ICMH Journal 2020; 11(1): 27–30

Review Article

The Role of Sweat Chloride Test in the Diagnosis of Cystic Fibrosis

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Abstract

The sweat chloride test (ST) is the gold standard for cystic fibrosis (CF) diagnosis in symptomatic patients. It is also used for evaluating infants with positive CF in newborn screening and the follow-up of CF patients during molecular therapies. This review aimed to examine the role of the sweat test in diagnosing CF.

Keywords:*Sweat chloride test, Cystic fibrosis.*

Introduction

The sweat chloride test (ST), a quantitative measurement of electrolytes in sweat, remains a crucial investigation in supporting the diagnosis of CF. A significant turning point in the diagnosis of CF occurred in 1959 with the introduction of the Gibson and Cooke sweat test. Since then, the primary CF diagnostic test has been the determination of sweat electrolytes by pilocarpine iontophoresis.[1]

Cystic Fibrosis (CF), a rare genetic disorder that affects numerous systems and eventually results in a progressive, potentially fatal lung disease, has been identified as the most prevalent hereditary fatal illness among the White population of Northern European heritage. Other populations, such as African Americans, Hispanics, and Asians are also affected by this autosomal recessive condition.[2]

The discovery of the CF gene initiated a greater understanding of the molecular processes causing CF and provided a new method of diagnosis. This gene is called the cystic fibrosis transmembraneconductance regulator (CFTR)gene.[3]

As routine screening tests cannot detect all CFTR gene mutations, a negative screening test does not ensure a normal CFTR genotype. Genotyping has also confirmed that some CF mutations are associated with milder disease phenotypes as well as a normal or borderline abnormal concentration of sweat electrolytes.[4] The sweat test is a reliable test for the diagnosis of CF in approximately 98% of patients with CF.[4]

Since the discovery of the CF gene in 1989, which codes for the protein cystic fibrosis transmembrane conductance regulator (CFTR) protein, there have been reports of more than 2000 mutations in the CF gene. The cystic fibrosis transmembrane regulator is at the apical surface of the epithelial cells in the airways, gastrointestinal tract, pancreas, genitourinary system, and sweat glands in the skin. The defective, deficient, or absent CFTR function results in abnormal chloride transport across the chloride channels and abnormal sodium transport, along with the secondary effect on water movement across the cell membrane. Decreased chloride secretion along with increased sodium reabsorption (along with water as a secondary effect) across the apical surface of the epithelial cells results in increased viscosity of secretions in the organs involved and inthe case of

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skin, elevated levels of chloride in the sweat. Detection of elevated values of sweat chloride, in a suspected patient, by quantitative pilocarpine iontophoresis test (QPIT) is considered to be the gold standard for the diagnosis of cystic fibrosis.[2]

There is a widespread misconception that CF does not exist in the Indo-Bangladesh peninsula since the disease is rarely suspected and even when it does, the diagnosis is not always made because of inadequate diagnostic facilities like ours.[5]According to a most recent KAP(Knowledge Attitude & Practice) study observation, it is plausible to assume that doctors miss CF cases because of knowledge gaps.[6] Kabra et al.[7] anticipate that it is frequently delayed by parents' failure to seek medical advice in a timely manner due to a lower suspicion index.

CF is the most common lethal genetic disease affecting Caucasians, with an incidence of 1 in 2500.[8] The inheritance isautosomal recessive.[8] CF affects the epithelial cells of several organs, including the respiratory tract, exocrine pancreas, intestine, vas deferens, hepatobiliary system, and the exocrine sweat gland. This results in multi-organ disease, characterized by suppurative lung disease, pancreatic insufficiency, multifocal biliary cirrhosis, male infertility, and high sweat electrolyte loss.[9]

The airway surface fluid is thought tobecome hypertonic with reduced depth of the periciliary fluid. Airway mucus is poorly hydrated, which in conjunction with the changes in airway surface fluid, impedes mucociliary clearance. This causes obstruction of small airways and promotes airway infection. Recurrent infections and the resulting inflammation leads to submucosal gland hypertrophy, excessive mucus secretion, and airway damage.[10] In early life, CF patients become infected with a limited spectrum of bacteria (most commonly Staphylococcus aureus and non-typable Haemophilus influenzae), and as the disease progresses, Pseudomonas aeruginosa becomes the most common pathogen.[10]

The diagnosis of CF has been well-reviewed by the US CF Foundation consensus panel.[11] Clinical features, CFTR gene mutations, measures of CFTR function (principally sweat electrolytes, but also nasal potential difference) and newborn screening results.

Nasal Potential Difference: The impairedion transport of CF respiratory epithelia can be studied in vivo by measuring the potential difference (NPD) in the nasal mucosa, which is a significantly more complex test of CFTR function than the measurement of sweat electrolytes.[12]

A consensus statement: the diagnostic criteria for CF

The diagnosis of CF will be suggested in individuals with:

1. One or more characteristic phenotypic features
   – or a history of CF in a sibling
   – or a positive New born Screening (NBS) result
2. Laboratory evidence of CFTR dysfunction
   – Two abnormal quantitative pilocarpine iontophoresis sweat chloride concentrations
   – Presence of two disease-causing mutations in the CFTR
   – Demonstration of abnormal NPD

Sweat collection for the sweat test

It is recommended that ST be conducted by a qualified technician in a facility with accreditation. The ST is typically performed on the patient's arm or leg. The test begins with the iontophoresis of pilocarpine, a parasympathomimetic alkaloid that stimulates sweat gland production by acting on cholinergic receptors by imitating acetylcholine. It is advised to collect two samples at once due to the test's unpredictability and insufficient sample risk.[13]

The original Gibson and Cooke method for doing iontophoresis involved inserting two electrodes on the patient's arm or leg, covering one with gauze soaked in pilocarpine and the other with gauze soaked in deionized water. Then, for 5 minutes, a maximum of 1.5 mA electric current is applied to promote sweat production. There is no discomfort or agony associated with the electrical stimulation. Sweat is collected for up to 30 minutes. The gauze or filter paper application area must be 2 inches by 2 inches. After that, the filter paper is put in a lab dish with a known weight so that the amount of sweat collected can be quantified. The minimum quantity required for a sweat test is 75 mg.[13]

The WescorMacroduct sweat collection system was developed in 1983.[14] Compared to the standard QIPT, this method was simpler to use and required only 15 ml of sweat. Pilocarpine-containing gel discs are used, and an iontophoretic current running through them induces sweating. The iontophoretic current source must be battery-powered for safety's sake.

Indications of the sweat test

Indications for the sweat test include individuals suspected of having cystic fibrosis, either through a positive newborn screening test or clinically. CF genotyping is recommended when the sweat test results are borderline, or the sweat test is not technically possible (e.g., severe eczema) and to help decide CF

mutation-specific therapy. The CFF recommends CF genotyping in all patients.[2]

Sweat chloride (S.Cl) levels: Interpretation

- Less than 30 mmol/L: CF is unlikely
- 30 to 59 mmol/L: CF is possible; further testing may be required
- Sixty or greater mmol/L: diagnostic of CF.

For patients with intermediate sweat chloride levels (30 to 60 mmol/L), genetic testing may help to confirm or exclude the diagnosis. In patients with two CF-causing mutations on separate chromosomes, no further diagnostic testing is necessary, i.e., CF confirmed.[2]

Fig 1: Iontophoresis and sweat collection by Gibson-Cooke method

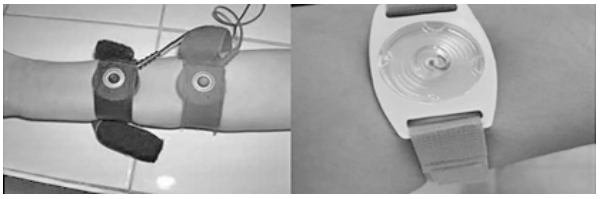

Fig 2: Iontophoresis and sweat collection by Macroduct System.

Interfering Factors

False positives STis less likely, but sweat chloride may elevate falsely in other pathologic syndromes and situations, including:

- Improper testing technique
- Atopic dermatitis
- Untreated adrenal insufficiency
- Glycogen storage disease
- Panhypopituitarism
- Hereditary nephrogenic diabetes insipidus
- Hypothyroidism
- Pancreatitis
- Malnutrition
- Mucopolysaccharidosis
- Ectodermal dysplasia
- Prostaglandin E1 infusion

Newborns may not produce enough sweat and may need to wait until later in infancy before an adequate sweat quantity can be collected. Infants with a positive newborn screen can undergo testing as early as two days of life. However, the Cystic Fibrosis Foundation recommends waiting until the child is ten days old. For premature infants, testing should wait until they are two kilograms in size and greater than 36 weeks of corrected gestational age, if possible.[15,16]

Conclusion

Currently, both the Gibson and Cooke QPIT and the Macroduct® systems are recommended for sweat collection in CF diagnosis. The electrical stimulation is painless and does not cause discomfort and may be functioning by battery powered. After a positive result, either a second testisdone, or genetic testing is performed to confirm the diagnosis. Testing should only be performed at CFF-accredited cystic fibrosis centers.

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