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Alimentary Tract

Natural history of pancreatic involvement in paediatric inflammatory bowel disease

Massimo Martinelli[a], Caterina Strisciuglio[a], Maria Teresa Illiceto[b], Sabrina Cardile[c], Graziella Guariso[d], Silvia Vignola[e], Marina Aloi[f], Mario Rocco D'Altilia[g], Patrizia Alvisi[h], Silvia Salvatore[i], Annamaria Staiano[a], Salvatore Cucchiara[f], Erasmo Miele[a,*], on behalf of IMIBD Group of the Italian Society for Paediatric Gastroenterology, Hepatology and Nutrition

[a] Department of Translational Medical Science, Section of Pediatrics, University of Naples "Federico II", Naples, Italy
[b] Pediatric Gastroenterology Unit, Spirito Santo Hospital, Pescara, Italy
[c] Endoscopy and Gastroenterology Unit, Department of Pediatrics, University of Messina, Italy
[d] Department of Pediatrics, Unit of Gastroenterology, University Hospital of Padova, Italy
[e] Gastroenterology and Endoscopy Unit, G. Gaslini Institute for Children, Genoa, Italy
[f] Pediatric Gastroenterology and Liver Unit, Sapienza University of Rome, Italy
[g] Division of Pediatrics, General Hospital I.R.C.C.S., S. G. Rotondo (Fg), Italy
[h] Pediatric Unit, Maggiore Hospital, Bologna, Italy
[i] Department of Pediatrics, University of Insubria, Varese, Italy

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ABSTRACT

Background: Few case reports describe the clinical features of pancreatic involvement in inflammatory bowel disease.
Aim: To investigate prevalence and disease course of inflammatory bowel disease children with pancreatitis and with exclusive hyperamylasemia and hyperlipasemia.
Methods: We used a web-registry to retrospectively identify paediatric inflammatory bowel disease patients with hyperamylasemia and hyperlipasemia. Participants were re-evaluated at 6 months and 1 year.
Results: From a total of 649 paediatric patients, we found 27 with hyperamylasemia and hyperlipasemia (4.1%). Eleven patients (1.6%) fulfilled diagnostic criteria for acute pancreatitis. Female gender was significantly associated with acute pancreatitis ($p = 0.04$). Twenty-five children (92.5%) had colonic disease. At 6 months 1/11 children with acute pancreatitis (9%) showed acute recurrent pancreatitis, while 1 patient (9%) had persistent hyperamylasemia and hyperlipasemia. At 12 months, 1 patient showed chronic pancreatitis (9.1%). Of the 16 children with exclusive hyperamylasemia and hyperlipasemia, 4 developed acute pancreatitis (25%), while 1 patient (6.2%) still presented exclusive hyperamylasemia and hyperlipasemia at 6 months. At 12 months, 11/16 patients (68.7%) reached a remission of pancreatic involvement, whereas 5 remaining patients (32.3%) had persistent hyperamylasemia and hyperlipasemia.
Conclusions: In inflammatory bowel disease children, acute pancreatitis is more common in colonic disease and in female gender. Pancreatic function should be monitored, considering that pancreatic damage may evolve.

1. Introduction

Inflammatory bowel disease (IBD), characterized by chronic, relapsing immune-mediated inflammation of the gastrointestinal tract is often associated with extra-intestinal manifestations (EIMs) affecting multiple organs. EIM are reported to occur in 18–47% of paediatric and adult patients with IBD [1–5]. Acute and chronic

* Corresponding author at: Department of Translational Medical Science, Section of Pediatrics, University of Naples "Federico II", Via S. Pansini, 5, 80131 Naples, Italy. Tel.: +39 081 7464565; fax: +39 081 7464565.
E-mail address: erasmo.miele@unina.it (E. Miele).

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pancreatitis as well as pancreatic insufficiency have been reported as one of EIMs in IBD [6].

Acute pancreatitis (AP) in children is a costly and increasingly recognized disease. Several studies have documented an increase during the past 10–15 years [7]. Estimated incidences range from 3.6 to 13.2 cases per 100,000 children per year [8,9]. The reasons for the increase are not entirely clear and may be multifactorial. An Australian study suggests that the increasing number is mainly due to the complications of systemic illness [9]. Patients with IBD are at increased risk of developing both acute and chronic pancreatitis. Clinical symptoms of IBD-associated pancreatitis are found in about 2% of patients but the actual frequency of the disease could be much higher. According to several studies, hyperamylasemia and exocrine pancreatic insufficiency are found in 6–16 and 21–80% of adult patients, respectively, whereas histological changes are observed in 38–53% of postmortem pathological examinations [6,10–12]. There are only limited published data on the incidence of acute pancreatitis in paediatric patients with IBD [13,14]. Although pancreatitis can be seen in association to drugs assumption, biliary lithiasis, Crohn's disease (CD) duodenal involvement or sclerosing cholangitis, the contribution of these etiological factors to histopathology-proved pancreatitis appears to be low and IBD itself seems to contribute to the pathogenesis [5]. In addition, a previous study also indicates that the rarer variant, autoimmune pancreatitis, occurs more often among IBD patients [15]. Regards to drugs, several case reports about drug-induced pancreatitis have been published [16]. Nevertheless, it is always difficult to establish a causal role for medications in the pathogenesis of pancreatitis, but a few medications are clearly associated with a high risk for drug-induced pancreatitis. This is true with regard to some medications used in IBD management. Of the medications, the possible agents inducing pancreatitis include sulfasalazine, 5-aminosalicylic acid (ASA) compounds, azathioprine (AZA), metronidazole and steroids [17,18]. Complicating the scenario it appears that IBD-associated pancreatic involvement may be often a silent disease in children. Various possible explanations for asymptomatic hyperamylasemia and hyperlipasemia in IBD patients have been proposed. The pancreatic enzyme elevation observed in more extensive or active disease can represent the abnormal passage of pancreatic amylase from the gut lumen to the blood due to increased permeability of the inflamed mucosa [19]. In addition, there are several potential mechanisms for the suggested enzyme leakage from the pancreas. First, the pancreas might be affected in some way directly by the extent of IBD. Another explanation could be an enzyme increase related to the pancreatic effects of inflammatory mediators and cytokines released from the inflamed gut. A third mechanism might be associated with inflammation of pancreatic ducts [6].

Despite scattered case reports, the relationship between pancreatic involvement and IBD has not been further investigated. The primary aim of the present study was to investigate prevalence and disease course of paediatric IBD patients presenting with pancreatitis; secondary aim was to evaluate the clinical significance of exclusive hyperamylasemia and hyperlipasemia in children with IBD.

2. Subjects and methods

We retrospectively reviewed data collected in the IBD web-registry of the Italian Society for Paediatric Gastroenterology, Hepatology and Nutrition (SIGENP). Paediatric gastroenterologists from all the Italian paediatric IBD centers belonging to the SIGENP, established in 2008 a prospective registry to collect demographic, clinical, and epidemiologic data from paediatric patients with IBD. The registry started the 1st January 2009 and included patients less than 18 years with a new diagnosis of IBD. Data of all paediatric patients enrolled and stored in the registry from January 1, 2009 to November 30, 2012 (data retrieval date) were used for this study. Nine sites participated to this study; trained investigators at each centre obtained information from the medical records (electronic and paper charts) and standardized information was entered into the registry. Eligible subjects included all patients with any form of IBD [ulcerative colitis (UC), CD and inflammatory bowel disease unclassified (IBD-U)]. Diagnosis of IBD was based on clinical history, physical examination, endoscopic appearance, histologic findings, and radiologic studies, according to Porto criteria [20]. All patients presenting with serum amylase $\geq$100 IU/L (normal range: 28–100 IU/L) and serum lipase $\geq$60 IU/L (normal range: 13–60 IU/L) were included in the study. Participants were additionally evaluated within 6 months, and 1 year from enrolment. AP was defined as the presence of 2 of the following criteria: (a) abdominal pain compatible with AP, (b) serum amylase and/or lipase values $\geq$3 times upper limits of normal, (c) imaging findings of AP [21]. Acute recurrent pancreatitis (ARP) was defined as: $\geq$2 distinct episodes of AP with intervening return to baseline. The severity of AP episodes was assessed with the Paediatric Acute Pancreatitis Score (PAPS), developed by DeBanto and colleagues [22]. The system has eight parameters, scored at admission and at 48 h. The admission criteria include: age <7 years, weight <23 kg, white blood cell count >18,500/mm^3, and LDH > 2000 U/L. The 48-h criteria are trough calcium < 8.3 mg/dl, trough albumin < 2.6 mg/dl, fluid sequestration > 75 ml/kg/48 h, and a rise in BUN > 5 mg/dl. One point is assigned for each criterion met; a score of $\geq$3 is predictable of a severe course of disease [22]. Chronic pancreatitis (CP) was diagnosed if one of the following criteria was present: (a) typical abdominal pain plus characteristic imaging findings; (b) exocrine insufficiency plus imaging findings; (c) endocrine insufficiency plus imaging findings. Exclusive hyperamylasemia and hyperlipasemia was used to describe those patients who did not meet diagnostic criteria for pancreatitis [20].

The information retrieved for the purpose of this study included demographic features (age, gender), IBD type (CD, UC, IBD-U), median lag time period between the diagnosis of IBD and pancreatic involvement episodes, and disease location. The disease location at the diagnosis and at follow-up was established by endoscopic and imaging evaluations in all patients according to the availability of individual methods for each centre and reported in the registry. For the purpose of this manuscript, disease location was described according to Paris classification [23]. Disease activity at the diagnosis was scored by the Paediatric Crohn's Disease Activity Index (PCDAI) [24] or the Paediatric Ulcerative Colitis Activity Index (PUCAI) [25] for CD and UC, respectively. Laboratory tests included full blood count, C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR), nutritional, renal, and liver function parameters. In addition, pancreatic laboratory studies including serum amylase and lipase, were collected. Data on imaging methods used for the diagnosis of pancreatic involvement including transabdominal ultrasound (US), magnetic resonance cholangiopancreatography (MRCP), abdominal computed tomography scan (CT) or endoscopic retrograde cholangiopancreatography (ERCP), were evaluated. In patients with CP if available, details on genetic testing (CFTR, SPINK1, PRSS1) or on exocrine pancreatic function assessed with the faecal elastase, were recorded. In addition, pancreatic involvement episode characteristics, including drug exposure, severity, complications, in-hospital stay, actions taken post-pancreatic involvement were reported.

Institutional review board approval for the registry protocol and the informed consent and assent forms were obtained at each site before subject enrolment and data collection. Signed parental and patient informed consent and signed youth assent when appropriate were required from all patients enrolled.