Diagnosing cystic fibrosis in patients with non-diagnostic results: the case for intestinal current measurements

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Cystic fibrosis (CF) is a well-described genetic disease with characteristic defects in ion transport in disease-affected tissues. CF results from dysfunction of the cystic fibrosis transmembrane conductance regulator protein (CFTR) which is an ATP binding cassette protein that, in addition to chloride channel function, regulates other ion transport pathways such as sodium channels, other chloride channels and bicarbonate transport.1 Diagnosis of CF is generally straightforward in patients with classic disease and builds upon these basic ion transport features, with well-defined clinical manifestations combined with elevated sweat chloride values, nasal ion transport abnormalities and/or common CFTR mutations.2

Newborn screening algorithms have added elevated serum immunoreactive trypsinogen levels to the diagnostic pathway (typically prior to symptoms), and together allow healthcare providers to confidently provide diagnostic and prognostic information to the majority of families and patients with CF.3 Unfortunately, there is a spectrum of disorders that have been linked to CFTR dysfunction which may not fulfill the diagnostic criteria for CF. In general, these milder manifestations of CFTR dysfunction can present in numerous ways such as recurrent upper and lower airway respiratory symptoms, pancreatic disease, male infertility, liver disease and vague gastrointestinal symptoms.3–5 Standard CF diagnostic testing may provide information that is conflicting or sits squarely in the ‘grey zone’, with intermediate sweat chloride values (above the normal range but below the CF diagnostic cut-off), nasal potential difference measurements with both CF and non-CF features, inconclusive genetic testing and additional (less specific) clinical measurements that may support a CF diagnosis but are not able to define the disease (such as abnormal stool elastase measurements, intermittent detection of CF respiratory pathogens or evidence of obstructive airway disease but without clearcut bronchiectasis). These patients are difficult to counsel and care for, as the absence of a clear diagnosis can undermine adherence to treatments and long-term prognostic information is insufficient. Carrying an erroneous CF diagnosis can have detrimental emotional, financial and quality of life implications for the patient and family, while failing to secure a diagnosis of CF puts patients at risk of permanent organ damage and premature death. Thus, for these diagnostic dilemmas, there remains a need to isolate and define CFTR function (or dysfunction) in patient-derived tissue. All available clinical tests of CFTR function are performed in vivo, which limits the available reagents and assays to those that can be performed safely in patients.

In this issue of Thorax, Derichs and colleagues6 describe the use of intestinal current measurements (ICM) to diagnose CF, examining this assay in subjects with classic pancreatic-insufficient CF, pancreatic-sufficient CF, non-CF participants and

patients presenting with an unclear CF diagnosis (see page 594). The use of biopsied tissue from the distal rectum to examine CFTR and supplement CF diagnostic testing has many advantages, including access to high levels of CFTR expression in ‘undamaged’ epithelia, the ability to isolate CFTR in living (patient-specific) tissue, the use of CFTR reagents ex vivo that are not suitable for in vivo testing, the ability to perform testing in very young patients (even in the newborn period) and the potential to define other features of CFTR expression that may contribute to reduced CFTR function (such as quantification of mRNA and protein levels and CFTR maturation). The authors’ institution serves as a centralised referral area for evaluation of patients with an unclear diagnosis, allowing for the development of standardised testing methodology and diagnostic criteria.

So how is ICM performed? Tiny bits of rectal epithelia (typically 2–3 mm in diameter) are obtained via suction biopsy apparatus from the rectal vault (~5 cm from the anal verge). This biopsy procedure is a commonly used method to evaluate gastrointestinal pathology in the neonatal period (such as obtaining tissue to diagnose Hirschsprung’s disease). The procedure, while perhaps a bit uncomfortable (as one might expect from a rectal examination), does not produce biopsy-related pain as the rectal tissue is devoid of pain fibres. Obtaining tissue is rapid (<5 min) and typically does not require sedation. The rectal tissues are mounted in Ussing chambers (which allow measurement of ion conductance in the still living tissue) and are then exposed to carbachol and histamine) that segregate the known CF from the non-CF groups, and that applying these CF diagnostic ICM criteria to the large group of ‘unclear’ patients (n=61) helped to classify ~10% in the CF range and 90% out of the CF range. They also demonstrated moderate correlations of ICM values with sweat chloride values in the CF groups, providing further validation of the assay for CF diagnostic testing. While there are some limitations to the study, such as relatively small numbers of pancreatic-sufficient CF patients in the sample, a continuing subpopulation of subjects with borderline sweat and/or ICM data and lack of long-term follow-up clinical information, the study is an important step in defining the utility of ICM in the diagnostic algorithm for challenging ‘CF-like’ cases. It does confirm that the assay can isolate CFTR function for use in CF diagnostic testing, and it opens the door to using exciting new CFTR modulators to better define CF disease in a patient-specific ‘personalised medicine’ fashion.

While ICM is likely to remain a research tool and a diagnostic assay in a limited number of CF care and research centres (due to the technical expertise needed to work with these small pieces of tissue, the limited timeframe of tissue viability and the specialised equipment needed for ICM), its role in defining CFTR-related disease should continue to grow. We as a research community need to continue to work towards common ICM methodology across centres (allowing us ‘to compare apples with apples’) and to collect clinical data in these borderline patients with specialised functional testing of CFTR to define how ICM results (or other specialised tests such as nasal potential difference) change over time and whether they predict long-term clinical outcomes. We also need to think about CFTR gastrointestinal outcome measures as novel biomarkers, with potential utility in the therapeutic development of future CFTR modulators. ICM can be of clear clinical benefit today and has the potential to help shape CF care tomorrow.

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