Cystic fibrosis

Key facts

- Cystic fibrosis (CF) is an autosomal recessive inherited, multisystem condition that is most commonly associated with early death due to progressive lung disease.
- CF presents most commonly during early childhood, but the extent to which different organ systems are affected varies by individual, with some remaining unaffected until adulthood.
- Early diagnosis, treatment and management improves outcome and quality of life for those affected with CF.
- CF is caused by variants in the *CFTR* (cystic fibrosis transmembrane conductance regulator) gene.
- All newborn babies in the UK are now screened for CF by the newborn blood spot test. This means that the majority (90-95%) of children with CF will now be diagnosed shortly after birth, before symptoms develop.
- CF affects between 1 in 2,000 to 1 in 3,000 newborns of northern European ancestry. It is less common in other ethnic groups.

Clinical features

- The clinical features of CF occur due to the production of abnormally thick mucus from the affected glands. The most common features are:
  - chronic respiratory infections;
  - malabsorption (failure to thrive);
  - prolonged diarrhoea;
  - infertility in males/reduced fertility in females; and
  - meconium ileus in newborns.
- Less common (but still prevalent) features include diabetes and osteoporosis.

Diagnosis

- In the UK, CF is usually diagnosed at birth as part of the national newborn screening programme. As screening will not identify all affected individuals, a sweat test should be undertaken where there is still a clinical suspicion of CF (even if the baby has had newborn screening).
- The sweat test is the standard test for confirming a diagnosis of CF, as people with CF produce more salt in their sweat than unaffected individuals.
- DNA testing can be useful in helping to make the diagnosis, particularly when the result of the sweat test is equivocal. Moreover, a genetic diagnosis is increasingly important for new targeted therapies that have recently become available to patients.

Genetic basis and genetic testing

- CF is an autosomal recessive condition, which means that the affected individual has two variant copies of

the *CFTR* gene. The parents of an affected individual usually only have one variant copy of the *CFTR* gene and so are healthy: they are said to be carriers for CF. Each child of two carriers has a 25% (one-in-four) chance of inheriting both gene alterations and developing CF.

- Between 1 in 22 and 1 in 27 people in the UK are carriers; a previously known family history of CF is uncommon.
- More than 2,000 different variants in the *CFTR* gene have been identified worldwide, often with geographic or ethnic variations in frequency. These are found in CF, and other related phenotypes, named CFTR-related disorders (CFTR-RD).
- CFTR-RD are clinical entities associated with CFTR dysfunction where the diagnosis of CF cannot be unambiguously established; for example, congenital bilateral absence of vas deferens, disseminated bronchiectasis, chronic pancreatitis or chronic rhinosinusitis.
- About 30 relatively common variants account for 85-90% of all alterations, while the others are individually rare. Currently, the most commonly used laboratory tests will detect these 30 common variants. The single most common variant is known as delta-F508 (technically now known as c.1521_1523delCTT: p.Phe508del), which is present in about 90% of those affected by CF in the UK.
- Variant analysis does not always provide prognostic information, but individuals affected by CF who have two copies of the delta-F508 variant usually have pancreatic insufficiency.

Clinical management

- There is currently no cure for CF, however the following treatments are effective:
  - » Physiotherapy and antibiotics, used to prevent and treat chest infections.
  - » Enzyme tablets taken with food and support from a specialist dietitian, to help keep the patient well-nourished and to control digestive symptoms.
  - » Cystic fibrosis modulator therapies, which act on CFTR pathways, can be used in those with specific gene alterations; it is recommended they are prescribed by specialist CF physicians.
- Patients and their parents should be offered genetic testing to look for variants in the *CFTR* gene, and may wish to be seen by a clinical geneticist. Genetic testing may also be appropriate for other family members to determine their carrier status.
- In the UK, children and adults with CF are usually cared for by local doctors, with the help and support of specialist centres with multidisciplinary teams. Referral to specialist centres may become increasingly important to obtain access to new targeted therapies.

Direction to further reading, guidelines and patient groups

- Newborn blood spot screening programme: supporting publications
- Orphanet: Cystic fibrosis
- Cystic Fibrosis Trust
- CFTR2 website

This information is intended for educational use and was current in December 2019. For clinical management, it is recommended that local guidelines and protocols are used.

Produced in collaboration with Birmingham Women's NHS Foundation Trust's Clinical Genetics department and Imperial College Healthcare NHS Trust.