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An analysis of factors contributing to poor outcomes in Cystic Fibrosis

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ABSTRACT

Cystic fibrosis [CF] is one of the most common inherited conditions in Europeans and affects 1 in 2381 births in the UK.[1,2] It is an autosomal recessive condition resulting from a mutation in the CFTR (cystic fibrosis transmembrane conductance regulator) gene on chromosome 7.[3] This affects the transport of chloride ions leading to disruption of sodium and water movement with the resultant generation of abnormally thick secretions.[3] These thick secretions cause inflammation and cell damage and adversely affect organ functioning.

Introduction to Cystic Fibrosis

There are many different clinical presentations of cystic fibrosis and this now includes neonatal screening as every child born in the UK undergoes a Guthrie test one week after birth. Blood is collected via a heel prick and tested for several inherited conditions including cystic fibrosis which is demonstrated by a raised immunoreactive trypsin activity.[4,5] In a study by Jackson et al. (2010) it was shown that, in the absence of a neonatal screening programme, cystic fibrosis presents with meconium ileus (18.5%), symptoms (gastrointestinal, respiratory or both) (66.4%) or family history (15.1%).[6] Gastrointestinal symptoms include malnutrition (failure to thrive), steatorrhoea (foul stools due to fat malabsorption) or both.[5,6] Respiratory symptoms include wheeze and cough productive of sputum.[5] Infants with meconium ileus present early (median age of presentation 0.47 months) whilst those with a family history or gastrointestinal/respiratory symptoms tend to present later (1.3 months and 11.0 months respectively).[6]

The diagnosis of cystic fibrosis is based on the clinical features, genetic screening for a CFTR gene mutation and an abnormal sweat test indicated by repeatedly elevated chloride levels.[5] In addition, faecal elastase is measured to help identify patients with pancreatic insufficiency.[7]

Treatment includes chest physiotherapy twice daily to aid clearance of the thick secretions from the airways.[5,7] Patients are treated with prophylactic antibiotics, for example young children receive oral flucloxacillin to protect against Staphylococcus aureus infection.[7] Patients with pancreatic insufficiency take pancreatic enzymes with each meal and fat-soluble vitamin supplements; pancreatic sufficient patients may also need fat soluble vitamin supplementation.[5,7] Some patients are also treated with inhaled bronchodilators and steroids.

At every clinic appointment at a specialist CF centre the patients are reviewed by a team including a consultant, nurse specialist, physiotherapist, dietician and a psychologist.[7] They will also have contact with a social worker and pharmacist if necessary. A cough swab or sputum sample from the patient is sent to microbiology for culture and treatment with antibiotics is given based on the culture and sensitivity results.[7] For example, amoxicillin can usually be used for Haemophilus influenzae or Streptococcus pneumoniae infection.[5] BMI is recorded at every clinic appointment to monitor nutritional status. Patients undergo an annual oral glucose tolerance test to screen for cystic fibrosis related diabetes (if aged over 12 years), spirometry testing to review lung function (if aged over 5-6 years) and a chest X-ray to screen for bronchiectasis.[7] Every 2 years, they undergo a liver ultrasound to screen for liver disease (if aged over 5 years) and every 1-3 years, a DEXA scan is carried out to measure bone mineral density (if aged over 10 years).[7]

Analysis of factors associated with poor outcome

A- Infection

There are certain pathogens which correlate with a poor prognosis, such as Pseudomonas aeruginosa and Burkholderia cepacia that are both gram negative organisms.[8] McCloskey et al. (2001) carried out a study involving 3 groups of patients: group 1 had grown Burkholderia cepacia and Pseudomonas aeruginosa on sputum culture, group 2 had grown Pseudomonas aeruginosa only on sputum culture and group 3 had grown neither organism.[8] It was shown that the lung function of patients in group 1 declined much faster (5.4% average decrease in FEV1 over 9 years) than that of patients in group 3 (1.6% decrease) and also faster than that of patients in group 2 (3.9% decrease).[8] Burkholderia cepacia is also associated with a higher mortality rate. In the study 28 patients died over the 9 years; 16 of which had grown Burkholderia cepacia and 8 of which had grown Pseudomonas aeruginosa.[8] Burkholderia cepacia infection is associated with increased morbidity and mortality because it is very difficult to treat. It is resistant to many antibiotics with different strains of the pathogen being susceptible to different antibiotics.[9] According to the CF Trust, antibiotics which can be useful for the treatment of Burkholderia cepacia infection include ceftazidime, piperacillin, tazobactam, meropenem, imipenem, ciprofloxacin, trimethoprim, cotrimoxazole and tetracyclines.[10] The Tayside Guidelines suggest that ceftazidime and gentamicin should be used for a paediatric exacerbation of cystic fibrosis due to Pseudomonas aeruginosa infection.[11]

However, there are now policies to segregate cystic fibrosis patients in clinics and in hospital according to bacterial colonisation and this has led to a reduction in the spread of infection, including Burkholderia cepacia.[10] As a result, Burkholderia cepacia infection is less prevalent but management remains difficult. Patient segregation cannot eradicate the infection as it can still be acquired from the environment, for example, from water or soil.[10]

Cepacia Syndrome is when the pulmonary function of patients who have grown Burkholderia cepacia on sputum culture declines quickly; some patients also develop

"fulminant necrotising pneumonia" and die very quickly.[5,8] Some strains of Burkholderia are more likely to cause Cepacia Syndrome than others, for example Burkholderia cenocepacia, multivorans and dolosa.[10]

B- Cystic Fibrosis Related Diabetes

Another factor associated with a poor outcome is cystic fibrosis related diabetes which affects approximately 20% of adolescents and 40-50% of adults with cystic fibrosis.[12] CFRD cannot be classified as type 1 diabetes (because it is not autoimmune) or type 2 diabetes (because the problem is insulin insufficiency, not insulin resistance) and it is thus placed in a category of its own. CFRD is due to thick secretions causing inflammation and damage to beta cells of the Islets of Langerhans in the pancreas.[12] The mass of the Islets of Langerhans decreases by approximately 50% leading to reduced insulin production and insulin insufficiency.[12] Patients with CFRD are, however, unlikely to develop diabetic ketoacidosis as the residual Islets of Langerhans still produce small amounts of insulin and there is also damage to alpha cells thus leading to decreased glucagon production.[12]

CFRD is associated with increased morbidity and mortality as it leads to microvascular complications such as peripheral neuropathy which is present in approximately 50% of cystic fibrosis patients who have had CFRD for more than 10 years.[12] Nephropathy and retinopathy are not as frequent in CFRD as in type 1 and 2 diabetes.[12] However, the main reason why CFRD patients have increased morbidity is because CFRD worsens CF lung disease. For example, it adversely affects nutrition by increasing the breakdown of fat and protein[12] that has a negative impact on lung function. Also, hyperglycaemia caused by CFRD encourages the growth of bacteria in the lungs.[12]

C- Socioeconomic Status

A study by Schechter et al. (2001)[13] indicated that low socioeconomic status was associated with a poor outcome. In this study, a low socioeconomic status was indicated by a requirement for coverage by Medicaid insurance (as Medicaid entitlement is based on income).[13] Results showed that Medicaid patients were more likely to have a lower FEV_1 (78.1%) and a lower weight (28.6 percentile) than non-Medicaid patients (84.8% and 34.3 percentile respectively).[13] Medicaid patients were also much more likely to have a pulmonary exacerbation (44.5%) and be hospitalised (43.4%) than non-Medicaid patients (28.6% and 25.9% respectively).[13] Over the 8 year study period, 8% of Medicaid patients died compared to 6% of non-Medicaid patients.[13]

Balmer et al. (2008) also showed a correlation between low socioeconomic status and poor lung function in children.[14] They split patients into 3 groups: socially advantaged (household income >$75,000 per year, living with 2 parents and parental education of at least a college degree), socially disadvantaged (household income <$20,000 per year, living with 1 parent or parental education of less than a high school degree) and not socially disadvantaged.[14] It was found that children in the socially advantaged group had a higher weight, BMI and FEV_1 than the other two

groups.[14] They also had less hospitalisations per year and less absences from school.[14]

Although this is American data, this also applies to Scottish patients. Poorer lung function in low socioeconomic status patients may be due to smoke (which can cause deterioration of lung function in children), as smoking is more common in low socioeconomic status households.[13] Poorer understanding of the condition or of the treatment may be more frequent in less educated families, which could lead to non-compliance with medical treatment. In households with only 1 parent or with several children, time constraints may lead to poor compliance with disease management, especially physiotherapy. Non-compliance or poor compliance with treatment may cause poor nutrition leading to poor weight (if pancreatic enzyme replacement therapy is not taken) and poor lung function (if prophylactic antibiotics are not taken or physiotherapy is not completed). Children with several siblings (especially siblings with cystic fibrosis) or children who spend time at nursery/school will perhaps be more exposed to infection, which may have a negative impact on lung function over time.

D-Genotype

Genotype also predicts prognosis in cystic fibrosis. The mutations on the CFTR gene were divided into 6 classes by Welsh et al. (1993).[15] Class I mutations due to insertions (for example, stop codons), deletions, splice site mutations or nonsense mutations lead to abnormal production of the CFTR protein with absent protein production or production of a non-functioning protein.[15] Class II mutations lead to incomplete glycosylation of the CFTR protein resulting in an abnormal protein that is broken down. This class includes the delta F508 mutation which is the most common mutation seen in European patients.[15,16] Class III and IV mutations lead to the protein channel not reaching the cell membrane. Class III mutations lead to defects in the nucleotide binding sites on the protein, thus the channel cannot be controlled properly and class IV mutations lead to reduced ion flow through the channel.[15] Class I, II and III mutations lead to a severe disease phenotype as they are associated with pancreatic insufficiency.[17] In contrast, class IV, V and VI mutations lead to a mild disease phenotype as they are not associated with pancreatic sufficiency.[17]

Cleveland et al. (2009),[17] examined the link between genotype and pulmonary disease using chest radiographs, FEV_1 and FVC. Patients were divided into groups depending on the class of their genotype. Group S contained the severe disease (pancreatic insufficient) patients and was divided into subgroups A, B and C: subgroup A had two class I mutations, subgroup B had one class I and one class II or III mutation and subgroup C had either two class II mutations or one class II and one class III mutation. Group M contained the mild disease (pancreatic sufficient) patients with at least one mutation from class IV, V or VI. The chest radiographs and FVC of group S declined more rapidly (-0.174 and -1.080 decline in points per year respectively) than those of group M (-0.064 and -0.179 respectively).[17] Subgroup A declined faster than subgroup B and subgroup B declined faster than subgroup C as expected.[17] Therefore, genotype does have a negative impact on pulmonary function as well as pancreatic function. However, it should be noted that pancreatic

insufficiency may be a factor in poor lung function as pancreatic insufficiency can lead to malnutrition, which has an important negative impact on lung function.

Table 1: Summary of genotype classification summarised from *Table 1. Classes of CFTR Mutations That Cause CF* (Welsh et al. 1993)[15]

Class	Defect	Examples	Frequency	Clinical Phenotype
I	Protein production Insertions Deletions Splice site mutations Nonsense mutations	G542X	3.4	Pancreatic insufficient
II	Protein processing Incomplete glycosylation of the CFTR protein	ΔF508	67.2	Pancreatic insufficient
III	Regulation of protein trafficking Defect of binding sites	G551D	2.4	Pancreatic insufficient
IV	Channel conduction Reduced ion flow	R117H	0.8	Pancreatic sufficient

E- Ethnicity, gender, age at diagnosis and BMI

In the UK, Asian patients have a poorer prognosis than patients of other races.[18] McCormick et al. (2005) demonstrated that female Asians have a worse FEV_1 than male Asians and both groups have a worse FEV_1 than their matched UK white controls.[18] This may be a result of the Asian genotype (many of which remain unknown) or a combination of diet, socioeconomic status and barriers to quality healthcare such as language.[18]

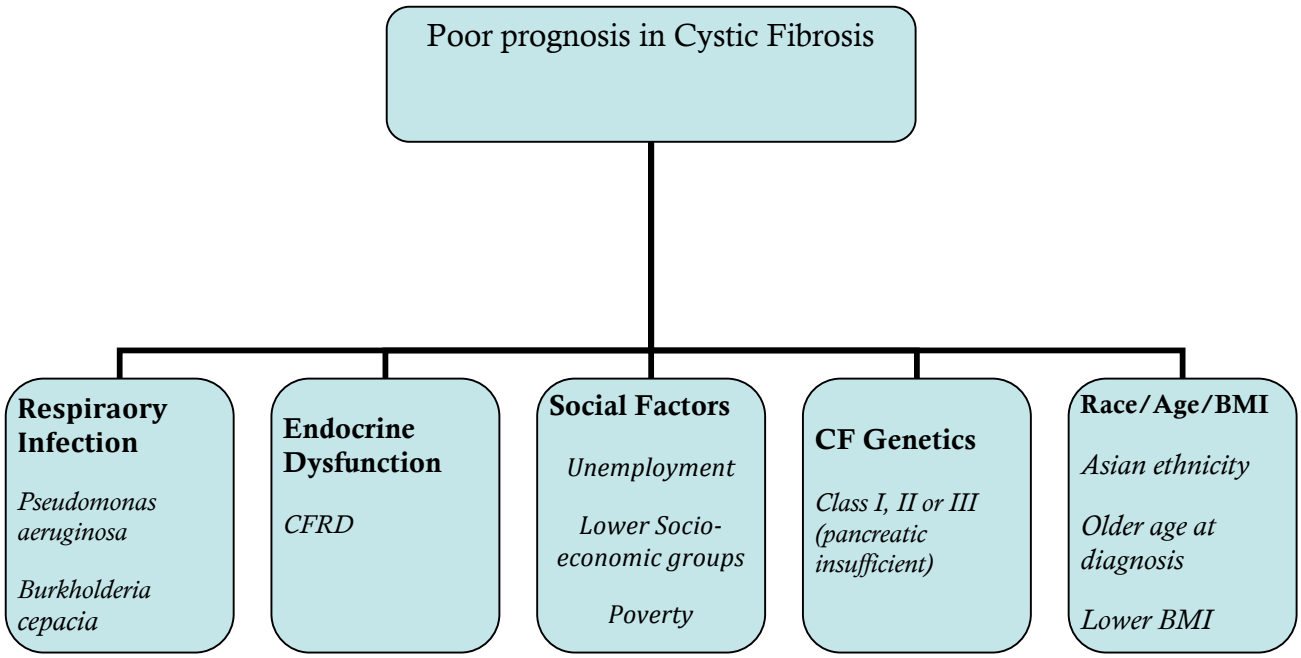
Verma et al. (2005) stated that gender did not affect prognosis in cystic fibrosis.[19] However, Gee et al. (2003) found that although BMI and FEV_1 did not differ between genders, females described a worse health related quality of life with regard to "chest symptoms, emotional functioning, concerns for the future and career issues".[20] Males described a worse health related quality of life with regard to "body image"; this may be due to the fact that males prefer to be heavier whereas females are content with a low BMI.[20] Also, male cystic fibrosis patients are more likely to be infertile (due to an associated congenital absence of the vas deferens) than female cystic fibrosis patients.[16] Age at diagnosis also has an impact on long term prognosis. Patients diagnosed at an early age by screening have a better height and weight at diagnosis, and these differences are maintained in the long term.[21] A greater weight

and height (and therefore, BMI) correlates with a better lung function and this reinforces the value of screening tests as they improve prognosis by allowing patients to be treated earlier.[21]

Conclusion

In conclusion, there are many factors that contribute to a poor prognosis in cystic fibrosis. The prevalence of severe infections, such as Burkholderia cepacia, can be reduced by patient segregation and by sterilising equipment after use. However, the infection is very difficult to eradicate when established. CFRD can be controlled and the long-term effects of diabetes reduced by insulin therapy and good glucose control. Factors associated with a low socioeconomic status could be reduced by teaching patients and their families about the disease and treatment in order to optimise compliance with treatment. Health promotion and disease prevention in the form of smoking cessation could also improve prognosis in this group. Genotype, gender and ethnicity cannot be modified, but perhaps patients with a more severe genotype require more aggressive therapy to improve their prognosis as much as possible. Screening programs are important for early detection of the disease as they allow patients to receive prompt treatment.

Table 2: Summary of factors contributing to poor prognosis in cystic fibrosis



There have been many developments to the management of cystic fibrosis and there are more future treatments under development, including drugs to block ENaC channels (epithelial sodium channels) to reduce the transport of sodium and water out of the airways.[22] This would lead to less viscous secretions which could be more easily cleared from the airways.[22] Other improvements in cystic fibrosis management

for the future include gene therapy that aims to restore the expression of intact functional CFTR protein.[23] All of these advances will continue to contribute to the ever-improving prognosis for cystic fibrosis patients.

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