Acute pancreatitis in children and rotavirus infection. Description of a case and minireview

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INTRODUCTION

Even though acute pancreatitis is less common in children than in adults, its incidence in the pediatric age group has increased significantly in the past 2 decades. It is estimated that 2 to 13 new cases occur annually per 100,000 children (Lautz et al., 2011; Morinville et al., 2010). The etiology is often elusive, with many cases being idiopathic (Nydegger et al., 2006). A wide variety of infectious agents, including viruses, bacteria, fungi and parasites, have been associated with acute pancreatitis, but only few cases due to rotavirus infection have been described so far. We describe a 2-year-old boy with acute pancreatitis following rotavirus gastroenteritis. The characteristics of this case are analyzed and discussed in the light of another 4 cases of pancreatitis associated with rotavirus infection found through a systematic review of the international literature. None of the five children underwent surgery or was referred to an intensive care unit and all 5 children recovered with normalization of pancreatic enzymes within 5-10 days. The pathogenesis of this rare complication remains unsettled, and its actual incidence may be higher than reported. Although acute pancreatitis associated with rotavirus gastroenteritis seems to be a mild disease, attention must be paid by the pediatrician fearing possible complications. Rotavirus infection should be amended to the differential diagnosis panel of pancreatitis in toddlers.

KEY WORDS: Pancreatitis, Children, Gastroenteritis, Rotavirus.

This report describes a case of acute pancreatitis in a 2-year-old boy following rotavirus gastroenteritis. Its characteristics are analyzed and discussed in the light of another 4 cases of pancreatitis associated with rotavirus infection found through a systematic review of the international literature. None of the five children underwent surgery or was referred to an intensive care unit and all 5 children recovered with normalization of pancreatic enzymes within 5-10 days. The pathogenesis of this rare complication remains unsettled, and its actual incidence may be higher than reported. Although acute pancreatitis associated with rotavirus gastroenteritis seems to be a mild disease, attention must be paid by the pediatrician fearing possible complications. Rotavirus infection should be amended to the differential diagnosis panel of pancreatitis in toddlers.

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INTRODUCTION

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CASE REPORT

A two-year-old boy was referred to our department because of increased levels of lipase and slight enlargement of pancreatic body-tail on ultrasound. In detail the anteroposterior diameter at the level of pancreas body was 1.4 cm (normal values, 0.7-1.3 cm) with a hypoechochogenic pattern. In the preceding ten days, he had been suffering from vomiting, malaise, abdominal pain and diarrhea with watery stool; diagnosis of rotavirus gastroenteritis had been made in a first level hospital and an intravenous fluid therapy started. History and family anamnesis were unremarkable.
On admission, the child looked ill; his activity was poor and he had a temperature of 37.3°C. Physical examination disclosed pale skin and mucosa, decreased skin turgor, distended abdomen without hepatosplenomegaly. Initial laboratory results were consistent with mild dehydration (hematocrit, 32.3%), and also showed: hemoglobin, 10.8 g/dL; white blood cell count (WBC), 7.63x10^3/mm^3 with a differential of 60.5% neutrophils, 25.5% lymphocytes, 5.8% monocytes, 0.5% eosinophils, 0.7% basophils; increased levels of C-reactive protein (CRP) (2.42 mg/dL; normal values, <0.5 mg/dL), alpha-amylase (197 U/L; normal values, 5-65 U/L), lipase (113 U/L; normal values, 8-78 U/L) and pancreatic amylase (86 U/L; normal values, 8-53 U/L). Serum electrolyte concentration including calcium and phosphorus, blood glucose level, renal and liver function tests (including transaminases, alkaline phosphatase, total and direct bilirubin, pseudocholinesterase, gamma-glutamyl transpeptidase), serum lipidic profile, uric acid, lactate dehydrogenase and creatine kinase were normal. Stool examination confirmed rotavirus infection using the Rapid Test® ROTA-ADENO. Intravenous rehydration therapy was continued, and gastroprotective treatment with intravenous ranitidine and refeeding only with carbohydrates, monitoring pancreatic enzymes, were initiated. Investigations on the following day indicated increasing levels of pancreatic amylase (161 U/L) and lipase (239 U/L). On the 4th hospital day pancreatic amylase, alpha amylase and lipase began to decrease (83 U/L, 218 U/L and 106 U/L, respectively). Abdominal ultrasound reevaluation demonstrated no pathological signs. The patient’s condition improved over a few hours, and fatty and proteic foods were gradually integrated and well-tolerated. On the

<table>
<thead>
<tr>
<th>Author year</th>
<th>Sex/age/Nation</th>
<th>Signs and symptoms</th>
<th>Amylase/lipase (higher values)</th>
<th>WBC (N%)</th>
<th>Radiological findings</th>
<th>Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Nigro, 1991)</td>
<td>F/2y8mo/Italy</td>
<td>Vomiting and diarrhea for three days. Then, convulsion without fever. Hypoglycemia</td>
<td>840/382</td>
<td>6400 (68)</td>
<td>US: moderately enlarged edematous pancreas</td>
<td>NR</td>
<td>Cured, normalization of pancreatic enzyme within 7 days</td>
</tr>
<tr>
<td>(De La Rubia et al., 1996)</td>
<td>M/10y6mo/Spain</td>
<td>Acute epigastric pain, watery stool 48 h after the onset of the pain</td>
<td>872/1478</td>
<td>14700 (82)</td>
<td>US: normal</td>
<td>Rehydration, ranitidine</td>
<td>Cured, discharged after 9 days</td>
</tr>
<tr>
<td>(Kumagai et al., 2009)</td>
<td>M/&lt;1y/Japan</td>
<td>Diarrhea, tachycardia, fever, dehydration</td>
<td>322/41</td>
<td>NR</td>
<td>CT: a mildly enlarged edematous pancreas, small amount of accumulated fluid</td>
<td>Intravenous rehydration</td>
<td>Cured, normalization of pancreatic enzyme within 10 days</td>
</tr>
<tr>
<td>(Parri et al., 2010)</td>
<td>M/2y/Italy</td>
<td>History of 3 days of fever, vomiting, malaise, upper abdominal pain, and diarrhea with watery stool</td>
<td>1037/236</td>
<td>10300 (76)</td>
<td>US: pancreas not assessable due to abundant intestinal air</td>
<td>Intravenous rehydration</td>
<td>Cured, discharged after 5 days</td>
</tr>
<tr>
<td>Present case</td>
<td>M/2y/Italy</td>
<td>Ten days before being admitted to our department he had had repeated vomiting, malaise, abdominal pain and diarrhea with watery stool</td>
<td>197/239</td>
<td>7600 (60)</td>
<td>US: slight enlargement of pancreatic body-tail</td>
<td>Intravenous rehydration, ranitidine</td>
<td>Cured, discharged after 5 days</td>
</tr>
</tbody>
</table>

CT, computed tomography; F, female; M, male; mo, months; NR, not reported; US, Abdominal ultrasonography; y, years; WBC, white blood cells.
5th and last day of hospitalization, laboratory data showed the normalization of pancreatic amylase (53 U/L) and a further reduction of alpha-amylase (114 U/L) and lipase (85 U/L); blood examinations also revealed negativization of CRP and a switch of WBC towards lymphocytosis. The patient was then discharged in an asymptomatic condition.

**Literature search strategy**
A computerized search without language restriction was conducted using PubMed combining the terms (rotavirus OR HRV) AND (pancreatitis OR pancreatic OR amylase OR lipase) without limits. An article was considered eligible for inclusion in the review if it reported detailed data on patients with pancreatitis associated with a HRV infection. Pancreatitis was defined as requiring 2 of the following conditions:
1) abdominal pain compatible with AP,
2) serum amylase and/or lipase values ≥3 times upper limits of normal, 
3) imaging findings of acute pancreatitis 
(Morinville et al., 2012).
PubMed search identified 92 publications, a scrupulous analysis of which resulted in 4 eligible articles describing 4 patients. Data regarding the clinical characteristics, therapy and outcome of these patients, along with our case, are analytically showed in table 1.

All cases occurred in children with a median age of 2 years (range: 1 year–10). Most of them (4/5) were male and came from Italy, one from Japan. Abdominal pain was present only in two of the 5 children. In 4/5 children symptoms of HRV infection preceded the diagnosis (from 2 to 10 days) of pancreatitis, in one case diarrhea appeared 2 days after abdominal pain. One case presented with convulsion without fever associated with hypoglycemia. Abdominal ultrasonography (US) or computed tomography (CT) scan showed moderately enlarged edematous pancreas in 3 cases, normal finding in one case; in one case the pancreas was not assessable due to abundant intestinal air. The median value of the amylase and lipase peaks were 840 (range: 153-1037) and 236 (range: 41-1478), respectively. None of the patients underwent surgery or was referred to an intensive care unit. The only treatment was rehydration. All the patients recovered with normalization of pancreatic enzymes within 5-10 days.

**DISCUSSION**
Worldwide, rotaviruses are the single most important cause of severe acute diarrhea in young children. Rotaviruses are responsible for high morbidity in developed countries and high mortality in developing countries (Amisano et al., 2011; Arista et al., 2006; Arista et al., 2003; Barnes and Bishop, 1997). Common Symptoms of rotavirus infection are vomiting, watery diarrhea and fever. Children may have profuse watery diarrhea up to several times per day. Symptoms generally persist for three to eight days. Abdominal pain is not a symptom frequently reported in the course of rotavirus gastroenteritis (Albano et al., 2007; Cascio et al., 2001; De Grazia et al., 2007).

Acute pancreatitis has a variable presentation in children and symptoms may range from mild abdominal pain to severe systemic involvement characterized by metabolic disturbances and shock. Nearly a quarter of children with acute pancreatitis develop a severe complication, and the mortality rate is approximately 4% despite significant advances in the treatment of this disease (DeBanto et al., 2002; Lautz et al., 2011). However, severe disturbance occurs less commonly in children (Nydegger et al., 2006). The results of a recently published survey offer insights into how pediatric pancreatitis practice differs from adult practice. For example, there was infrequent use of invasive work-ups (e.g. ERCP, EUS) as first-line testing. By contrast, ultrasonography was used in the initial presentation more commonly than computed tomography scanning in order to limit radiation exposure (Morinville et al., 2010).

Currently, acute pancreatitis (AP) is defined as requiring 2 of the following conditions:
1) abdominal pain compatible with AP; 
2) serum amylase and/or lipase values ≥3 times upper limits of normal, 
3) imaging findings of AP (Fabre et al., 2012; Morinville et al., 2012).

From an analysis of the described cases, acute pancreatitis associated with rotavirus infection seems to be a mild disease. It is strange that although rotavirus gastroenteritis is globally present, most of the cases occurred in Europe. This aspect may be explained by the following:
1) a higher degree of attention to this disease by European pediatricians;
2) different rotavirus strains circulating in the different geographic areas;
3) a different individual response to rotavirus infection linked to genetic factors. Perhaps further studies will clarify these aspects.

Of note, increased amylase levels are not uncommon in patients with acute gastroenteritis (Tositti et al., 1972). Several hypotheses have been suggested. Firstly, intestinal inflammation could lead to an increased permeability allowing the reabsorption of macromolecules such as amylase. This condition of barrier dysfunction of the intestinal mucosa during infectious diarrhea, a state defined as “leaky gut”, was described by Gnadinger et al. in 2 patients with Salmonella enteritis and elevated amylase and lipase levels, without US evidence of pancreatitis (Gnadinger et al., 1993). Hyperamylasemia and hyperlipasemia could also be the result of reduced excretion due to either a transient impaired renal function, linked to severe dehydration, or liver function (Pezzilli et al., 1999; Schmid et al., 1999).

Several pathogens have been identified as causal agents of acute pancreatitis following gastroenteritis, with Salmonella infection being the most reported (Castilla-Higuero et al., 1989; Renner et al., 1991). The pathogenic mechanisms subtending pancreatic damage during infectious gastroenteritis are not clear. Clinical evidence has suggested that obstruction caused by edema and inflammation of the ducts and direct infection of the acinar cells may be the attack mechanism of viruses to the pancreas (Naficy et al., 1973; Ursing, 1973). Rotaviruses infect mature, differentiated enterocytes of the small intestine and, by an unknown mechanism, escape the gastrointestinal tract and can cause viremia (Crawford et al., 2006). In a neonatal rat model of rotavirus infection, it was demonstrated that rotavirus was able to disseminate to and replicate in a variety of organs, including the liver, lungs, spleen, kidneys, thymus, heart, pancreas, and bladder (Crawford et al., 2006). Histopathological changes due to rotavirus infection included acute inflammation of the portal tract and bile duct (Crawford et al., 2006). Another hypothesis could be that obstruction of pancreatic fluid outflow through an edematous ampulla of Vater might have led to pancreatitis, as demonstrated in mice experimentally infected by Coxsackie virus (Tsui et al., 1972). Since in our case no cholestasis mark-

ers or US findings of bile flow obstruction or dilatation of the pancreatic duct were found, we rule out this pathogenetic mechanism.

CONCLUSIONS

Notwithstanding the high prevalence of rotavirus gastroenteritis, pancreatitis related to rotavirus infection seems not to represent a major health issue. However, it should be entertained in the management of gastroenteritis in children, fearing possible complications. Given the rarity of this condition in the pediatric age, the fact that detection of high values of serum amylase during gastroenteritis is uncommon, and the possible aspecificity and mildness of the clinical signs, the diagnosis of acute pancreatitis in children, especially in the infants, still represents a challenge for the pediatrician. More studies are needed to better understand how rotaviruses could cause acute pancreatitis, if predisposing factors exist, and the real incidence of this disease.

REFERENCES


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