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Dr Christabella Ng
BMedSci (Hons) BM MRCPCH
Clinical Research Fellow in Child Health

Professor Alan R Smyth
MBBS MA MD MRCP FRCPCH
Professor of Child Health

Division of Child Health, Obstetrics and Gynaecology,
University of Nottingham, Nottingham, UK

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AUTHORS
Dr Christabella Ng
BMedSci (Hons) BM MRCPCH
Clinical Research Fellow in Child Health

Professor Alan R Smyth
MBBS MA MD MRCP FRCPCH
Professor of Child Health

Division of Child Health, Obstetrics and Gynaecology, University of Nottingham, Nottingham, UK



FIGURE 1
A young girl with cystic fibrosis performing chest physiotherapy with a positive expiratory pressure mask

How is cystic fibrosis diagnosed in children?

What are the mechanisms involved?

What are the treatment strategies?

CYSTIC FIBROSIS (CF) IS AN AUTOSOMAL RECESSIVE GENETIC DISORDER AFFECTING ABOUT 1 IN 2,500 live births in the UK.[1]

Although all newborns undergo screening for CF, around 15% of infants will present shortly after birth with meconium ileus[2] and some will already have faltering growth when the screening results are available at 3-4 weeks of age. Infants who present with meconium ileus should be treated with a high index of suspicion for CF until proven otherwise. Around 93% of children are diagnosed in the first three months of life and another 5% before the age of 12 months.[2]

CF is a multisystem disease that affects the respiratory and gastrointestinal systems in particular. Respiratory symptoms may be non specific initially including cough and wheeziness, frequent respiratory infections and, in older children, sinusitis. In CF, these symptoms are a consequence of abnormal CF transmembrane conductance regulator (CFTR) function. The CFTR protein regulates ion and water content of epithelial secretions.

Symptoms of malabsorption include meconium ileus, steatorrhoea, faltering growth, distended abdomen and constipation.[3]

Since 2007, CF has been part of the UK newborn blood spot screening programme, with a dried blood spot specimen collected from all infants at 5-7 days of age.[4]

The CF screening test measures immunoreactive trypsin (IRT) levels. The sensitivity of the current IRT protocol is around 97%. If IRT is consistently raised, the same blood sample is tested for the four most common CF gene mutations. If two mutations are found, the baby is identified as 'CF suspected'. If there is only one mutation, an extended panel of up to 31 genes is tested. If a second mutation is not found, the IRT is repeated, with a higher threshold. A result above the threshold is designated 'CF suspected' and a result below the threshold is categorised as 'probable carrier'. The parents of suspected carriers should receive a home visit, from a health professional, within one working day. An information sheet for parents of suspected carriers is available online (see Useful information, p21).

If no mutation is found, a second blood sample may be collected and the IRT repeated. If the IRT remains high, »

the child is identified as 'CF suspected'. If not, the designation is 'CF not suspected'.

Where CF is suspected, the screening centre will notify the CF centre which will arrange immediate care and a confirmatory sweat test.

GENE MUTATIONS

CF is an autosomal recessive disorder caused by mutations affecting chromosome 7, which encodes the CFTR protein.[5] The most common mutation is the codon deletion encoding phenylalanine at position 508 of the CFTR protein, p.Phe508del (F508del). There are currently 312 known disease causing mutations of the CF gene.[6]

Loss of CFTR function in the lungs, impairs the mucociliary escalator leading to accumulation of mucus in the airways and secondary infection. In the gut, pancreatic function is impaired in most children, leading to malabsorption and faltering growth.

The different mutations affect CFTR function in different ways and there are currently six classes of CFTR mutations.[5]

Many new approaches to treating the basic defect are the subject of current or recently completed clinical trials, including: gene replacement (gene therapy) and RNA repair, which are not dependent on mutation class, and read through agents (circumventing the stop codon in class I mutations). Ivacaftor is a CFTR modulating drug. It is approved by specialist commissioning for patients with CF, aged two years and over, who have at least one copy of the G551D mutation or of one of eight other less common mutations.

CONFIRMING DIAGNOSIS

The gold standard as recommended by the European Cystic Fibrosis Society is a sweat test and genetic testing. The three pillars of the diagnosis are:

- Clinical features (or family history or positive newborn screening test) and
- Sweat chloride > 59 mmol/L and/or
- Two CF-causing CFTR mutations[7]

COMMON COMPLICATIONS

Advances in CF treatment have helped improve the survival of patients with CF. However, most children will have malabsorption, requiring pancreatic enzyme replacement therapy (PERT) and a progressive deterioration of respiratory function.

Respiratory

Most infants diagnosed by newborn screening have few symptoms. However, later on children will experience recurrent respiratory infections.

Symptoms may be as subtle as a wet cough but must be treated to avoid progression to bronchiectasis and ultimately respiratory failure.[8] Antibiotic choice should be guided by previous microbiology results and national guidelines.[9] Some of these infections may become chronic unless treated promptly – a particular problem with *Pseudomonas aeruginosa*. Further investigation by the CF centre should take place if a wet cough persists in spite of a two-week course of oral antibiotics or if sputum cultures are repeatedly negative.

'Symptoms may be as subtle as a wet cough but must be treated to avoid progression to bronchiectasis and ultimately respiratory failure'

Allergic bronchopulmonary aspergillosis, another respiratory complication seen in CF, results from a hypersensitivity reaction to *Aspergillus fumigatus* mould which has colonised in the bronchi. The release of IgE and IgG antibodies results in bronchial obstruction through mucus plugging and causes increased cough and haemoptysis.[10] Suspected cases should be discussed with the CF team.

Gastrointestinal

Most children with CF have malabsorption requiring PERT, fat-soluble vitamins and, in some cases, nutritional supplements. Distal intestinal obstruction syndrome is a serious complication that presents with acute abdominal pain and constipation. Viscous fluid in the intestine causes obstruction in the terminal ileum and is a surgical emergency.

By ensuring children are adequately hydrated and have the appropriate laxatives, gut transit time is improved and the risk of distal intestinal obstruction syndrome reduced.[11]

Liver disease results from damage caused by fatty replacement and interstitial fibrosis resulting from inspissated secretions.[12] CF related diabetes (CFRD) becomes prevalent in the teenage years, often presenting with poor weight gain in a young person who had previously been thriving, and one third of adults with CF have CFRD.[2] Treatment is usually with a long-acting insulin formulation and should be commenced by the CF centre.[7]

Other complications include:[13]

- Nasal polyposis and sinusitis
- Reduced bone mineral density
- CF arthropathy
- Renal and hearing complications secondary to aminoglycoside use
- Delayed puberty
- Psychosocial difficulties
- Male infertility
- Reduced female fertility

MANAGEMENT

It is important to manage symptoms of CF and slow down the progression of lung disease, to delay the complications described above.

Most newly diagnosed infants with CF will commence once daily physiotherapy for airway clearance delivered by their parents. As children get older they will increasingly be in charge of their airway clearance. Many use positive expiratory pressure devices that require sustained expiration against resistance, followed by a series of 'huffs' and coughs (see figure 1, p19).[7]

Preventing or attenuating respiratory infections in patients with CF helps slow the progression of lung disease. Young children are vulnerable to respiratory infection with *Staphylococcus aureus* and, in the UK, most receive a prophylactic antibiotic, commonly flucloxacillin, until the age of three years.[9,14]

'Preventing or attenuating respiratory infections in cystic fibrosis patients helps slow the progression of lung disease'

Children may present to primary care with exacerbations of respiratory symptoms (wet cough, sometimes with sputum). Initial management in primary care, prior to consulting with or referring to the CF centre, can help achieve more rapid resolution of symptoms. A sputum sample should be taken. Alternatively, in children who do not produce sputum, hold a sterile swab at the back of the throat and ask the child to cough (cough swab). For children who live

key points

SELECTED BY

Dr Phillip Bland
Former GP, Dalton-in-Furness, UK

Cystic fibrosis (CF) is a multisystem genetic disorder affecting approximately 1 in 2,500 live births in the UK. Although all newborns undergo screening for CF, around 15% of infants will present shortly after birth with meconium ileus and some will already have faltering growth when the screening results are available at 3-4 weeks of age. Infants who present with a meconium ileus should be treated with a high index of suspicion for CF until proven otherwise. Around 93% of children are diagnosed in the first three months of life and another 5% before the age of 12 months.

Mucociliary dysfunction leads to accumulation of mucus in the airways and secondary infection. Respiratory symptoms may be non-specific initially and include cough and wheeziness, frequent respiratory infections and, in older children, sinusitis. Pancreatic function is impaired in most children, and symptoms of malabsorption include meconium ileus, steatorrhoea, faltering growth, distended abdomen and constipation.

Distal intestinal obstruction syndrome is a serious complication that presents with acute abdominal pain and constipation. Liver disease may result from fatty replacement or interstitial fibrosis due to inspissated bile. CF related diabetes becomes prevalent in the teenage years, often presenting with poor weight gain in a young person who had previously been thriving.

Most newly diagnosed infants with CF will commence once daily physiotherapy for airway clearance. At first this is delivered by their parents but as children get older they will increasingly be in charge of their airway clearance. Young children are vulnerable to respiratory infection with *Staphylococcus aureus* and, in the UK, most receive a prophylactic antibiotic, commonly flucloxacillin, until the age of three years. Exacerbations (worsening cough which is wet or associated with sputum) must be treated proactively with antibiotics and increased airway clearance. Children with CF should have antibiotics when a wet cough has been present for more than a week even if there is little to hear on auscultation of the chest. The CF centre should be contacted for advice on the choice of oral antibiotics and whether intravenous antibiotics might be needed. Pancreatic enzyme replacement therapy has been shown to improve fat absorption with concomitant improvement in calorie intake. Supplements of fat-soluble vitamins (A, D, E and K) may also be necessary as these vitamins are poorly absorbed.

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some distance from a CF centre, antibiotics can be prescribed in primary care, following national guidelines[9] or advice from the CF centre. Longer courses, commonly two weeks, of oral antibiotics are required and children should have effective chest physiotherapy. The CF centre should arrange early review to assess the response to treatment.

PERT has been shown to improve fat absorption with concomitant improvement in calorie intake. Children will generally have a daily dose of 10-20 capsules of a PERT formulation (containing 10,000 units of lipase) and so prescriptions should be for larger quantities of PERT to avoid parents running out of this essential medication. Supplements of fat-soluble vitamins (A, D, E and K) may also be necessary as these vitamins are poorly absorbed. [4,15]

MONITORING

Children should be seen regularly by a specialist centre every few months and have a formal detailed annual review. Each clinic review should involve the multidisciplinary team: CF specialist physician, CF nurse, physiotherapist, dietitian, clinical psychologist, social worker and pharmacist.[3] The annual review should assess all systems and identify any areas where symptom and disease control is not optimal and needs to be addressed.

Respiratory function should be monitored with lung function tests and chest imaging. It is also important to monitor sputum cultures to allow early diagnosis of infections with organisms such as *P. aeruginosa* which will require eradication treatment. *P. aeruginosa* eradication requires combined treatment, usually with oral ciprofloxacin and nebulised colistin for periods of between three weeks and three months.[9,16]

‘Parents of a baby newly diagnosed with cystic fibrosis should be offered genetic counselling’

Children should see their GP for regular prescriptions and immunisations, including annual influenza vaccination.

Parents of a baby newly diagnosed with CF should be offered genetic counselling to help with decisions regarding future pregnancies. Testing for older siblings may also be carried out.

Competing interests
Professor Alan Smyth has provided consultancy for Vertex, PTC, Roche and Gilead. He has taken part in clinical trials sponsored by Vertex, Raptor and Insmed. He has also given lectures at meetings sponsored by Gilead, Teva and Vertex. Dr Christabella Ng has no competing interests.

See also Managing complications of cystic fibrosis in adults, p23.

REFERENCES

1 Dodge JA, Morison S, Lewis PA et al. Incidence, population, and survival of cystic fibrosis in the UK, 1968-95. UK Cystic Fibrosis Survey Management Committee. *Arch Dis Child* 1997;77(6):493-96
2 UK Cystic Fibrosis Trust. UK CF Registry. Annual Data Report 2016. Cystic Fibrosis Trust. London. 2017
3 Standards for the clinical care of children and adults with cystic fibrosis in the UK. 2nd edition. Cystic Fibrosis Trust. London. 2011
4 A laboratory guide to newborn screening in the UK for cystic fibrosis (CF). 4th edition: NHS Newborn Blood Spot Screening Programme; 2014 www.gov.uk/topic/population-screening-programmes
5 Boyle MP, De Boeck K. A new era in the treatment of cystic fibrosis: correction of the underlying CFTR defect. *Lancet Respir Med* 2013;1(2):158-63
6 CFTR2 database. www.cftr2.org. [Last accessed 7 November 2018]
7 Castellani C, Duff AJA, Bell SC et al. ECFS best practice guidelines: the 2018 revision. *J Cyst Fibros* 2018;17(2):153-78
8 Sly PD, Gangell CL, Chen L et al. Risk factors for bronchiectasis in children with cystic fibrosis. *N Engl J Med* 2013;368(21):1963-70
9 Antibiotic treatment for cystic fibrosis - Report of the UK Cystic Fibrosis Trust Antibiotic Working Group. Cystic Fibrosis Trust. London. 2009
10 Thia LP, Balfour Lynn IM. Diagnosing allergic bronchopulmonary aspergillosis in children with cystic fibrosis. *Paediatr Respir Rev* 2009;10(1):37-42
11 Green J, Gilchrist FJ, Carroll W. Interventions for preventing distal intestinal obstruction syndrome (DIOS) in cystic fibrosis. *Cochrane Database Syst Rev* 2018:Issue 6. Art. No.: CD012619
12 Debray D, Kelly D, Houwen R et al. Best practice guidance for the diagnosis and management of cystic fibrosis-associated liver disease. *J Cyst Fibros* 2011;10, Supplement 2(0):S29-S36
13 National Institute for Health and Care Excellence. NG78. Cystic fibrosis: diagnosis and management. NICE. London. 2017 www.nice.org.uk/guidance/ng78
14 Smyth AR, Rosenfeld M. Prophylactic anti-staphylococcal antibiotics for cystic fibrosis. *Cochrane Database Syst Rev* 2017:Issue 4. Art no. CD001912
15 Smyth A, Elborn JS. Exacerbations in cystic fibrosis: 3. Management. *Thorax* 2008;63(2):180-84
16 Langton-Hewer SC, Smyth AR. Antibiotic strategies for eradicating Pseudomonas aeruginosa in people with cystic fibrosis. *Cochrane Database Syst Rev* 2017:Issue 4. Art. No.: CD004197

Useful information

Cystic Fibrosis Trust
www.cysticfibrosis.org.uk

Information for parents of suspected carriers
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/701859/NBS_screening_cystic_fibrosis_carrier_final_web_240418.pdf