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Original Article

Real life practice of sweat testing in Europe

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Abstract

Evidence based guidelines exist for sweat testing, which remains a key component of a diagnosis of cystic fibrosis (CF), especially following newborn bloodspot screening (NBS). There are emerging challenges with respect to maintaining a valid sweat test service, notably a smaller number of sweat tests ordered in regions with established NBS programmes where Pediatricians refer less children for sweat testing, younger patients and equipment becoming obsolete. The ECFS Diagnostic Network Working Group has undertaken a comprehensive survey to better define sweat test practice across Europe. The survey was completed by 136 European respondents representing a CF center or laboratory providing a sweat test service (65% from regions with NBS for CF). There was considerable variance in practice, often not consistent with guidelines. In particular collection of sweat from two sites was rarely reported in European centres in contrast to US guidelines. There was a range of different references quoted for cut-off for both a positive and intermediate test. Most responses suggest cost is becoming an increasing issue and is not sufficiently reimbursed. This work will inform best practice guidelines and resources to sustain and improve sweat testing in Europe.

1. Introduction

The diagnosis of cystic fibrosis (CF) is made with one of the following presentations: characteristic clinical features, a family history of CF or a positive antenatal or newborn bloodspot CF screening (NBS) result. Confirmatory diagnostic tests are required and these should always include a sweat test, even when two CF causing mutations are identified of the Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*) gene [1–2]. Recent international consensus guidelines reduced the upper cut-off value for a normal sweat chloride to 30 mmol/L for all ages [1].

The sweat test requires experienced staff who can follow standard operating procedures. There are clear national and international guidelines available for laboratories providing a sweat test service [3–6]. For most people with CF the diagnosis is straightforward and the sweat test demonstrates the characteristically raised salt levels in the sweat (chloride being the most repeatable and reliable diagnostic measure) [7]. For some patients the diagnosis is less clear and in these cases, the sweat test result is important in guiding designation and management [8–10]. Moreover, recently published guidelines have changed the borderline cut-off chloride values to 30 mmol/L

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for all ages [1]. The sweat test also has a key role in the exclusion of a diagnosis of CF, given the extensive number of recognised *CFTR* mutations and the possibility of detecting new *CFTR* mutations. As such, sweat testing is a critical element of the follow-up of a positive newborn screening result, irrespective of the screening algorithm employed [11].

Providing a sweat test service has become increasingly challenging, particularly in regions that undertake NBS for CF. In these regions referrals for sweat testing are decreasing and those referred after NBS are by definition younger than 3 months of age [12]. In addition, equipment that has been used by many laboratories for decades is now becoming obsolete and commercially available systems have cost and training implications.

Results from different national CF registries in Europe demonstrate the significant number of patients with CF, who have either missing sweat test documentation or misdiagnosis of CF as a result of inadequate performance and false interpretation of sweat test [13–14]. Surveys conducted at national level have shown that monitoring the performance of laboratories and CF centres together with quality improvement initiatives improves the performance of sweat testing [15–17].

The aim of this project was to record current sweat test practice among Europe, to inform the requirements and contents of a future best practice document.

2. Methods

The questionnaire for the survey was developed by a core group of experts, referring to international guidelines and tested by another panel of experts (from the European CF Society (ECFS) Diagnostic Network and Neonatal Screening Working Groups). The questionnaire comprised 66 items covering six areas; 1) CF centre/laboratory details, 2) information provided to patient/parent/carers, 3) the method of sweat stimulation, 4) the method of sweat collection, 5) sweat analysis and 6) processing of the result. The questionnaire was in English, web-based and open from 15th October to 15th December 2015 to ECFS members, Cystic Fibrosis Europe members, national CF scientific societies and national sweat test working groups. Information on the project was disseminated several times and a help desk was established to assist participants, in particular with language issues. For three questions, there was overlap of potential responses, but respondents did not comment on this design error and the results were considered valid, as the questions were enquiring about approximate numbers (Table S1).

CF centres and laboratories were asked to send a scanned anonymised copy of their sweat test report sheet and the information leaflet (if available) for patients/parent/carers. Although informative responses were obtained from all over the globe (n = 143), only results from Europe (and Israel) were included in the analysis (n = 136). For the four countries with the highest number of respondents, the results were compared as a proportion of responses from each country (France, Germany, Italy and the United Kingdom). (Table 1).

3. Results

The survey was completed by 136 European sites across 29 countries (Fig. 1). For 127, the response jointly represented a CF centre and sweat test laboratory, for 8 a CF centre only and one respondent a laboratory only. The full questionnaire with responses is available (online Supplement Table S1) and the main findings are reported in this paper.

3.1. Institution and staff involved in test

Respondents represented CF centres of variable size and laboratories. The sweat test service was provided in a region with NBS for CF in the majority of respondents (65%). Sweat stimulation and collection was undertaken by laboratory technicians (49%), nurses (45%) and physiotherapist, physician, biologist and other laboratory staff (6%), most in a permanent employment (90%). Most respondents (72%) had considerable experience (>100 tests/year), although 42% reported undertaking <25 sweat tests pa/annum on infants with a positive NBS result. Nineteen percent indicated the cost of a sweat test (including staff) was less 20 Euros, for 30% between €20 and 50, for 26%

Table 1
Comparison of selected data from most represented countries (sites/country n=: France, 19; Germany, 25; Italy, 15; United Kingdom, 22).

Proportion of centres that:	France (%)	Germany (%)	Italy (%)	United Kingdom (%)
Are certified	100	88	80	86
Perform >100 tests per year	58	96	93	36
Have dedicated staff performing >30% of the total tests/year	53	72	87	68
Sweat test newborn screened babies	95	48	80	73
Report costs (including staff) <20 Euros	26	4	13	5
Receive reimbursement <20 Euros	58	56	67	5
Undertake bilateral testing	37	0	40	9
Use Wescor sweat inducer to stimulate sweat production	37	60	80	73
Collect sweat using a macroduct coil	37	84	13	82
Have a quantity not sufficient rate <5% in all ages	68	56	47	41
Have a quantity not sufficient rate <5% for infants <1 month of age	37	32	40	41
Use internal quality control as recommended	84	64	67	86
Participate in an external quality assurance scheme	74	24	44	46
Use <30 mmol/L as lower cut-off for normal sweat chloride	47	84	20	9
Use >60 mmol/L as the cut-off for a positive sweat chloride result	74	64	87	96

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