THE PATHCARE NEWS

CYSTIC FIBROSIS (CF) TESTING UPDATE

1. THE SWEAT TEST

The sweat test is considered the "gold standard" for the diagnosis of the classical form of CF. The diagnosis of CF is confirmed by two or more positive sweat test results on separate occasions in a patient with suggestive clinical features. CF is associated with an increased amount of sodium and chloride in sweat - usually more than 60 mmol/L.

Test limitations:

- **Pre-analytical factors** such as dehydration or inadequate sweat weight may affect test results.
- A number of patients may have chloride levels within t**he "grey area"**.
- **Poor test reproducibility** may be related to certain physiological variations (patient's diet, temperature, and other factors at present unrecognized). Not all patients with compatible clinical features have a raised sweat chloride and some individuals with a raised sweat chloride have no clinical features of CF.
- Sweat testing cannot be performed accurately in the first two days after birth, and it may be difficult to obtain an **adequate sweat sample** during the first two to three weeks after birth, especially for premature babies.
- **Where sweat testing is not available, the faecal elastase test can be used to demonstrate pancreatic insufficiency (PI).** Interpretation is as follows: Normal exocrine pancreatic function: > 200 ug/g faeces; slight to moderate pancreatic insufficiency: 100 - 200 ug/g faeces; severe exocrine pancreatic insufficiency : < 100 ug/g faeces

2. SWEAT CONDUCTIVITY TESTS (NANODUCT®)

Nanoduct® testing is generally more readily available but current international guidelines recommend Nanoduct® testing only as a screening test which should be followed by a traditional sweat test. Interpretation as follows:

Normal: < 50 (mmol/L eq NaCl)

Intermediate: 51 - 80 (mmol/L eq NaCl)

Positive screen for cystic fibrosis: > 80 (mmol/L eq NaCl)

Patients with conductivity measurements > 50 mmol/L eq NaCl should be followed up by a quantitative sweat chloride measurement.

3. PCR TESTING FOR CF-RELATED MUTATIONS

Indications:

- Patients with chloride levels in the **"grey area"**.
- CF **carrier testing**, as well as **prenatal diagnosis**.
- Couples in **consanguineous unions**.

All CF patients should have their blood examined to identify their CF-causing mutations.

The identification of two identical mutations in a patient confirms the diagnosis of CF. **If the patient does not have two recognized CFTR mutations, a third sweat test should be performed a year or so later.**

The CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) gene is located on the long arm of chromosome

number 7. More than 1800 mutations have been identified. In South Africa significant differences in the CFTR mutation are found between population groups. The commonest mutation in the **white population is ΔF508**. In the coloured population, the **Δ F508 and 3120+1G→A mutations account for 74% of mutations. Among blacks, the 3120+1G→A is the most common mutation.**

PathCare routinely tests for the Delta F508 mutation in the CFTR gene. The test is performed daily with results available within 24 hours. Should further investigation be required, the laboratory offers a full screen for the CFTR gene using Next Generation Sequencing (NGS). This test is able to detect previously described and novel mutations in this gene. The turnaround time for this test is approximately 4 weeks. **In a small number of patients, the diagnosis of CF cannot be confirmed or excluded by CFTR mutations analysis. In addition, genotype analysis cannot be used to predict prognosis in individual patients with CF. CF-affected individuals and their families must be offered genetic counseling.**

4. PRENATAL DIAGNOSIS

Prenatal diagnosis can be performed using either chorionic villus sampling (CVS) or amniocentesis. Interpretation is enhanced by a detailed family history of known mutations.

5. PRE-IMPLANTATION DIAGNOSIS

Following in vitro fertilization, the developing embryos can be screened at a very early stage for their CF status. Only embryos free of CF are transferred during IVF.

6. BLOOD IMMUNOREACTIVE TRYPSINOGEN (IRT)

This test, also referred to as trypsin-like immunoreactivity, is done on serum to help identify infants at risk of developing CF. Very often these infants have no clear manifestations of the disease. The screening process is not a diagnostic test. Confirmation of the diagnosis is obtained by a positive sweat test at an age of approximately 2 weeks, or a positive CFTR gene mutation screen.

CONCLUSION

The diagnosis of CF is made in individuals with one or more clinical features of CF who have either an elevated sweat chloride concentration on two or more occasions or have CF-causing mutations in the CFTR gene. False positive and false negative sweat tests do occur. An inconclusive CFTR mutation screen does not rule out the diagnosis of CF. IRT is a screening test that must be confirmed.

References

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