Diagnosing cystic fibrosis: what are we sweating about?

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Over the last few decades, the paradigm has shifted as cystic fibrosis (CF) is no longer a fatal disease of childhood and should be considered a chronic condition where survival into adulthood is expected. Median survival for current newborns is predicted to be at least 50 years and over 55% of patients in the UK are adults.1 Over these decades, our knowledge of the underlying pathophysiology has grown exponentially, from its original description in 1938 to the identification of the mutated gene (cystic fibrosis transmembrane conductance regulator, CFTR) in 1989.2 This has driven the development of effective therapies and brought about an increased understanding of the wide spectrum of diseases that result from abnormal CFTR function. During this time, the humble sweat test has remained at the heart of the diagnostic algorithm, with only modest changes from the original pilocarpine iontophoresis technique first described by Gibson and Cooke over half a century ago.3 Abnormal sweat electrolytes result from dysfunctional or absent CFTR protein in the epithelial cells of sweat glands.4 CFTR is widely distributed throughout the body and has many functions, such as encoding a CAMP-activated chloride channel and regulating transepithelial ion movement—a phenomenon identified by the measurement of potential difference across the nasal mucosa and later used as the basis of the nasal potential difference (NPD) diagnostic test.5 6

With the identification of the mutated gene and extensive knowledge of the associated basic defect, why is there still such a debate about the criteria for diagnosis and why do different diagnostic algorithms exist? When is CF atypical or non-classic and why introduce yet more algorithms exist? Despite CF being a monogenetic disease, molecular (genetic) testing is not always definitive, as failure to identify two CFTR mutations does not rule out the diagnosis. Over 1900 mutations have been identified thus far and the number is continuing to rise.16 First-line genotyping identifies the most common alleles in a given population (usually 29–50 mutations, which account for 85–90% of mutations), and whole CFTR scanning can be performed but this is expensive, time consuming and, with a detection rate of approximately 95%, some patients will still be missed. This is complicated further by a limited understanding of the functional and clinical implications of very rare mutations and the impact of other genetic variations, such as single nucleotide polymorphisms. For this reason, after first-line genotyping, the American guidelines recommend only testing for the 25 mutations recognised as ‘disease-causing’ by the American College of Medical Genetics compared with the European guidelines, which recommend sequencing the whole gene and classifying patients according to the number of CFTR mutations identified. The latter approach will help us to better understand the relationship between genotype, phenotype and CFTR function, but, interestingly, in the study by Ooi et al, extended genotyping failed to improve the diagnostic yield by the American algorithm. An ambitious project is currently under way with the aim of fully categorising all CF mutations to enrich our understanding of the link between genotype and phenotype.17

Another important difference between the American and European guidelines is the thresholds for sweat chloride concentration. Both recognise that CF is very likely for a sweat chloride value >60 mmol/l, but the equivocal range is wider in the European algorithm (30–60 vs 40–60 mmol/l for patients older than 6 months)—recognition of a small but important cohort with low sweat chloride

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values and two disease-causing mutations (eg, compound heterozygote 3849+10 kb C→T). The American guidelines argue that this introduces too many false positives, as the upper limit of sweat chloride concentration in healthy controls has been determined as 59.5 mmol/l. The role of other physiological tests of CFTR function, such as NPD measurement, has been strongly debated for years. NPD is not fully incorporated into the American algorithm as it is regarded as an ancillary test, in contrast to the European algorithm, where it is an integral component used to provide definite evidence in uncertain cases. This discrepancy is justified in the American guidelines by the lack of clear reference values, validation studies and standardised technical protocols for NPD measurements. While diagnostic overlap and uncertainty can still occur with NPD, it has an important role in delineating the extent of CFTR function, thus moving individuals from one diagnostic classification to another, for example, CFTR-related disorder to ‘CF’ or ‘unlikely CF’ (17% of the total group in the study by Ooi et al were reclassified when NPD was introduced into the American algorithm). This is important because patients with an equivocal sweat chloride concentration with or without an abnormal NPD have been shown to differ phenotypically.

Where does this leave the term CF-related disorders? The study by Ooi et al may be reassuring in the fact that concordance between the American and European guidelines was good to excellent with an overall agreement of 84.8%, but differences were identified due to the lower limit of sweat chloride concentration and interpretations of genotypes. Importantly, NPD may not have improved concordance, but it did significantly shift individuals into different diagnostic classifications. A label of CFTR-related disorder goes some way to reduce the negative implications for individuals and their relatives of receiving the ‘full’ CF diagnosis (eg, psychological, reproductive, social, employment and insurance). However, as disease progression may still occur and prognostication is fraught with difficulty throughout the CF spectrum, confirmation of either diagnosis (CF or CFTR-related disorder) provides a framework by which to deliver specific care to ensure appropriate long-term surveillance and timely therapeutic interventions if necessary.

In spite of the issues discussed, it is important to recognise that for the majority of patients confirming the diagnosis of CF is straightforward, as they will fit the classic description of one or more phenotypic features with a sweat chloride value >60 mmol/l and/or two CFTR mutations. Guidelines provide a structured, systematic and evidenced-based framework, but with this uncertainty may still exist, especially as our understanding of a complex disease like CF is evolving. Even now, some patients do not fit securely into a CF diagnostic category (they are termed ‘inconclusive’ by European guidelines)—these patients may still be at risk of future complications and, therefore, should be followed-up carefully in the long term, at least until better diagnostic and prognostic biomarkers are identified. We agree with the concluding comment by Ooi et al, that the diagnostic algorithms should be regarded as guidelines, not dogma. It is vital we continue to characterise the disease throughout its spectrum to fully understand the interactions between mutated CFTR, its dysfunctional protein and the downstream clinical manifestations. With this we can furnish our knowledge, ameliorate uncertainty and work towards a robust unified diagnostic algorithm.

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Reference


2 of 3


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