

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

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## SUMMARY

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.

**KEY WORDS:** Pancreatitis, Children, Gastroenteritis, Rotavirus.

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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.

## 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 hypoechogenic 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.

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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),  $7.63 \times 10^3/\text{mm}^3$  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 4<sup>th</sup> 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 1 - Clinical characteristics, therapy and outcome of 5 children with pancreatitis associated with rotavirus gastroenteritis.

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

CT, computed tomography; F, female; M, male; mo, months; NR, not reported; US, Abdominal ultrasonography; y, years; WBC, white blood cells.

5<sup>th</sup> 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  $\geq 3$  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  $\geq 3$  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.*, . 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.

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