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Alimentary Tract

Bowel ultrasound imaging in patients with cystic fibrosis: Relationship with clinical symptoms and CFTR genotype

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ABSTRACT

Background: Ultrasound imaging is used to assess bowel abnormalities in gastrointestinal diseases. We aimed to assess the rate of predefined bowel ultrasound signs and their relationship with gastrointestinal symptoms and the cystic fibrosis transmembrane conductance regulator (CFTR) genotype in cystic fibrosis patients in regular follow-up.
Methods: Prospective study of 70 consecutive patients with cystic fibrosis and 45 controls who underwent abdominal ultrasound; pertinent findings were related to gastrointestinal symptoms and, in cystic fibrosis patients, to pancreatic status, malabsorption degree, lipase intake, CFTR genotype (classified as severe or mild against functional class of CFTR mutations).
Results: 96% patients showed at least one abnormal bowel ultrasound sign. Most frequent signs were lymph node enlargement (64%), bowel loop dilatation (55%), thick corpuscular intraluminal content (49%), bowel wall hypervascularization (26%), thickened bowel wall (22%) and intussusception (17%). Patients with recurrent abdominal pain showed more bowel wall hypervascularization than patients without recurrent pain (47% vs. 19%, respectively; $p = 0.02$) and intussusception (58% vs. 17%, respectively; $p < 0.01$). Genotype was not associated to specific bowel ultrasound signs. Patients with bowel loop intussusception showed greater lipase intake than those without intussusception (8.118 ± 2.083 vs. 5.994 ± 4.187, respectively; $p < 0.01$).
Conclusion: Cystic fibrosis patients present a higher rate of bowel ultrasound abnormalities than controls. Bowel ultrasound abnormalities are associated with abdominal symptoms.

1. Introduction

Cystic fibrosis (CF) is the most common genetic defect in Caucasian populations. It is an autosomal recessive disease caused by mutations in the CFTR gene on chromosome 7. The disease is owed to the lack or dysfunction of CFTR protein – a chloride channel that regulates ion transport in the apical membrane of epithelial cells – and results in the production of abnormally thick secretions and damage in multiple organ systems, including the lungs, pancreas, liver, intestine, and reproductive tract [1].

Gastrointestinal symptoms occur in 85–90% of CF patients as a result of pancreatic insufficiency (with malabsorption and steatorrhea), pancreatitis, distal intestinal obstruction syndrome (DIOS), liver disease (focal or multilobular biliary cirrhosis) and biliary tree abnormalities including gallstones [2,3]. Although recurrent pulmonary infections and respiratory failure are the main causes of morbidity and mortality, gastrointestinal symptoms often precede the pulmonary findings and have a significant impact on the course of the disease through their influence on the nutritional status of patients at all ages.

CFTR is expressed throughout the intestine and over the last few years there has been an increasing interest in the possible consequences of CFTR dysfunction in terms of obstruction, infection

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and inflammation, as it occurs in the airways [4,5]. Patients with CF may develop constipation and frank obstruction, mucus accumulation, disturbed motility, dysbiosis with small-bowel bacterial overgrowth and chronic intestinal inflammation, which may predispose to malignancy. Many of these aspects have been explored in animal models [6].

Imaging studies with computed tomography (CT) or magnetic resonance (MR) often show small bowel alterations [7,8]. Imaging plays an important role in the evaluation of CF patients: however there are several drawbacks, including radiation exposure and costs, both of which may limit its use in the long-term follow-up of CF patients. Recent technological advances in ultrasonography (US) with the availability of high-frequency transducers have facilitated the increasing use of US for the evaluation of the small and large bowel (B-US) [9]. Several studies have shown that B-US examination may be useful in the identification and follow-up of inflammatory bowel diseases (IBD) and in diseases associated to malabsorption, e.g. celiac disease or intestinal lymphoma, with an overall good inter-observer agreement [10–14]. In these conditions the most commonly observed findings are: bowel wall irregularities (e.g. bowel wall thickening and/or luminal narrowing or hypervascularization) and abnormalities of adjacent structures (e.g. lymphoadenomegalies, mesenteric adipose tissue alteration or fluid within the abdominal cavity). Thanks to its many advantages, B-US has been proposed as a useful tool for these patients, preliminary to other more expensive invasive investigations in assessing gastrointestinal complications [10]. In CF populations the most common US findings described in previous studies comprised the presence of thickening or alterations of small intestine or colonic bowel wall, the presence of enlarged mesenteric lymph nodes or, more rarely, the presence of an enlarged appendix [15–17].

The aim of this study was to assess the rate of some predefined B-US signs in CF patients, who presented with or without gastrointestinal symptoms, and the correlation of those signs with clinical symptoms and CFTR genotype.

2. Patients and methods

2.1. Study design

A prospective study was performed on CF patients with an established diagnosis of CF (one or more phenotypic characteristics and a sweat chloride concentration of >60 mmol/l) [18] and on regular follow-up as outpatients at our Centre during the period from January 2012 to June 2013. Controls were recruited among outpatients referred to the Gastroenterology Unit of the same University Hospital, in whom a gastrointestinal disease had already been adequately excluded. The study protocol was approved by the Ethics Committee of the Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan and all the participants, or their parents/guardians, provided written consent before enrolment.

Genetic analysis of the CFTR gene had previously been performed on all the CF patients. Genotypes were classified into mild or severe based on the functional class of CFTR mutations. The patients with both mutant alleles in class I, class II or class III (which are associated with the lack of functional CFTR protein at the apical membrane of epithelial cells) were grouped together as having a severe genotype, while the patients with at least one mutant allele belonging to class IV and class V (which in contrast are associated with some residual functional CFTR protein) were considered to have a mild genotype [17]. The patients carrying at least one mutation that could not be attributed to a specific functional class were excluded from the genotype analysis (7 patients). All CF patients had pancreatic status assessment by means of faecal elastase-1 levels. All patients with pancreatic insufficiency were receiving pancreatic enzyme replacement therapy (PERT) and were regularly monitored for the correction of steatorrhea by means of a semi-quantitative test, the steatocrit [20]. Steatocrit data concomitant to B-US evaluation were available in 51 out of 58 patients. Values <3 were considered indicative of no significant steatorrhea.

2.2. Bowel ultrasound

B-US was performed on all the patients and controls, in fasting conditions from the midnight of the previous day, by four experienced (i.e. having practiced bowel ultrasound for at least five years) ultrasonographers (MF, AB, SDV, CBC) who were blind to clinical and laboratories data. B-US was performed with the same ultrasonographic equipment (Philips iU22, Bothell, USA) using both a convex low-frequency (3.5–5 MHz) and then a linear-array high-frequency transducer (5–12 MHz). The following B-US parameters [21–23] were considered (see Fig. 1 for exemplificative images).

Bowel wall thickness, obtained as the average of three measurements in a transverse section of both the ileal and colonic tract. The measurement was taken from the central hyperechoic line of the lumen to the outer hyperechoic margin of the wall (representing serosa), using the linear-array transducer. The bowel wall was considered "normal" if its thickness was less than 4 mm for all the intestine with the exception of the descending and sigmoid colon, which was considered "normal" if less than 5 mm [22].

Vascularization within the bowel wall, normal or increased, as documented at power Doppler examination [21]; the sign was considered positive in case of visualisation of blood signals at the Power Doppler examination.

Bowel wall pattern, either normal multi-layered pattern or disruption of the multilayered feature.

Bowel compressibility, either maintained or reduced; this sign was assessed by the change in shape of the transverse section of the bowel under gentle compression with the probe [21].

Bowel content characteristics [21], either transonic or corpuscular.

Bowel motility, either normal or impaired; during the examination the presence/absence of bowel peristalsis with particular attention to the luminal content movement was observed for few minutes [21].

Mesenteric adipose tissue alteration, defined as the presence of a hyperechoic sometimes inhomogeneous area surrounding the thickened bowel wall [22].

Enlarged mesenteric lymph nodes were defined as a shorter axis greater than 5 mm [21]. Free fluid within the peritoneal cavity [21].

Luminal narrowing or stenosis or intussusception, the latter defined as the sliding of part of the intestine into an adjacent part of the intestine [15].

Hepatic parenchymal inhomogeneity and surface nodularity [23]. The normal liver parenchyma is of medium homogenous echogenicity, usually slightly darker than the spleen and slightly brighter than the renal cortex. The normal surface (detected with a high frequency transducer) is smooth and regular, whereas in chronic liver diseases the liver surface appeared as a dotted or irregular line and/or the liver parenchyma is not homogeneous.

2.3. Statistical analysis

Categorical data were compared with Fisher's exact test. Quantitative variables were compared with Wilcoxon's test or Student's *t*-test, as appropriate. The threshold for significance was 0.05 ($p < 0.05$). The R software was used for the statistical analysis (R Core Team, 2014 – R: a language and environment for statistical