

A Simple Screening Test for Cystic Fibrosis?

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Cystic Fibrosis (CF) is one of the commonest life-shortening autosomal recessive diseases in Caucasian populations, caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Aggressive treatment of lower respiratory tract infections and nutritional support are the cornerstones of management, and are required lifelong following diagnosis. The therapeutic landscape is being transformed by treatments that target the underlying molecular defect in CFTR; however, these remain prohibitively expensive for many healthcare organizations and patients worldwide.

CFTR has many actions, and in the airways, it plays a crucial role in regulation of chloride ion transport across epithelial cells. Dysfunctional or absent CFTR results in altered airway hydration and impaired mucociliary clearance, with inflammation and chronic infection leading to progressive lung disease. As a marker of CFTR function, measurement of chloride concentration in sweat is of pivotal importance in diagnosing CF. The sweat test, first described in 1959 [1], remains the gold standard for diagnosis, and international recommendations state that diagnoses associated with *CFTR* mutations be established by evaluation of regulator function with a sweat chloride test [2].

In the UK, the incidence of CF is around 1:2500 live births, and average life expectancy is 47 years with a median age at death of 31 years [3]. Across the globe, many countries with a relatively high prevalence of CF (Europe, North America and Australasia) have population-wide CF screening programs for asymptomatic newborn infants. Despite a lower carrier frequency, CF is increasingly recognized in people from the Indian subcontinent, and is likely to be both under-recognized and underdiagnosed.

In this issue of *Indian Pediatrics*, Singh and colleagues [4] publish results of a single center study evaluating ‘aquagenic wrinkling’ as a screening test for CF. The terminology used is important. Wrinkling of the palms after water immersion is a normal physiological

response, occurring in health after an average of 11.5 minutes [5]. In contrast, aquagenic wrinkling of the palms (AWP) is a rare dermatosis characterized by rapid excessive skin wrinkling and white papules on the palms within three minutes of immersion in water. The majority of case reports for AWP in the literature are from European populations; however, it has also been reported in India [6]. It is known to be associated with CF (in children and adults), and CF carriers [7,8]. Authors of this study [4] suggest that immersion of the hands in water to test for ‘aquagenic wrinkling’ could be used as part of the diagnostic work-up in children with symptoms consistent with CF, as a positive test results in a higher likelihood of confirming a diagnosis of CF on a subsequent sweat test.

It was back in 1974 that Elliot first suggested that “three minutes and a bowl of water might provide a cheap screening test” for CF [9]. In the literature, the proportion of patients with CF with AWP is reported to be between 41% and 84% [8,10,11]. Singh, *et al.* [4] report a prevalence of aquagenic wrinkling of 81% within 3 minutes and 95% within 5 minutes. Gild, *et al.* [7] found that AWP occurs in around 25% CF carriers. Unexpectedly, Singh, *et al.* [4] found that time to skin wrinkling in carriers was longer than in controls. The inclusion of carriers in the study by Singh, *et al.* [4] introduces a number of variables that make it difficult to compare results between groups. As presumed heterozygotes for *CFTR*, the pragmatic carrier group was made up of parents of the children with CF, who were therefore significantly older (median age 36 vs 9 years) aside from any additional variation introduced by an absence of mutation analysis. Further investigation of confirmed pediatric CF carriers in India will be crucial to understanding these results. In addition, the results in controls reported by Singh, *et al.* [4] (56% specificity for aquagenic wrinkling by 3 minutes) greatly contrasts with existing literature where time to skin wrinkling in controls is significantly longer, and Arkin, *et al* [8] reported 0% prevalence of AWP in 25 pediatric controls. The influence of ethnicity on time to skin wrinkling in controls is unknown. Non-CF causes of AWP should also be

considered; it has been reported to occur with marasmus in infants [9], an important differential in India as despite decreasing prevalence, it remains more common than CF.

The possibility of a minimal cost ‘screening test’ that can be performed outside the specialist setting is attractive, particularly as sweat testing requires technical expertise and is performed only in a few centers across India. However, the relatively poor sensitivity and specificity reported in this study preclude the use of AWP for whole population CF screening. Alternatively, there may be a role for the test to assist diagnosis in symptomatic children. Should a simple ‘three minutes and a bowl of water’ test be used to improve estimates of the likelihood of a CF diagnosis in symptomatic patients lacking access to sweat testing and *CFTR* mutation analysis? Should it be used to ‘triage’ referrals to specialist centers (whereby patients with a positive test are referred for sweat testing and those with symptoms but no AWP are not)? A negative result must not preclude referral for sweat testing in those with symptomatology consistent with CF, as some of these children will have CF. Children with recurrent respiratory tract infections and failure to thrive are at risk of long-term illness and require close follow-up, even if they don’t have CF. The availability of resources will likely dictate response – in an ideal world, all children with clinical suspicion of CF would have a sweat test. However, given that this situation is some way off, wrinkling test represents an extremely simple method of aiding clinical decision making when CF is considered clinically likely, and yet referral for sweat test is complicated by geographical, financial or accessibility constraints. However, for accurate diagnosis and treatment, and to improve population-wide data on the number of patients with CF in any country, the goal must remain for definitive diagnostic testing.

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