Gastro-intestinal manifestations in cystic fibrosis patients

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Abstract

Cystic fibrosis (CF) is a life-limiting disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR). This defective chloride channel, present in different organ systems such as respiratory system, gastrointestinal tract, reproductive system and sweat glands, disturbs the ion and water transport over the membranes leading to the well known CF symptoms.

CF has outgrown paediatric care, as half of CF patients are currently adults. The CF gastrointestinal tract has its own particularities. Some gastrointestinal manifestations are the direct consequence of the CFTR defect whilst others are secondary to treatment.

The gastrointestinal diseases are classified according to the way they usually present in symptoms at diagnosis, acute and chronic abdominal pain and silently evolving conditions. (Acta gastroenterol. belg., **2016**, 79, **481-486**).

Key words : cystic fibrosis, DIOS, meconium ileus, CF liverdisease, Colon cancer, and bacterial overgrowth.

Introduction

Cystic fibrosis (CF) is an autosomal multisystemic recessive disorder caused by mutations in the cystic fibrosis transmembrane regulator (CFTR) gene. Over 1500 mutations have been described. They are classified into 6 different groups according to the effect on the CFTR protein. Classes I, II and III result in absent CFTR function and classes IV, V and VI in decreased CFTR function (1).

The CFTR protein is present in the apical epithelial membrane of different organ systems such as the respiratory tract, the gastrointestinal system, sweat glands and the reproductive system. It regulates chloride and associated fluid secretion (2). Improved pulmonary care and lung transplantation resulted in an increased life expectancy for CF patients (3). The association between nutritional status and pulmonary function is well known. Therefore nutritional experts are always involved in the multidisciplinary approach of these patients.

Recently new drug developments not only target the downstream consequences of a dysfunctional CFTR protein but also try to enhance CFTR protein function (4). Since this development, understanding the molecular defect of a specific mutation has become even more important (4). Read-through agents allow translation through class I non-sense mutations. Correctors facilitate class II protein processing, increasing the CFTR protein quantity in the membrane and potentiators increase the class III CFTR function (5). The first CFTR potentiator (Ivacaftor) is since the beginning of this year available for Belgian patients with specific class III mutations. How the future of these patients will change, remains to be determined although intermediate evaluations are optimistic (6).

With a median survival of patients approaching the age of 40 years, non-respiratory complications are becoming increasingly important (3). As gastrointestinal symptoms are the second most frequently encountered manifestations in CF, it is important to know the particularities of the CF gastrointestinal tract.

Gastrointestinal presenting symptoms

Meconium Ileus

This neonatal intestinal obstruction syndrome, caused by abnormal meconium in the terminal ileum, is the presenting sign in 10-20% of CF newborns (7). The obstruction may be complicated by an ileal atresia or perforation and may be associated with a microcolon (7,8). Term babies with meconium ileus have CF in 80% of cases, but also 25% of preterm babies (7,9). CF should be suspected and a sweat chloride test is warranted. Treatment depends on the condition of the neonate. Hyperosmolar enemas and nasogastric decompression may be applied but in case of failure or clinical deterioration surgical management will be necessary. There is no difference in outcome for CF infants presenting with or without meconium ileus (10).

Neonatal cholestasis

About 5% of all CF neonates develop cholestasis, which may be associated to acholic stools (11). Patients with meconium ileus have an increased risk to develop

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cholestasis (11). The cholestasis resolves spontaneously within 10 months (2-19 months) (9). Neonatal cholestasis is not a predicting factor for the development of CF related liver disease later in life (11,12). Treatment consists of classic CF treatment associated with ursodeoxycholic acid.

Exocrine pancreatic insufficiency

The pancreas is the first failing organ in CF. Seventy per cent of CF patients have pancreatic insufficiency at birth and another 15-20% will develop it within the first 3 years of life (13). This is in contrast to patients diagnosed at older age, which have a higher likelihood to be pancreatic sufficient (65% pancreatic insufficient) (14).

There is an insufficient enzyme secretion and bicarbonate production resulting in low volume pancreatic secretions with increased protein concentration and a low duodenal pH, promoting bile acid precipitation (15, 16). In more than 90% of cases, CF is the cause of pancreatic insufficiency during childhood (17).

The major symptom of pancreatic insufficiency during childhood is failure to thrive despite often an enormous appetite (18). Steatorrhoea may not be recognised by the parents but orange stools should ring a bell (Fig. 1). More subtle symptoms such as vitamin K dependant coagulation disorders, hypoalbuminemia and acrodermatitis enteropatica due to zinc or essential fatty acid deficiency may also point towards pancreatic insufficiency and CF (19). Finally, rectal prolapse due to the bulky stools will be the presenting sign in 3,5% of CF patients (20).

Diagnostic tests are the 72-hours faecal collection for fat analysis to calculate the fat absorption coefficient or faecal elastase determination (21). Treatment consists of pancreatic enzyme replacement therapy (PERT) and fat-soluble vitamin supplementation based on serum vitamin concentrations (22,23). Dosing the enzymes is merely based upon expert opinion, as studies addressing this problem in CF are scarce (24). Some studies plead for the use of proton pump inhibitors in case of insufficient correction of the fat malabsorption with PERT. The rationale is based upon the increase in duodenal luminal pH. The pH optimum for dissolution of the enteric coat may be reached earlier in the gastrointestinal tract (25).

Metabolic alkalosis

Hyponatriemic, hypokalemic alkalosis may be the presenting sign of CF especially when the patient has an associated condition leading to increased sweat or gastrointestinal fluid losses (diarrhoea, vomiting) and decreased fluid intake (18,26,27). Extracellular dehydration and chloride depletion induce the observed electrolyte shifts (26). It is more frequently reported in young children (<2,5 years of age) and has a tendency to recur (26). The dehydration is often clinically underestimated. Acute treatment consists of correction of hydration and salt status, intravenously or orally. Prevention is managed using salt supplements and sufficient fluid intake in case of expected increased losses (28).

Acute (recurrent) pancreatitis

Acute recurrent pancreatitis occurs in 14-22% of the pancreatic sufficient CF patients (29,30,31). It may be the presenting symptom in adolescents or adults (31,32). The clinical picture is that of a classic pancreatitis with pain, increased serum lipase and amylase and a swollen pancreas on ultrasound. Repeated episodes of pancreatitis are reported in 2-13% of patients and may lead to pancreas insufficiency over time (31,32). Treatment is supportive but remaining pancreatic function should be monitored.

Acute abdominal pain in cystic fibrosis patients

Distal intestinal obstruction syndrome (DIOS)

DIOS is a partial or complete intestinal obstruction in the terminal ileum and caecum caused by sticky stools developing over a few days (33). Symptoms consist of acute right fossa pain, anorexia and eventually vomiting. An ileocaecal stool impaction may be palpated on

Fig. 1. — Orange fat containing stools

physical exam or visualised on ultrasound and plain abdominal radiography (34). It occurs in 5-9/1000 patient years in children (33). The incidence in adult CF patients using the same definition is not yet reported. Older studies claim an increased incidence (35,5 episodes/1000 patient years) around the age of 20-25 years (35). Patients with a previous DIOS episode, meconium ileus and mutations resulting in absent CFTR function and patients receiving lung transplantation are at higher risk.

The pathophysiology of DIOS is still unclear. The decreased water content of the mucus layer and stools has been blamed. There is no association with nutritional or enzyme intake (36). Some studies demonstrate the presence of transmural inflammation affecting the intestinal innervation suggesting an associated motility problem. Literature is unequivocal (37).

Conservative treatment with stool softeners and hydration is successful in most cases (38). Oral polyethylene glycol or picosulfate preparations are successful in cases of incomplete obstruction. Hyperosmolar enemas are recommended in cases of complete obstruction. When performing an enema it is important to achieve ileal filling. However, in 4% of cases surgery will be necessary (33, 34).

Intussusception

Intussusception is more frequent in CF and occurs also in atypical age categories (39). It may present as an acute abdominal pain syndrome but also as recurring pain as a result of intermittent and spontaneously reducing intussusception. Ileocaecal intussusceptions are most frequent. Diagnosis relies on ultrasound or CT scan (14). Treatment consists of reduction using enema or surgery in case of failure (40).

Cholelithiasis

Since it is advised to perform liver ultrasound on at least a yearly basis for the detection of CF related liver disease, asymptomatic gallbladder stones are detected in up to 25% of CF patients (12). Symptomatic disease will only be present in 3% of patients (41). CF patients have a lithogenic bile composition due to differences in pH and bile acid composition. Patients carrying a UGT1A1 promotor mutation for Gilbert's syndrome have an odds ratio of 7 for developing cholelithiasis (42).

Treatment should only be proposed when stones cause symptoms and consists of the classical endoscopical and/ or surgical methods to remove the bile stones.

Clostridium difficile infection

Clostridium difficile infection causes an atypical clinical picture in which diarrhoea might not be prominent. (43). Patients often vomit; have signs of obstruction and display fever. An important inflammation may be observed in the blood and imaging reveals an important colonic wall thickening due to inflammation. Stool cultures will be positive for toxogenic *Clostridium difficile*. One should be aware of the high carriage rate of non-toxigenic *Clostridium difficile* in CF patients (44). Treatment consists of metronidazole or vancomycin orally eventually associated with probiotics and even steroids in case of important inflammation (43,45).

Chronic gastrointestinal complaints

Gastro-oesophageal reflux

Pathological gastro-oesophageal reflux has been reported in 66% of children and 86% of adult patients (46, 47). An association between cough and reflux episodes (46,47) as well as earlier *Pseudomonas* colonisation and worsening pulmonary function in patients with gastro-oesophageal reflux has been described (48). Treatment with proton pump inhibitors does not result in increased pulmonary infections (48) while fundoplication, has variable outcomes according to literature (49,50).

Constipation

Constipation is a frequent chronic problem in about 50% of CF children but poorly described in adults (51). It may cause abdominal complaints and infrequent stools with increased consistency. It is more frequent in patients with a history of meconium ileus and poor fat absorption (52). Relationship with fibre or fluid intake is not observed (52). Treatment consists of optimising fat digestion and laxatives.

Fibrosing colonopathy

This complication was first reported in 1994 as an iatrogenic pathology in children with CF (53,54). Recently also adults with this problem have been described (55-57). It was initially attributed to high dose lipase treatment often exceeding 50.000 U lipase/ kg (3,8/1000 patient years) (53,54). However, as fibrosing colonopathy has been described in CF patients unexposed to high dose lipase (57, 58), the colonopathy may evolve in the absence of, although undoubtedly exacerbated by, exogenous lipase (59). Histologically concentric fibrotic rings beneath the submucosa starting in the proximal colon and extending over a different length are observed (60). This is associated with a muscularis mucosae hypertrophy and submucosal inflammation in the absence of mucosal inflammation (53,60). The clinical picture consists of abdominal pain, abdominal distension, stool changes (from constipation to diarrhoea) and sometimes blood and mucus discharge. Risk factors for developing fibrosing colonopathy are a history of meconium ileus, DIOS, previous intestinal surgery, male gender and dehydration periods. Treatment consisted initially of surgical resection of the attained colonic segment. Recent studies describe successful treatment with budesonide and antibiotics (56).

Table 1. — **Criteria for the diagnosis of CF related liver disease (67).**

Physical exam	Hepatosplenomegaly
Blood tests	Increased liver enzymes for at least 6 months
Ultrasound	HepatosplenomegalySigns of cirrhosis

Presence of 2 out of 3 criteria is suggestive for CFLD after exclusion of other causes.

Small intestinal bacterial overgrowth

The CF small intestine is particularly prone to bacterial overgrowth due to prior surgery as well as the frequent use of antibiotics and proton pump inhibitors. The CF intestine itself, however, has also a decreased mucosal barrier due to lower intestinal alkaline phosphatase activities (61-63). It is observed in 30-55% of CF patients (64,65). Symptoms associated to bacterial overgrowth are bloating, impaired nutrient absorption, abdominal pain and rarely diarrhoea (66). Treatment consists of antibiotics.

Silently developing problems

CF related liver disease

CF related liver disease (CFLD) consists of focal biliary cirrhosis, present in 30-40% of patients (67, 68). Some develop multilobular cirrhosis (5-15%), portal hypertension (2-5%) and liver failure (<1%) (67). Risk factors are CFTR mutations leading to absent protein function, pancreatic insufficiency and carriership of the Z-allele α1- antitrypsin gene (SERPINA1) (OR 5) (69). CFLD develops silently before puberty. Hepatosplenomegaly and manifestations of portal hypertension may become apparent later on. Because of the lack of specific diagnostic tests, the diagnosis is made based upon criteria (70). The presence of two out of three criteria are suggestive for CFLD (Table 1). Transient elastography is a promising non-invasive technique in the follow-up of liver involvement (71). Current treatment is limited to ursodeoxycholic acid, which will normalise liver enzymes (72), although it is not known whether this changes final outcome (73). If liver disease progresses, evaluation and treatment of portal hypertension, as well as liver transplantation in case of liver failure might be needed.

Intestinal malignancy

The incidence ratios for intestinal (6.2 (95% CI 4.2-9.0)) and colon cancer (11.5 (95% CI 4.2-25.4)) are increased in the adult CF population (74-76). Male patients, CFTR mutations resulting in absent CFTR function as well as patients with a history of DIOS have a higher risk for developing malignancies (74). Although the aetiology is unknown, the increased intestinal inflammation and epithelial cell turnover in CF have been suggested as promoting factors (77,78). Implementation of a universal colonoscopy screening program needs further evaluation for cost effectiveness, as well as timing.

CF related diabetes

CF related diabetes is an increasing problem with age. Thirty per cent of adolescents and 50% of adults develop diabetes. It is a combined problem of insulin resistance and insulin deficiency. Because patients have a steeper decline in pulmonary function and decreasing nutritional status 5 years before diabetes is diagnosed, good clinical care consists of yearly oral glucose tolerance tests starting from the age of 10 (79,80). Detecting diabetes early may prevent the decline in pulmonary function and nutritional status (81). Diabetes should be well controlled, as patients develop microvascular complications after 5-10 year of diabetes. Treatment consists of maintaining nutritional status, decreasing insulin resistance with physical activity, infection treatment and regulating blood glucose using insulin injections (81).

Conclusion

Cystic fibrosis patients often complain about abdominal pain, which has an important impact on quality of life. The particularities of the CF gastrointestinal tract, widens the differential diagnosis. This review discussed the symptoms and management of frequently encountered conditions according to their presentation. As more than 50% of cystic fibrosis patients are adults, adult gastroenterologists need to be aware of the specific CF gastrointestinal manifestations to provide appropriate follow-up of these patients.

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