PATTERNS OF GI DISEASE IN ADULTHOOD ASSOCIATED WITH MUTATIONS IN THE *CFTR* GENE

1153

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There has been tremendous growth in the population of adults with cystic fibrosis (CF). This demographic change has created the need for special clinics to care for adults with CF and has resulted in an awakening of interest in CF among physicians caring for adults. The protean and varied manifestations of CF disease in multiple organs call for expanded knowledge of the condition among physicians in a wide variety of subspecialties, including, but not limited to, pulmonary medicine, gastroenterology, hepatology, clinical nutrition, endocrinology, infectious diseases, rheumatology and andrology. This review will focus on disease pathobiology of the gastrointestinal and hepatic manifestations of CF disease which the internist is likely to encounter.

We will first examine the clinical manifestations of CF disease that are directly associated with loss of function of the cystic fibrosis transmembrane regulator (CFTR) protein and then summarise those which are secondary. We will elaborate the challenges of establishing or excluding a CF diagnosis in patients who present *de novo* in adulthood, with particular attention to conditions with CF-like phenotypes that are associated with an increased frequency of mutations in the *CFTR* gene. Finally, we will briefly discuss emerging knowledge of the potential contribution of mutations in the *CFTR* gene to other complex genetic conditions.

Over the past three decades the most striking result of advances in the care of patients with CF has been the dramatic improvement in survival. Whereas median survival in the United States was only 16 years in 1970, it has risen to over 32 years in 2005. For patients born in the 1990s median survival is predicted to exceed 40 years.¹ Of patients born in the United Kingdom in 1980, 82% were alive at age 20, whereas for children born in 1990, 96.5% are alive at age 15 (fig 1).² As a consequence, there has been a striking increase in the number and proportion of adults with CF disease. For example, this decade the proportion of patients with CF over the age of 18 in the United States has reached 40%, whereas in 1970 it was only 10% of the CF population. In other developed nations the proportion of adults in the CF population is similar to, or even greater than, those reported in the US CF patient data registry. In the UK, the percentage of adult patients reached 50.8% in 2003 (UK CF database).² This demographic change is largely attributable to improved survival of patients diagnosed in infancy and childhood, mainly owing to advances in nutritional and respiratory care. Furthermore, with advances in our understanding of the heterogeneity and spectrum of CF disease, together with improved awareness among internists, an increasing number of patients are being diagnosed *de novo* in adulthood. Both these factors have shifted the burden of illness to the third and fourth decades of life and beyond. With improvement in survival, the natural history of the disease is changing and new, hitherto unknown, complications are emerging.

CFTR GENE MUTATIONS, MODIFIER GENES AND THE ENVIRONMENT

The *CFTR* gene

The cystic fibrosis transmembrane conductance regulator gene, which is located on chromosome 7, was cloned in 1989.^{3–5} The CFTR protein, which includes two membrane spanning domains, two nucleotide binding domains and a unique regulatory domain, functions as a cyclic AMP-dependent chloride channel.⁶ It localises to the apical membrane of secretory and absorptive epithelial cells within the airway, pancreas, liver, intestine, sweat gland and the vas deferens. Many of the manifestations of CF are due to an inability of the duct lumens to hydrate macromolecules. Pathological evidence suggests that in most organs, damage arises from ductal or glandular plugging by macromolecules that have precipitated in concentrated secretions. For example, mucus secretions in the bronchi and the intestine are viscid and inspissated, and the crypts are distended as if obstructed. This situation arises as a result of a deficit of ductular fluid flow and altered biochemical and physiological properties of secretions.

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Figure 1 Survival of patients with cystic fibrosis by year of birth in the United Kingdom. Actual survival of patients in the registry has steadily improved since 1980. Of patients born between 1980 and 1984 (the earliest birth cohort shown here), 90.2% survived to age 15. For patients born between 1990 and 1994, 95.2% survived to age 15.

The *CFTR* gene is relatively large, encoding a protein of 1480 amino acids. Over 1300 mutations of the *CFTR* gene have now been described.⁷ The most common mutation, a base-pair deletion in exon 10, which encodes the first nucleotide binding domain of the CFTR protein, results in a deletion of phenylalanine at position 508.⁸ The F508del mutation is present in two-thirds of CF chromosomes world wide and is the most common mutation in northern Europe and North America. However, the frequency of different mutations varies considerably between different ethnic populations. Owing to the large number of mutations it is difficult to evaluate the effects of individual CF genotypes on phenotype. To help with this process, the known (or predicted) functional consequences of the various mutations in *CFTR* have been organised into six classes (fig 2).⁹ This classification system provides an opportunity to evaluate the effects of genotype on phenotype by considering the effects of *CFTR* mutations on CFTR protein function. Nevertheless, it should be emphasised that this classification system is limited by the fact that the functional consequences of many rare mutations (particularly missense mutations) are unknown and cannot be predicted.

A number of mutations give rise to more than one functional defect. Class I includes mostly nonsense, frameshift or missense mutations that result in defective protein biosynthesis (truncation, deletion, etc). The non-functional products are efficiently degraded within the cell. Class II mutations, such as F508del, produce a misfolded functional CFTR protein, which is degraded intracellularly, preventing trafficking to the apical surface of the cell. Class III mutations affect channel activation by preventing binding and hydrolysis of ATP at one of the two nucleotide

binding domains (NBD1; NBD2). Class IV mutations produce a protein with impaired function because of abnormal anion conduction. Owing to a variety of mechanisms, including abnormal splicing, promoter mutations or inefficient trafficking, class V mutations result in a reduced number of normally functioning CFTR molecules on the apical surface. Class VI mutations result from truncation of the C-terminus of CFTR and produce a functional protein, which is unstable at the apical membrane surface.

Mutations belonging to classes I–III and VI confer little or no functional CFTR at the apical membrane. As a consequence, inheritance of homozygous or compound heterozygous mutations belonging to these classes is predicted to have severe consequences. Mutations belonging to classes IV and V, on the other hand, which confer (or are presumed to confer) some residual CFTR-mediated channel function would be expected to have milder consequences. In fact, it is patients with at least one mutation belonging to classes IV or V who generally present with symptoms in late childhood or adulthood.

Pathobiology of CF disease

The clinical consequences of absent or reduced CFTR ion channel function result in complex, multiorgan characteristics of the CF phenotype, which are site-specific but vary considerably in severity and age of onset. These differences can in part be explained by the dependence of each organ on CFTR channel function, the modulating effect of CFTR on other channels, the existence of alternative epithelial ion channels, the presence of intraluminal macromolecules, as well as the diameter, length and degree of tortuosity of the ducts. For example, the sweat gland ductal system is narrow and tortuous and is highly dependent on CFTR to modulate the ionic concentration of secretions. In CF disease the sweat glands suffer no pathological consequences because their secretion lacks macromolecules. In contrast, the pancreas and the vas deferens appear to be highly susceptible to the pathological effects of the loss of CFTR channel function. The narrow and tortuous ducts, the high macromolecule concentration of their secretions, and their dependence on the CFTR chloride channel for maintaining fluid render them vulnerable to intraductal obstruction. Whereas CFTR expression on the epithelial surface of the airways is relatively low, there is considerably higher expression in the submucosal glands. Absent or reduced CFTR function leads to increased expression of the epithelial sodium channel, which increases fluid absorption and contributes to the relative dehydration of airway surface liquid.

Adding to the overall complexity of CF disease is the considerable variability of disease severity in specific organ systems. As will be discussed in greater detail below, some organs, such as the exocrine pancreas, show a good association between genotype and phenotype, whereas others show a

Figure 2 Molecular consequences of cystic fibrosis transmembrane conductance regulator mutations. The mutations can be classified according to the functional properties of the gene product with respect to chloride regulation. A modified classification originally proposed by Tsui⁷² is shown with the addition of a sixth class. (See text for explanation.)

Figure 3 Gastrointestinal consequences of cystic fibrosis transmembrane regulator (CFTR) dysfunction. The severity of disease in various organs affected in cystic fibrosis is modulated by intrinsic (genetic) or extrinsic (environmental, iatrogenic) factors.

relatively poor association. For example, severe intestinal diseases (meconium ileus) and hepatic complications (cirrhosis with portal hypertension) are more prevalent in patients carrying severe class I, II or III mutations on both alleles. However, disease penetrance is incomplete and seems to depend on additional genetic factors, termed modifier genes or environmental influences, or both. Almost all patients develop bronchopulmonary disease, but there is great variability in the age of onset, rate of progression and disease severity, even among patients who are homozygous for the same mutation. Although environmental influences such as age of onset of chronic infection may influence the severity of bronchopulmonary disease, the rate of decline of pulmonary function is undoubtedly affected, to a greater or lesser extent, by modifier genes. In this regard, polymorphisms in the *TGF β 1* gene were recently shown to be associated with more severe bronchopulmonary disease.¹⁰

Other sociological and iatrogenic factors, including social class, access to the healthcare system, whether or not a person attends a dedicated CF clinic and approach to nutritional support, have also been shown to have a marked effect on the rate of disease progression and survival.

PRIMARY GASTROINTESTINAL CONSEQUENCES OF CFTR DYSFUNCTION

Gastrointestinal manifestations in CF may be divided into two groups, those where the pathobiology is directly related to the

basic defect of CF and those which arise as a secondary complication of the disease or its treatment (fig 3).

The pathognomonic hepatic feature of CF is focal biliary cirrhosis. Intrahepatic biliary ductal secretion is dependent on CFTR-mediated chloride transport for adequate hydration of the lumen (fig 4). Loss of CFTR function causes the biliary ductules to become blocked with thick periodic acid–Schiff positive material, leading to acute and chronic periductal inflammation, bile duct proliferation and increased fibrosis in scattered portal tracts. Remarkably, adjoining portal tracts are often normal. Postmortem studies show evidence of mild focal disease in 11% of infants, 27% of those dying at 1 year, and in more than 70% of adults.²³ Clinically significant portal hypertension resulting from severe multilobular cirrhosis develops in only 5–7% of patients. The median age of diagnosis of this complication is 9–10 years. Most patients are asymptomatic at diagnosis and are often identified by evidence of hepatosplenomegaly after a routine examination or by laboratory evidence of hypersplenism. Splenomegaly is a consistent finding and the liver edge is often nodular and hard. Hepatocellular function remains well preserved for many years, even decades.

Exocrine pancreatic abnormalities

Exocrine pancreatic function

The CFTR protein is highly expressed in pancreatic ductal epithelia and permits anions and fluid to enter the ductal

Figure 4 Pathogenesis of cystic fibrosis (CF)-related liver disease. Absence of functional cystic fibrosis transmembrane regulator (CFTR) in the biliary ductules causes dehydration, increased concentration and lack of alkalinisation of the duct contents. This causes precipitation of biliary secretions, and ductular obstruction. In most patients the pathological changes arise focally and seem to be clinically inconsequential. However, about 5% of patients with CF develop clinically significant liver disease, with evidence of multilobular cirrhosis and portal hypertension. Susceptibility to more severe liver disease may be modulated by other genetic or environmental factors, or both.

lumen. Luminal chloride is exchanged for bicarbonate. There is also evidence that CFTR is permeable to bicarbonate.¹¹ The net result is an increased volume of alkaline fluid, allowing the highly concentrated proteins secreted by the acinar cells to remain in a soluble state. Absent or reduced CFTR channel function impairs entry of chloride and bicarbonate into the ducts, which results in a reduced volume of a more acidic fluid.^{12–13} The acidic milieu within the acinar lumen also leads to impaired reuptake of GP2, the zymogen granule associated protein.¹⁴ The consequences of mutations in the *CFTR* gene have been demonstrated by pancreatic function studies, which show that patients with CF have low flow secretions with a high protein concentration that presumably will precipitate in the duct lumina causing obstruction, damage and atrophy (fig 5). In patients with severe disease, this destructive process begins in utero and within the first few years of life the pancreas is completely destroyed. This obstructive, destructive process forms the basis of newborn screening for CF disease by measuring serum trypsinogen concentrations in cord blood. High serum trypsinogen concentrations in newborn infants with CF almost certainly result from release of enzymes into the circulation owing to ductal obstruction and acinar cell damage.

One of the most remarkable observations is that genetic factors exquisitely influence the degree of pancreatic disease and its rate of progression. Large studies of patients with CF resulted in their classification as pancreatic insufficient (PI) or pancreatic sufficient (PS). PI patients comprise 85% of all patients with CF and have maldigestion, as defined by evidence of steatorrhoea after 72-hour fat balance studies; these patients require pancreatic enzyme replacement therapy with meals. In contrast, PS patients have evidence of pancreatic damage but retain sufficient endogenous exocrine pancreatic function to sustain normal digestion. This is due to the fact that ductal CFTR in PS patients is partially functional, thereby allowing anions and fluid to enter the ductal lumen. There is also evidence that mutant CFTR may cause other apical anion exchangers to conduct rather than conducting chloride ions itself.¹⁵

Exocrine pancreatic status is directly linked to genotype.^{16–17} Analysis of particular *CFTR* mutations in patients with these pancreatic phenotypes (PI vs PS) showed two categories of alleles: “severe” and “mild”. Patients homozygous or compound heterozygous for severe alleles belonging to classes I, II, III or VI confer pancreatic insufficiency, whereas a mild class IV or V allele sustains pancreatic function in a dominant fashion, even if the second mutation is severe. This observation has a plausible explanation because all known mild alleles belong to class IV or class V, all of which are (or are predicted to be) associated with some residual chloride channel activity at the epithelial apical membranes. Although these mutations confer sufficient CFTR function to prevent the pancreas from being completely destroyed, many PS patients have reduced exocrine pancreatic capacity and, as discussed below, have an increased risk of pancreatitis. A small proportion (2–3%) of patients carrying severe mutations on both alleles are PS at diagnosis but most experience gradual transition from PS to PI. A few missense mutations (eg, G85E) confer a variable pancreatic phenotype.

Pancreatitis

Recurrent acute and chronic pancreatitis is a relatively uncommon complication of CF, first reported by Shwachman *et al* in 1975.¹⁸ In their retrospective study only 0.5% of patients with CF had pancreatitis. More recently, we reported that in a cohort of over 1000 patients, followed up for 30 years, the incidence was 1.7%.¹⁹ All the patients with pancreatitis were PS. In fact, this subgroup of PS patients seems to be highly susceptible to pancreatitis, because nearly 1 in 5 was affected by this complication. There have been reported suggestions that PI patients may have pancreatitis, but most probably the pancreatic function of these patients was not fully investigated.²⁰ As we will describe in more detail below, patients with idiopathic pancreatitis carry a high frequency of mutations in the *CFTR* gene and a subset of these patients have CF disease based upon current diagnostic criteria.

CF-related diabetes

CF-related diabetes mellitus causes considerable morbidity such as worsening malnutrition and lung disease and almost certainly contributes to premature death. The diagnosis is usually established by a high degree of awareness or by routine screening because characteristic symptoms attributable to

Figure 5 Pathogenesis of pancreatic disease in cystic fibrosis (CF). Acinar cells secrete large quantities of protein, primarily in the form of digestive enzymes, into the acinar lumen. Under normal circumstances anions (chloride and bicarbonate) are secreted into the ductal lumen via the cystic fibrosis transmembrane regulator (CFTR) and bicarbonate exchangers. This provides a driving force for the movement of fluid into the lumen of the duct and maintains the solubility of secreted proteins in a dilute, alkaline solution. In CF impaired anion transport into the proximal ducts results in decreased secretion of more acidic fluid, which leads to precipitation of secreted proteins. Intraluminal obstruction of the ducts then causes progressive pancreatic damage and atrophy.

hyperglycaemia are usually absent or mild. The prevalence increases dramatically, starting in preadolescence. It is common in adults with CF, and has been reported to affect as many as 32% of patients over 25 years old.²¹ There is a strong association between CF-associated diabetes mellitus and the PI phenotype.²² Microvascular complications are commonly seen with disease duration. However, macrovascular complications have not been observed.

Hepatobiliary disease

Almost all patients with CF have evidence of hepatobiliary disease, but for the vast majority of patients there are no clinical consequences. A wide variety of hepatobiliary disorders is associated with CF in adults (table 1).

Biochemical markers of liver disease do not reliably identify patients with multilobular cirrhosis nor do they predict the development of end-stage liver disease. About 40–50% of patients with CF exhibit intermittent increases of aspartate

aminotransferase, alanine aminotransferase or γ -glutamyl-transferase, which are generally 1–2.5 times above the upper reference limits. Furthermore, patients with advanced multilobular cirrhosis may have normal liver biochemistry test results. Hyperbilirubinaemia is rare, and a raised serum γ globulin level is more likely to be associated with chronic pulmonary inflammation. Clinically significant cystic fibrosis liver disease (CFLD) occurs predominantly in PI patients and thus severe class I, II or III mutations on both alleles seem to be a risk factor.²⁴ Most studies have showed a male preponderance of severe CFLD.

Why a minority of patients with the same severe *CFTR* mutations progress to CFLD is unclear. However, it has been suggested that non-CF modifier genes, such as polymorphisms in genes that upregulate inflammation, fibrosis or oxidative stress, confer an increased susceptibility. Preliminary studies even suggest that heterozygote inheritance of the Z α -1-protease inhibitor allele confers an increased risk of developing severe CFLD.²⁵ Hitherto undefined environmental factors are also likely to play a part.

There is also an increased incidence of a variety of intrahepatic and extrahepatic abnormalities of the biliary tree. Gallstones develop in 1–10% of patients with CF. Non-functioning microgallbladders are common; less frequently, patients with CF have distended gallbladders that seem to be obstructed. Common duct obstruction resulting from extrinsic compression by fibrosis within the head of the pancreas has been postulated as the principal cause of CF-associated liver disease, but this remains controversial.²⁶ After endoscopic retrograde cholangiopancreatography or transhepatic cholangiographic imaging, changes resembling primary sclerosing cholangitis (ie, beading and stricturing of the intrahepatic and extrahepatic ducts) are quite commonly seen.²⁷ These changes are probably due to accumulation of protein, mucus, or sludge

Table 1 Hepatobiliary complications of CF in adults

Complications	Approximate prevalence (%)
<i>Hepatic</i>	
Steatosis	20–60
Focal biliary cirrhosis	11–70
Multilobular cirrhosis	5–7
Liver failure rare	
<i>Biliary</i>	
Microgallbladder	5–20
Distended gallbladder	3–20
Cholelithiasis and sludge	10–25
Intrahepatic sludge/stones	Unknown
Extrinsic compression of common bile duct	Unknown
Cholangiocarcinoma	Unknown

within the biliary lumina. Stones may also be commonly visualised within the larger intrahepatic and extrahepatic biliary tree.

Intestinal complications

1158

With the exception of the exocrine pancreas, manifestations of CF disease in the liver and the intestinal tract are primarily associated with patients who have classic CF disease, most of whom carry severe class I, II or III *CFTR* mutations on both alleles. However, the earliest gastrointestinal complication of CF disease, meconium ileus (MI), occurs in only 20–25% of neonates with classic CF disease. This observation, together with a strong familial association for MI, suggests the contribution of other genetic factors.

The CF mouse model has proved to be an excellent animal model of CF-like intestinal disease. Ileal obstruction from inspissation of mucofeculent intestinal contents causes death from perforation in a high percentage of animals, either at birth or after weaning to solid chow. Based upon the hypothesis that the genetic background of the CF mice was influencing the severity of intestinal obstruction (hence survival), genetic linkage was established to a single locus on mouse chromosome 7.²⁸ In a subsequent study linkage analysis identified a modifier locus for MI on human chromosome 19q13 which is systemic for the same locus on mouse chromosome 7.²⁹ Thus it appears that modifier gene(s) together with two severe *CFTR* alleles confer an increased likelihood of MI. It remains possible that modifier genes with or without environmental factors may explain the variability and severity of other intestinal complications such as distal intestinal obstruction syndrome (DIOS).

Distal intestinal obstruction syndrome

DIOS is a chronic, recurrent form of partial intestinal obstruction which occurs frequently in adults with CF. On rare occasions the bowel is completely obstructed. DIOS, which occurs almost exclusively in PI patients, is a poorly defined condition, which is often confused with other common causes of abdominal pain in patients with CF. Consequently, the reported prevalence is variable, but a recent study gives a prevalence of 18% in adults.³⁰ DIOS is unique to CF and results from a build up of adherent, thick intestinal contents in the terminal ileum and proximal colon. Patients usually have intermittent episodes of pain, which may or may not be localised to the right lower quadrant. Invariably, a non-tender, or mildly tender, palpable mass can be felt in the right lower quadrant. Patients with incomplete bowel obstruction due to DIOS usually pass bowel motions which are normal in consistency and frequency. Some patients have intractable chronic pain which is difficult to treat.

DIOS should not be confused with simple constipation, which is also common in PI patients with CF, but unlike DIOS a right lower quadrant mass is usually not palpable and stooling patterns and consistency are abnormal. Although the exact cause of DIOS is unknown, various precipitating factors have been proposed, including abnormal properties of intestinal mucus, dehydration of intraluminal contents, poor compliance with pancreatic enzyme therapy and a prior history of meconium ileus. Patients undergoing major surgery, such as lung or liver transplant, carry an increased risk of DIOS during the immediate postoperative period.

Appendiceal disease

The incidence of acute appendicitis in CF is reported to be lower than in the general population. In a study from Toronto, 1.1% of patients in a large clinic population underwent appendicectomy compared with 7% reported for the general population.³¹ Nevertheless, patients who develop this complication have a greater risk of a delayed diagnosis and an increased incidence of complications such as appendiceal abscess. The reasons for this are unclear, but possible factors include luminal obstruction of the appendix with thick mucus, delayed intervention due to mistaken diagnosis of DIOS, or masking of acute symptoms by chronic antibiotic use.

Intussusception

Intussusception occurs in 1–2% of adult patients with CF, a rate approximately 10–20 times higher than in the general population. Most cases are ileocolic and 25% are associated with a small bowel obstruction.³² Sticky, mucofaeculent material which adheres to the intestinal epithelium may act as the lead-point in intussusception. Presentation is usually with intermittent abdominal pain. Plain abdominal x ray findings are often non-specific, showing faecal loading, or less often a small-bowel obstruction. Classical appearances of intussusception may be seen on barium studies and include a lobulated soft tissue mass and a “coiled spring” usually situated in the right iliac fossa. Ultrasound examination findings include the “doughnut sign” on transverse scan and “pseudo-kidney” on longitudinal scan. It is noteworthy that intussusception in adult patients with CF is often intermittent and resolves spontaneously. It may also be seen in asymptomatic patients as an incidental finding during abdominal imaging.³³

DIAGNOSTIC CHALLENGES IN ADULTS

Because of the cloning of *CFTR* our understanding of the spectrum of disorders associated with functional alterations in the *CFTR* gene has changed considerably. Consequently, CF and disorders associated with mutations in *CFTR* are frequently being diagnosed de novo in adolescence and adulthood. This, in turn, causes difficulties in clearly defining what constitutes a diagnosis of CF. A consensus statement from the US Cystic Fibrosis Foundation defined CF as the presence of a clinical syndrome plus either evidence of *CFTR* dysfunction (an abnormal sweat chloride concentration or nasal potential difference measurement) or confirmation of CF-causing mutations on both alleles.³⁴ Patients are diagnosed with CF if they have at least one phenotypic characteristic of the disease plus a sweat chloride concentration above 60 mmol/l, or loss of *CFTR*-mediated transepithelial conductance in the nasal epithelium, or two disease-causing mutations of the *CFTR* gene. The phenotypic CF characteristics include chronic sino-pulmonary disease, characteristic gastrointestinal and pancreatic abnormalities and absence of the vas deferens.

For the vast majority of patients with classic CF who are diagnosed in infancy or childhood with characteristic symptoms, the diagnosis is usually established without difficulty. Almost all these patients have sweat chloride concentrations well within the CF range and carry established CF-causing mutations on each allele.

However, the diagnosis of CF disease is less clear cut among people who carry at least one copy of a class IV or V mutant

gene that confers partial function of the CFTR protein. The proportion of CF adults carrying at least one partially functionally *CFTR* mutation has greatly increased in comparison with patients with CF who are diagnosed in childhood. This seems to be due to two major factors: (a) a survivor effect. As a group, median survival of patients with a mild *CFTR* mutation is almost double that of patients presenting with classic CF disease, and (b) an increase in the frequency of de novo diagnosis in adulthood, based upon the current diagnostic criteria. Nonetheless, a significant number of patients who have diseases linked to mutant CFTR with residual protein function do not meet the current diagnostic criteria for CF disease. These subjects are considered to have CFTR-related disease and should be followed up appropriately.³⁵ In a proportion of these patients disease progression may occur in the organ affected and phenotypic expression may occur in an additional organ system.

The sweat test remains the hallmark diagnostic test for CF.³⁶ Repeat sweat tests should be performed when borderline values are obtained or when CF is suspected. Normal or borderline values do not exclude the diagnosis, especially in adults. Genetic screening for the most common CF-causing mutations is of limited value as a diagnostic tool in adults. Screening panels tend to include only the most common mutations associated with the onset of classic CF in childhood. Adult presentation of CF is often associated with rare mutations, which are not routinely screened for. Furthermore, identification of many of the rare mutations is unhelpful for establishing

or excluding a diagnosis of CF disease, because very few of them have been proved to be CF-causing mutations.

Electrophysiological testing using nasal potential difference (NPD) measurements may aid in the diagnosis of patients with CF with normal or borderline sweat tests and negative or uninformative genetic test results.^{37, 38} This test measures transepithelial sodium and chloride transport in the nasal epithelium. The function of CFTR in chloride secretion is intimately related to the inwardly directed sodium transport via the epithelial sodium channel. The activity of these two channels is the basis for NPD. A catheter is placed under the inferior turbinate and is connected by a series of electrodes to a voltmeter and recorder. The nasal epithelium is perfused with solutions which inhibit sodium transport and activate chloride transport. In patients with CF the readings are markedly dissimilar from those of controls. Another electrophysiological tool is "intestinal current measurement", which measures CFTR function *ex vivo* in rectal biopsy using a modified Ussing chamber.³⁹ Neither NPD measurement nor intestinal current measurement have been validated or standardised as diagnostic tests. Because they are still experimental the results should be interpreted with extreme caution and testing should only be carried out by an experienced operator in a specialist research centre where objective reference values have been established.

Recurrent "idiopathic" pancreatitis

Several studies have shown that patients with idiopathic acute, recurrent and chronic pancreatitis carry a significantly higher

Figure 6 Sweat chloride and nasal potential difference (NPD) measurements. The range and variability for sweat chloride concentration (left) and the CFTR-mediated changes in NPD to chloride-free solution plus isoproterenol (right). The relationships between the groups are demonstrated by arranging box plots for each group along the x axis according to the value of the median. Box plots represent values within the 25th to 75th centile. Values outside the 25th and 75th centiles are represented by circles, and solid circles represent outliers. Thick lines within boxes represent medians. Horizontal dashed lines depict the 95% confidence intervals for the medians of each group. CF-PI, cystic fibrosis with pancreatic insufficiency; CF-PS, CF with pancreatic sufficiency; Control, healthy subjects; Het, obligate heterozygotes for CF; PANC-0, idiopathic pancreatitis and no cystic fibrosis transmembrane regulator (CFTR) mutations; PANC-1, idiopathic pancreatitis and one CFTR mutation; PANC-2, idiopathic pancreatitis and two CFTR mutations. Sweat chloride concentrations and NPD measurements among the PANC-0 and PANC-1 patients were similar to those of the healthy controls and the CF heterozygotes. However, the median sweat chloride value and NPD measurements for the PANC-2 patients with pancreatitis and two mutations were intermediate between the median in the obligate heterozygotes and the median in the CF-PS patients. (Adapted from reference 43.)

frequency of *CFTR* gene mutations than the general population.^{40–42} Bishop *et al* prospectively examined 56 patients with idiopathic recurrent acute or chronic pancreatitis by performing extensive genotyping and transepithelial measures of ion channel function and comparing the findings with those of healthy controls, obligate CF heterozygotes and patients with a prior diagnosis of CF disease (PS and PI phenotypes).⁴³ Genetic analysis showed that 24 (40%) patients carried at least one *CFTR* mutation or variant while 6 (10%) carried alterations on both alleles.

The sweat chloride and NPD results in the patients with pancreatitis ranged from the values for healthy controls and obligate heterozygotes to the values for PS and PI patients with CF (fig 6). Median sweat chloride and NPD results in patients with no mutation or one mutation were clustered with values obtained in controls and obligate heterozygotes. In contrast, in patients with pancreatitis carrying *CFTR* mutations on both alleles, median ion transport values were intermediate between those of the controls and obligate heterozygotes and those of PS patients with CF. Some individual values overlapped with the patients with CF and in 21% of patients the diagnosis of CF could be confirmed by abnormal ion channel measurements. Thus, *CFTR*-mediated ion channel abnormalities are influenced by the number or severity of the *CFTR* mutations and show a range of abnormalities similar to those in patients with mild or severe classic CF at one extreme and controls and obligate CF heterozygotes on the other. This continuum of electrophysiological abnormalities is not surprising as PS patients have a 17% risk of developing pancreatitis and many of these presentations are in adulthood.

Similar observations have been made in people with other CF-like phenotypes such as men with infertility due to congenital bilateral absence of the vas deferens,⁴⁴ who are known to carry a high frequency of *CFTR* gene mutations. A relatively large population was examined, and as for the patients with idiopathic pancreatitis, a wide range of electrophysiological abnormalities was observed. Abnormalities of *CFTR* function correlated closely with the number and severity of *CFTR* mutations. Adults who are referred for recurrent pancreatitis and have evidence of *CFTR* dysfunction should be investigated for CF phenotype in other organ systems and require follow-up at a specialist centre.

Gastrointestinal malignancy

Improved life expectancy among patients with CF has unmasked a significant increase in the incidence of gastrointestinal malignancies. Because the higher prevalence of cancer appears to be associated with *CFTR*-expressing sites, including epithelial surfaces of the intestine and the pancreatic and biliary ductal system, there could be a primary association with loss of *CFTR* function. Case reports^{45–50} led to two sequential epidemiological studies to evaluate the risk of cancer among large CF cohorts. Neglia *et al* used data from 28 511 people recorded in the United States and Canadian Cystic Fibrosis Foundation Patient Registries between 1985 and 1992.⁵¹ Although the overall risk of cancer was similar to that of the general population, they identified a marked increase in risk of malignancies affecting the gastrointestinal tract, pancreas and hepatobiliary system, with an observed to expected ratio of 6.5 (95% CI 3.5 to 11.1). Similarly, Sheldon

et al reported a significant excess of gastrointestinal and other malignancies in 412 patients who were followed up for nearly 30 years.⁵² Unlike Neglia *et al*, they concluded that there was an overall increase in cancer risk and an increased risk of specific gastrointestinal cancers. The risk of malignancies clearly increases with age and peaks after the third decade of life. Because median survival in most developed countries is now in the late 30s, further improvement in patient survival is likely to confer an even greater risk of malignancies. It has been speculated that this phenomenon may be related to the high degree of *CFTR* expression in gastrointestinal epithelia or to the *CF*-related pathological changes on the organs affected. Thus, patients with CF do not seem to have a higher risk of malignancy in the airways or the male genital tract. The relatively higher degree of *CFTR* expression in the gastrointestinal epithelium may in some unknown way account for the preponderance of gastrointestinal cancers. It has even been suggested that *CFTR* should be added to the growing list of genes conferring an increased susceptibility to cancer.⁵³

Consequently, physicians caring for adults with CF should be highly aware of the possibility of malignancy, particularly if symptoms such as unexplained weight loss, jaundice, abdominal pain or bowel obstruction unrelated to DIOS or rectal bleeding are seen. Patients being considered for lung or liver transplant should be carefully screened for malignancies of the pancreas, hepatobiliary tree and gastrointestinal tract.

SECONDARY GASTROINTESTINAL MANIFESTATIONS IN ADULTS WITH CF

Gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease (GORD) is common in patients with CF. In a survey of 50 adults with CF, the majority had symptoms of GORD. Eighty per cent had a history of heartburn and 56% had a history of dyspepsia.⁵⁴ GORD is a multifactorial problem with contributions from both the severity and treatment of lung disease, physiotherapy, transient inappropriate lower oesophageal sphincter relaxation and delayed gastric emptying.

There is some evidence that GORD may contribute to the progression of respiratory disease either by pulmonary aspiration of refluxed gastric contents or by neurally mediated reflex bronchoconstriction secondary to irritation of the oesophageal mucosa.⁵⁵ However, this is debatable and GORD may be secondary to the lung disease. Other complications include malnutrition due to increased losses through emesis, or reduced energy intake from dysphagia and oesophageal strictures. Because silent GOR is common in patients with CF, the absence of reported symptoms does not exclude the presence of GOR.

Fibrosing colonopathy

In 1994, a new complication of CF, affecting mainly the colon, was reported in young patients with CF.⁵⁶ The term “fibrosing colonopathy” was coined to describe what became recognised as an iatrogenic complication, which resulted in considerable morbidity and some mortality. Symptoms include worsening abdominal pain, intermittent bowel obstruction and passage of blood and mucus. Many patients were initially diagnosed as having inflammatory bowel disease. The proximal colon developed a concentric ring of fibrosis below the submucosa, but in some patients the concentric fibrosis extended to the

entire colon, producing the shrunken “pipe stem” effect. There is considerable hypertrophy of the muscularis mucosa and the submucosa shows variable degrees of inflammation with eosinophils and mixed inflammatory cells. Case–control studies in the United Kingdom and the United States showed a strong statistical association between this complication and the dose of pancreatic enzymes (often in excess of 50 000 U lipase/kg body weight).^{57–58} This led to a re-evaluation of the safety of pancreatic enzymes. Notwithstanding, there was no evidence that the excessive doses of enzymes that were used by many clinicians actually improved efficacy or improved abdominal symptoms attributable to maldigestion.

Although several countries have implemented strict dosing guidelines for pancreatic enzyme replacement therapy, a few additional cases of fibrosing colonopathy have been reported in the United States and the United Kingdom. These data give further evidence that “enzyme overdosing” still occurs and also emphasise the need for close monitoring of enzyme doses in all patients with CF. Although fibrosing colonopathy has been confined primarily to infants and young children with CF, there have been isolated case reports in adult patients, some of whom appear to have developed colonic lesions that resemble fibrosing colonopathy.⁵⁹

Intestinal infections

As is the case with healthy neonates, patients with CF demonstrate significantly higher rates of carriage of *Clostridium difficile* (32–50%) than the general population (2%).⁶⁰ The vast majority of patients are asymptomatic, but on rare occasions severe, potentially fatal cases of pseudomembranous colitis have been reported.⁶¹ The clinical manifestations may be atypical, presenting with acute toxic megacolon without diarrhoea. The absence of diarrhoea might be due to the lack of intestinal CFTR function.

There are several possible explanations for the protection from diarrhoea in patients with CF. It is possible that chronic antibiotic treatment allows chronic colonisation with this pathogen, which may induce an immunological protection from diarrhoea. Alternatively, the unique intestinal environment in patients with CF may provide a favourable milieu for this organism. Another hypothesis is that the reduced risk of clinical complications in CF is due to an abnormality in receptor binding of the toxin.⁶¹

Although the clinical significance is unclear, patients with CF have also been noted to have increased colonisation rates of other bacterial species including *Lactobacillus* spp, *Pseudomonas* spp, *Staphylococcus* and *Enterococcus*. A suggestion has been made that CFTR itself acts as a receptor for certain organisms, and thus loss of CFTR affords a form of protection from the consequences of infection.

Giardia lamblia is a common intestinal parasite which may be more common in PI patients from any cause, including CF.⁶² Thus this should be considered in a patient with increased diarrhoea, abdominal distension and anorexia.

Small intestinal bacterial overgrowth

There is indirect evidence that bacterial overgrowth of the small intestine is present in a high percentage of patients with CF, with estimated prevalence up to 50%.⁶³ Risk factors include reduced alkaline flushing of the upper intestine, abnormal

accumulation of surface mucus, which may allow proliferation and adhesion of bacteria, and altered intestinal mucins, which may have limited protective functions. There is also an increased risk of small intestinal bacterial overgrowth after intestinal resection owing to meconium ileus. Although the data are limited, it may be that small-intestine bacterial overgrowth contributes to malabsorption in some patients with CF. The prominent histological feature of the CF mouse small intestine is mucus accumulation, which occludes the crypts and coats the villus surfaces. Mucus obstruction of the crypts is believed to interfere with innate defence mechanisms of the Paneth cells that reside at the base of the crypts and secrete a variety of antibacterial products. There is also evidence of intestinal inflammation characterised by increased mucosal infiltration of mast cells and neutrophils and a 40-fold increase in luminal bacteria. Furthermore, treatment of the bacterial overgrowth reduces mucus accumulation. One may speculate that small intestinal bacterial overgrowth in the CF mouse small intestine is similar to that reported in humans.^{64–66} Adult patients with CF with refractory or unexplained symptoms merit thorough investigation.

OTHER CLINICAL CONDITIONS ASSOCIATED WITH CFTR DYSFUNCTION

Several reports suggest that heterozygosity for a *CFTR* mutation has the potential to act as a disease susceptibility factor in combination with an anatomical abnormality, environmental or social class effect or other complex genetic traits. For example, the potential cause–effect relationship between pancreas divisum and pancreatitis has been debated for many decades. To examine a potential link with CFTR dysfunction Gelrud *et al*⁶⁷ performed NPD on 12 adults with pancreas divisum and recurrent pancreatitis. CFTR-mediated ion conductance, was intermediate in the patients with pancreas divisum—between the results observed for healthy controls and patients with CF. This interesting observation suggests that loss of functional CFTR may be a risk factor for recurrent pancreatitis in a subset of patients with this anatomical variant of the pancreas. Nevertheless, this observation does require confirmation in a larger patient cohort with pancreas divisum (with and without pancreatitis). If confirmed, there may well be ramifications for patient selection of therapeutic options.

Cholangiographic studies of patients with CF and liver disease sometimes show intrahepatic ductal abnormalities which resemble the characteristic beading picture of primary sclerosing pancreatitis (PSC). For this reason several studies have evaluated patients with PSC for evidence of loss of CFTR function by CFTR mutation analysis and NPD measurements. The results of one study suggested that patients with PSC have a higher frequency of *CFTR* gene mutations than the general population, and some NPD measurements were intermediate between those for controls and CF subjects.⁶⁸ None of the patients were found to carry a diagnosis of CF nor did they carry two *CFTR* mutations. Although the second study failed to show evidence of a higher frequency of *CFTR* gene mutations in patients with PSC, genotyping was limited to a small number of CF-causing mutations.⁶⁹

Less than 70 years ago CF was first described as a distinct clinical entity from coeliac disease. Subsequently several reports have suggested that the prevalence of coeliac disease in patients

with CF is higher than that expected in the general population.⁷⁰ However, definitive studies using antibody and HLA testing remain to be done.

Lloyd-Still *et al* reported that the prevalence rate of Crohn's disease in patients with CF is seven times higher than in controls.⁷¹ However, many cases were reported before the description of fibrosing colonopathy. Some cases may have been due to the complications of high-dose enzyme therapy.

SUMMARY AND CONCLUSIONS

Increased longevity of patients with CF diagnosed in childhood has resulted in changes in the natural history of the disease; an example is cancer, which will certainly be an increasing burden in the future. In addition, patients with a de novo diagnosis of CF in adulthood often present with more subtle symptoms affecting a single organ, which may not resemble the characteristic features of presentation in childhood. Furthermore, a large percentage of adults presenting with CF-like symptoms will have some ion channel abnormalities and/or mutations in the *CFTR* gene which do not fulfil the current diagnostic criteria for CF disease. Little is known about the clinical course, response to treatment, and life expectancy of these people. They can be informed that significant differences exist in their condition in comparison with the classic CF phenotype, and this may provide a measure of reassurance. In addition, gastroenterologists must be aware of the manifestations that may lead to a de novo diagnosis of CF in adulthood and should recognise the difficulties of definitively establishing or excluding the diagnosis of CF in every situation.

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EDITOR'S QUIZ: GI SNAPSHOT

Answer

From question on page 1123

The histological assessment shows antral-type gastric mucosa with free lying giardia (fig 1, arrow). The most likely predisposing factor is proton pump inhibitor (PPI) use. She also had *Helicobacter pylori* infection, which was treated for 7 days with metronidazole based triple therapy as she was allergic to penicillin. Seven weeks later her gastric as well as her duodenal biopsies did not show any evidence of the giardia infection. She was a frequent global traveller and had travelled widely in Asia and Europe. She did have very occasional episodes of diarrhoea with a frequency of 3–4 per day, on average, once a month.

Giardiasis is the most common small intestinal protozoal infection and is found worldwide. Gastric giardiasis (GG) is a rare disorder, of which fewer than 90 cases have been reported in the literature. It is a self-limiting infection in more than 85% of cases. Excystation occurs in the acidic conditions of the stomach and is maximal at pH 1.3–2.7. "Optimal" pH for giardia trophozoites is 6.38–7.02. Normally, the acidic milieu in the stomach causes excystation releasing the trophozoites which then colonise the small bowel where bile serves as a primary growth stimulant.

Conditions of increased gastric pH such as hypochlorhydria (primary or secondary to medications), partial gastrectomy, atrophic gastritis or biliary reflux can result in giardia colonisation of the gastric epithelium. GG is usually seen in the antrum, probably as a result of biliary reflux, and is usually associated with *H pylori* infection. It has been reported that GG can be induced by the use of PPI therapy and the infection can disappear within 4 weeks of stopping PPI therapy without any specific therapy for GG.¹

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