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Cystic Fibrosis

Miss Mary Dolan

Abstract
Cystic fibrosis, a genetic disease with an autosomal recessive mode of inheritance, was first described in 1936 by Fanconi et al. He described the disease in a paper entitled The Coeliac Syndrome with congenital cystic pancreatic fibromatosis and bronchietasis. Since then the disease has been known by various names such as Cystic Fibrosis of the Pancreas, Mucoviscidoses, fibrosis of the pancreas until it was shortened to Cystic Fibrosis in the 1960s.

Cystic Fibrosis represents the commonest autosomal recessive disorder in Caucasian populations. The mutant gene, recently identified on the long arm of chromosome 7 has a carrier rate equal to 1 in 22 among Caucasians. The overall incidence of the disease in 1 per 2000 live births. However it has a much lower incidence amongst non- Caucasian populations. Amongst the UK population there are 5000 cystic fibrosis sufferers. Slightly more than 300 affected babies are born annually.

The disease affects many tissues, especially the endocrine glands. It results in the production of abnormally viscous secretions which cause duct obstruction and are therefore responsible for pancreatic insufficiency, malabsorption syndromes, biliary cirrhosis and male infertility. The lungs of cystic fibrosis patients are found to be normal at birth but are very prone to infection. Recurrent infection is responsible for the irreversible secondary lung damage which is usually responsible for the shortened life expectancy of cystic fibrosis patients. Death usually results from a severe bacterial pneumonia or is related to the development of cor pulmonale from lung disease.

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ARTICLE

Cystic Fibrosis

Miss Mary Dolan

Every year members of the Royal Medical Society present dissertations at Private Business Meetings. Traditionally *Res Medica* has published those dissertations of wider interest. We are reintroducing this tradition with an article about cystic fibrosis which was presented last session by one of our current presidents, Miss Mary Dolan. Please note that the information provided in this article, especially with respect to prenatal diagnosis, predates the localisation of the C.F gene.

Cystic fibrosis, a genetic disease with an autosomal recessive mode of inheritance, was first described in 1936 by Fanconi *et al.* He described the disease in a paper entitled *The Coeliac Syndrome with congenital cystic pancreatic fibromatosis and bronchietasis.* Since then the disease has been known by various names such as Cystic Fibrosis of the Pancreas, Mucoviscidoses, fibrosis of the pancreas until it was shortened to Cystic Fibrosis in the 1960s.

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Clinical presentation occurs before the age of one year in approximately 50% of patients with recurrent respiratory infections, diarrhoea, rectal prolapse, failure to thrive. Tracheal epithelium show increased Na^+ transport with reduced Cl^- absorbance (Knowles 1981). Beta-stimulation of the

Table I. Special characteristics of the salivary glands and blood cells of cystic fibrosis patients

1. Decreased beta-stimulation response in salivary glands
2. ? calcium concentrations in both tissues
3. Erythrocytes: ● no active Ca^{2+} pumps
   ● low rate of passive entry of Ca^{2+}
   ● decreased Na^+/K^+-2Cl transporter
4. Lymphocytes and Granulocytes: decreased response to cAMP stimulation
5. Heterozygotes for the cystic fibrosis gene demonstrated an intermediate response (ie. greater than cystic fibrosis patients but less than normal) to cAMP stimulation

airway results in increased Na^+ absorption but no change in Cl^- secretion. Thus the signals operating via the cAMP system fail to increase chloride permeability. This reduced chloride secretion *has a drying effect on airway surfaces.*

Studies involving the salivary glands and erythrocytes of patients have shown several abnormalities (Table I). It is uncertain whether the viscid mucus secretion results from abnormal ion transport or is due to abnormal secretion. Uncertainties also exist regarding the increased respiratory infections of cystic fibrosis patients. These are either due to abnormal ion composition or mucus accumulation or both.

MANAGEMENT OF THE C.F. CHILD.

Current theories on the management of cystic fibrosis believe that early diagnosis and therefore earlier treatments is important in containing the development of disease complications. Currently it is thought that management of a cystic fibrosis child is improved by having the child's need coordinated by one regional centre. For example in the Victoria state cystic fibrosis centre in Melbourne, 80% of children have a life expectancy of 20 years. (Phelani Hay 1984). Management of the disease centres around pancreatic supplements, antibiotic therapy and physiotherapy. Vaccinations, especially for measles and pertussis and the annual influenza vaccinations are important for preventing the early demise of a cystic fibrosis child. Severe viral infections such as influenza or chicken pox may result in serious deterioration of respiratory function. The dose of influenza vaccine may be halved therefore allowing its use on children under four years. The use of enteric-coated pancreatic supplements has allowed the normal growth and development of cystic fibrosis children. It has also meant the introduction of a normal diet for cystic fibrosis children. They are now advised to take normal calorific values of fat and an excess of this is the suggested managements of some centres. Eventually some cystic fibrosis children will show some signs of slowing of growth and weight loss. This is

generally associated with increased respiratory infection and deteriorating pulmonary function.

Physiotherapy on a routine daily basis forms an important basis for the management of lung disease in children with cystic fibrosis. The aims are to clear the lungs of thickened mucus, irrespective of their infective status. The physiotherapy may involve the patients alone, a form of autogenic drainage. In this technique a form of controlled deep breathing is supplemented by the use of inhalations of moisture, breathing against a positive expiratory pressure and the forced expiratory technique (huffing). Physiotherapy may alternatively involve a therapist or parents and be based on the manual percussion of the chest, postural drainage and again forced expiration by the patients themselves. The autogenic technique allows patients independence and greater flexibility. Most children with cystic fibrosis comply with a physiotherapy routine lasting 20-30 minutes three times a day. Regular exercise programmes provide a means of coughing up secretions but must be a daily activity before they would substitute for physiotherapy.

Continuous antibiotic therapy ins aimed at preventing the development of irreversible lung damage. The antibiotic regime is rationed by continuous monitoring of bacterial pathogens in the sputum at 6 or 12 weekly check ups. Various different organisms culture the lungs at different ages in cystic fibrosis children. Culture of haemophillus influenza exacerbates treatment with amoxycillin and then Augmentin. This is often followed up by *Staphylococcus aureus* infection. The risk of staphylococcus pneumonia is much increased following a viral infection such as measles or chicken pox. Fear of staphylococcal infection precipitates the use of lifelong flucloxacillin therapy. Further infections are with *Pseudomonas Aeruginosa* which after infection cannot be eradicated. Pseudomonas infection can be treated aggressively by three monthly courses of intravenous antibiotics for 10-14 days in any patient in whom Pseudomonas cultures are positive. Training of parents and patients has facilitated the introduction of home intravenous antibiotics. Infections and other sources of Pseudomonas eg. *Pseudomonas Cepacea* are associated with a poor prognosis. This organism is resistant to antibiotic therapy and therefore may be responsible for further declines in respiratory function. One method of dealing with *Pseudomonas cepacea* has been to stop anti-pseudomonas therapy for short periods in the hope that the *P. cepacae* will be replaced by *Pseudomonas aeruginosa.*

PRENATAL DIAGNOSIS.

The prenatal diagnosis of cystic fibrosis involves two techniques. Both methods are best suited to families with a 1 in 4 risk of having an infected child. Chorionic Villous Sampling, occurring 6-8 weeks into pregnancy, involves the use of restriction fragments length polymorphism closely associated with the cystic fibrosis gene. Initially the cystic fibrosis affected family is typed first with the most favoured probe and enzyme. This is followed by establishing the phase relationships between markers and the cystic fibrosis gene. This usually involves examining bands on southern blot of DNA taken from blood of both parents and the already affected child. If the sample from the affected child or the index case is

not available for typing, then it is not possible to proceed with this form of diagnosis. The advantages and disadvantages of chorionic villous sampling is given in Table 2.

The alternative method of prenatal diagnosis involved the use of amniocentesis and the analysis of fetal microvillous enzymes (Glutaryl transpeptidase, aminopeptidase, intestinal alkaline phosphatase). Amniocentesis is carried out at 16-18 weeks and should be reserved for those with a 1 in 4 risk of an affected child. The advantages and disadvantages of aminocentesis are given in Table 3.

PROGNOSIS.

The long term prognosis for the disease has improved greatly over the last thirty years. The life expectancy of many children is now over 20 years, with approximately 25% reaching the age of 30 years. These improvements can be related to:

1. Introduction of antibiotics to treat severe infections and prevent a large decline in respiratory function related to infections.

2. Pancreatic supplements producing an improved diet for cystic fibrosis patients. These allow normal growth and improved quality of life for the patient. They also provide increased resistance to infection.

3. Early diagnosis and treatment of the disease can prevent the early development of complications eg.influenza vaccination prevents serious compromise of respiratory function due to viral infection.

4. Recognition of mild cases - ie. those with later diagnosis has led to improved survival figures.

Future hopes for the disease rest with the use of heart and lung transplantation for severe cor pulmonale; and with genetic research and identifying the defective proteins. Heart and lung transplantation has been used increasingly over the last 5 years as a treatment of severe cor pulmonale, a

Table II. Advantages and Disadvantages of Chorionic Villous Sampling

Advantages

- Increased accuracy of diagnosis.
- Earlier diagnosis allowing a first trimester termination for all affected fetuses

Disadvantages

- Need for blood sample from the 'index' affected child
- Requirements for early workup of nuclear family to assess theinformativeness
- Chance that some will be uninformative or only partially informative for DNA probes

Greater than 5% risk of spontaneous abortion

Table III. Advantages and Disadvantages of amniocentesis

Advantages

- All pregnancies with a 1 in 4 risk of cystic fibrosis can be assessed.
- No prior family workup is required
- Assays may be completed within 1 hour of receipt of the sample

Disadvantages

- Decreased accuracy of diagnosis (cf.CVS). Increased false positives and false negatives
- If termination is required then it will have to be a late termination (18-19 weeks).

major complication of advanced cystic fibrosis. Initially patients had a poor response to transplantation but success rates are now improving. There have been no reports of the epithelial transport defects occurring in the new lung, although the defects are still present above the site of the anastamosis.

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The Cystic Fibrosis Gene

S.J. Louise Smith

It's now well over a year since the cystic fibrosis gene was cloned and there is still much to be done before its localisation can be translated into an improvement in health care for affected people. I'm not going to go into any details on how the gene was located, for this information (which is rather technical) see ref.1. However to put it rather bluntly, despite the fact that the gene has been localised and sequenced has been sequenced, no-one really knows what it does. The cystic fibrosis gene has been named the CFTR gene (cystic fibrosis transmembrane conductance regulator). It is located on the long arm of chromosome 7 and is composed of 27 extrons which code for 1,400 amino-acid residues. There seem to be several different final products of the CFTR gene which result from the removal of exons from the first nucleotide binding fold. The functional significance of these products is not known.