[2] and the latter related to symptomatic individuals who present later in life with a single-organ manifestation of CF.[4] It is currently unknown whether the 2 cohorts represent the same population at different time points. A prospective follow-up study into adulthood of infants with CFSPID will ultimately be necessary to determine their natural history and to determine to what extent they overlap with individuals who present with single-organ manifestations of CF later in life.

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