Case Report / *Olgu Sunumu*

DOI: 10.5578/ced.201805 • *J Pediatr Inf 2018; 12(1): e26-e31*

Acute Pancreatitis Secondary to Rotavirus Gastroenteritis: Case Report and Review of the Literature

Rotavirüs Gastroenteritine İkincil Gelişen Akut Pankreatit: Bir Olgu Sunumu ve Literatürün Gözden Geçirilmesi

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Abstract

Serum amylase levels may increase during acute gastroenteritis; however, acute pancreatitis is a rare occurrence. Rotavirus infection is rarely accompanied by pancreatitis. The case described here involves a previously healthy patient with acute pancreatitis secondary to rotavirus gastroenteritis. Laboratory findings and radiological characteristics of eight cases of pancreatitis associated with rotavirus gastroenteritis have been reviewed and discussed here in the light of the international literature. None of those eight cases required intensive care, and pancreas enzymes returned to normal levels within 5-13 days in all cases. The pathogenesis of this rare coexistence remains unclear, and its actual incidence may be higher than reported. Although acute pancreatitis secondary to rotavirus gastroenteritis seems to be a mild disease, the clinicians must pay attention to avoid possible complications.

Keywords: Pancreatitis, gastroenteritis, rotavirus, child

Özet

Akut gastroenterit sırasında serum amilazı yükselebilir ancak akut pankreatit nadirdir. Rotavirüs enfeksiyonu ile pankreatit birlikteliği oldukça nadir görülür. Burada daha önceden sağlıklı olan, rotavirüs gastroenteritine ikincil olarak meydana gelen akut pankreatitli bir olgu sunulmuştur. Burada uluslararası literatür ışığında rotavirüs gastroenteriti ile ilişkili pankreatitli 8 olgunun klinik, laboratuvar ve radyolojik özellikleri irdelenmiş ve tartışılmıştır. Bu sekiz olgunun hiçbirinin yoğun bakım ihtiyacı olmamış ve tümünün pankreas enzimleri 5-13 günde normale dönmüştür. Bu nadir ilişkinin patogenezi net değildir ve gerçek insidansı raporlanandan daha fazla olabilir. Rotavirüs gastroenteritine ikincil akut pankreatit hafif hastalığa neden oluyor gibi görünmesine rağmen, olası komplikasyonlar nedeniyle klinisyenler bu duruma dikkat etmelidir.

Anahtar Kelimeler: Pankreatit, gastroenterit, rotavirüs, çocuk

Introduction

While acute pancreatitis is relatively rare among children, its incidence has been increasing over the last two decades. Every year, two to 13 out of 100.000 children are known to develop acute pancreatitis (1,2). Etiology of childhood acute pancreatitis mostly involves a trauma (22%), structural abnormalities (15%), multisystemic disorders (14%), drugs and toxins (12%), viral infections (10%), hereditary causes (2%), and metabolic disorders (2%), while the majority of cases are still idiopathic (23%) (3). Some viruses, bacteria, fungi and parasites have been shown to cause acute pancreatitis (3). The diagnosis can go unnoticed in children, as the disease is quite rare among children and presents with heterogeneous symptoms. The presence of at least two of the criteria shown below are required for a diagnosis of acute pancreatitis: 1) abdominal pain consistent

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with acute pancreatitis, 2) serum amylase and/or lipase values higher than at least three times the upper limit of normal, 3) presence of imaging findings consistent with acute pancreatitis (4).

Rotavirus infection, which is relatively common worldwide, is itself the most significant cause of severe gastroenteritis among young children and infants younger than two years of age. Almost every child in the world becomes infected by rotavirus at least once before the age of five years. Rotavirus gastroenteritis is a cause of high morbidity in developed countries and a cause of high mortality in developing countries (5). While rotavirus gastroenteritis is associated with several complications, acute pancreatitis is a very rare complication and only seven cases have been reported so far in the international literature (6-12).

A case of acute pancreatitis secondary to rotavirus gastroenteritis is presented here. Along with described case, cases of childhood acute pancreatitis secondary to rotavirus infection reported previously in the international literature have been reviewed and discussed here.

Case Report

A three year old, previously healthy, male patient referred to pediatric emergency care unit with complaints of vomiting persisting for the previous three days and soft, yellow, non-mucous and non-blooded diarrhea almost 20 times a day and abdominal pain that started on the day of referral. The patient was hospitalized for pneumonia when he was three months old and monitored for retarded speech. The family history revealed that the parents were healthy and there was no consanguinity, there was no family history of a metabolic disorder and the patient's grandfather was learnt to be monitored for diabetes. Physical examination showed that the patient's body weight was 14.5 kg (25-50 p), height was 104 cm (50-75 p), and vital signs were stable. The patient had moderate dehydration, increased bowel sounds and tenderness in epigastric region. Laboratory results were as follows: Hb: 11.6 g/dL, leukocytes: 5300/mm^3, platelets: 193.000/mm^3, urea: 25 mg/dL (10-38), creatinine: 0.5 mg/dL (0.5-1.2), sodium: 132 mmol/L (134-150), potassium: 3.1 mmol/L (3.5-5), alanine transaminase: 24 U/L (0-50), aspartate transaminase: 40 U/L (0-50), total bilirubin: 0.66 mg/dL, direct bilirubin: 0.13 mg/dL, C-reactive protein: 17 mg/L (0-5). Microscopic investigation of stool showed 4-6 leukocytes per field, and viral antigen screening in stool returned positive for rotavirus antigen. Stool culture was not positive for growth of salmonella or shigella species. The patient had abdominal pain and epigastric tenderness, therefore amylase and lipase measurements were requested and the corresponding levels were 74 U/L (28-100) and 236 U/L (5-31), respectively. Abdominal ultrasonography, which was requested for suspected acute pancreatitis, did not demonstrate any finding consistent with acute pancreatitis. The diagnosis of acute pancreatitis was made as the patient abdominal pain and hyperlipasemia, which were consistent with acute pancreatitis. Lipid panel, hepatitis and other virus screenings which were performed to reveal etiology returned negative. Oral uptake was stopped and the patient was given intravenous fluids and ranitidine treatment. During follow-up, the highest recorded levels of lipase and amylase were 380 U/L and 190 U/L, respectively. The patient was discharged on the sixth day of hospitalization without any complication, and levels of amylase and lipase measured one week later were found to be normal.

Discussion

Compared with adults, acute pancreatitis is very rare among children and its diagnosis may be quite challenging in pediatric cases. In particular, children usually present with non-specific symptoms but the disease has a wide spectrum varying from mild abdominal pain to serious systemic involvement accompanied by metabolic abnormalities and a picture of shock. Almost one quarter of childhood acute pancreatitis cases develops serious complications, and approximately 4% of patients eventually die despite improvements in the treatment of acute pancreatitis (1,13); however, children develop severe disease less commonly compared with adult patients (14). The case presented here also involved a mild clinical course of acute pancreatitis and the patient recovered without developing any complications.

While hyperamylasemia was predominantly reported with certain infectious agents, it can also develop after acute gastroenteritis but acute pancreatitis is a rare picture (15). In a study performed by Tositti et al. on 507 adult patients with gastroenteritis, 10.2 percent of the patients had hyperamylasemia and only one of those patients developed acute pancreatitis (15). Among 164 patients whose stool samples included a microorganism, 17 percent had hyperamylasemia. Patients with an identified agent, accompanied by hyperamylasemia, were reported to experience a more severe course of gastroenteritis and had elevated gastroenteritis severity scores that were identified based on the scoring system developed by Goodman et al. which took into account the daily number of diarrhea episodes and the presence of accompanying systemic symptoms (15,16). Hyperamylasemia was most commonly reported in the presence of gastroenteritis caused by *Salmonella* species, followed by rotavirus, *Clostridium difficile* and *Campylobacter* species. However, in that patient series, acute pancreatitis was not detected in neither of the cases with rotavirus gastroenteritis (n= 29) (15). In inter-

national literature, there is a very limited number of reports involving acute pancreatitis secondary to rotavirus infection in pediatric patients. Those cases were summarized in Table 1. Mean age of those cases were 42 months and 87.5 percent involved male patients. Acute pancreatitis is not associated with a significant gender-related difference; however, certain conditions such as biliary disease, medication use, systemic diseases, abdominal trauma and metabolic disorders were previously reported as risk factors (17). As with our case, all cases in the literature were screened for potential risk factors and their etiologies did not include a cause other than rotavirus gastroenteritis. Among the cases summarized, the most common complaints at presentation were vomiting, watery diarrhea and fever, which are the common symptoms of rotavirus gastroenteritis. It was interesting that abdominal pain, a relatively unexpected finding of rotavirus gastroenteritis, was also reported in five cases (17-19). During follow-up, our patient also developed severe abdominal pain particularly in the

Table 1. Clinical, laboratory and radiological characteristics of cases with acute pancreatitis secondary to rotavirus gastroenteritis

Author/year	Country	Age/gender	Signs and symptoms	Amylase/ Lipase (U/L, the highest value)	Radiological findings	Treatment	Outcome
Nigro et al., 1991 (6)	Italy	2 years 8 months, F	Vomiting, diarrhea, convulsions and hypoglycemia	840/382	US: moderately enlarged pancreas	Unspecified	Recovery without complication, pancreas enzymes normalized within 1 week
De La Rubia et al., 1996 (7)	Spain	10 years 6 months, M	Acute gastric pain, watery diarrhea	872/1478	US: normal	Rehydration, ranitidine	Recovery without complication, discharged in 9 days
Kumagai et al., 2009 (8)	Japan	< 1 year, M	Diarrhea, tachycardia, fever, dehydration	322/41	CT: mildly enlarged pancreas surrounded by a small amount of fluid retention	IV rehydration	Recovery without complication, pancreas enzymes normalized within 10 days
Parri et al., 2010 (9)	Italy	2 years, M	Fever, vomiting, watery diarrhea, weakness, abdominal pain	1037/236	US: pancreas could not be visualized due to severe flatulence	IV rehydration	Recovery without complication, discharged within 5 days
Giordano et al., 2013 (10)	Italy	2 years, M	Vomiting, weakness, abdominal pain, watery diarrhea	197/239	US: mildly enlarged pancreas	IV rehydration, ranitidine	Recovery without complication, discharged within 5 days
Cay et al., 2014 (11)	Turkey	2 years 6 months, M	Diarrhea, weakness, abdominal pain, vomiting	141/717	US: normal	IV rehydration	Recovery without complication, pancreas enzymes normalized within 12 days
Basturk et al., 2017 (12)	Turkey	5 years, M	Abdominal pain, vomiting, diarrhea	1230/810	US: mildly enlarged pancreas	IV total parenteral nutrition, lansoprazol	Recovery without complication
Our case	Turkey	3 years, M	Vomiting, diarrhea, abdominal pain	190/380	US: normal	IV rehydration, ranitidine	Recovery without complication, pancreas enzymes normalized within 13 days

upper quadrant and the levels of amylase and lipase, which were measured for that reason, were found to be elevated. Although the levels of amylase or lipase being higher than three times the upper limit of normal are commonly considered diagnostic, there are no confirmed definitive threshold levels for the diagnosis of acute pancreatitis in children (20). In all pediatric age groups, serum lipase levels are known to be both more sensitive and specific than amylase levels (21). This was rather associated with ongoing maturation of pancreatic amylase expression until the late infantile period (22). In particular it was shown that, compared to lipase levels, amylase levels may be negative in infantile patients with acute pancreatitis, and cause diagnosis to go unnoticed (23). The increase in lipase levels was also more pronounced than the amylase levels of our patient. While radiologic signs, as one of the diagnostic criteria for acute pancreatitis, are found to be positive in almost half of the cases; likewise in our patient, radiological findings of pancreas were also found to be normal in two cases previously reported in the literature. As it is not associated with the risk of radiation, abdominal ultrasonography is the most commonly preferred method of imaging for patients with mild clinical symptoms and a low potential of developing complications. Nevertheless, computerized tomography or magnetic resonance imaging may be the preferred imaging methods in patients who have severe clinical symptoms and an increased possibility of complications, and for whom ultrasonography does not allow visualization of the pancreas (4). Acute pancreatitis secondary to rotavirus infection was generally reported to cause a clinical picture of mild disease (10). All cases reported in the literature recovered without complication and the levels of pancreas enzymes normalized within 5-12 days. In the present case, abdominal pain started to regress on the third day of therapy, while the patient was discharged on the sixth day and pancreas enzymes normalized 13 days later.

Various hypotheses have been suggested to explain the cause of hyperamylasemia seen during acute gastroenteritis. One of those hypotheses involves the increase in reabsorption of macromolecules such as amylase due to development of barrier dysfunction in intestinal mucosa during infectious diarrhea. This was defined by Gnadinger et al. in two patients who had *Salmonella* enteritis, normal ultrasonography and elevated levels of serum amylase and lipase (24). Another hypothesis suggests that dehydration, frequently seen in patients with acute gastroenteritis, leads to transient renal dysfunction, thereby decreasing expression of amylase and lipase and consequently causing development of hyperamylasemia and hyperlipasemia (25,26). It was also shown that rotavirus may infect the mature and undifferentiated erythrocytes in small intestines, thereby escape through gastrointestinal system and cause viremia (27). In a rotavirus-infected rat model, it was demonstrated that rotavirus may spread to other organs and replicate in the liver, lungs, spleen, kidneys, thymus, heart, pancreas and bladder (27). In the same study, histopathological investigations also demonstrated that rotavirus infection caused acute inflammation in the portal system and biliary tract (27). In our patient, laboratory investigations or radiological imaging did not demonstrate any finding of biliary obstruction or pancreas dilatation.

Several factors are involved in pathogenesis of rotavirus infection. During rotavirus infection, nuclear factor-kB (NF-κB) was shown to be rapidly activated and affect several chemokines, particularly including NF-κB interleukin-8 (IL-8) (28). NF-κB is a fast-acting transcription activator (10,28,29). IL-8 belongs to chemotactic cytokine family and plays critical roles in deposition of inflammatory cells such as neutrophils, monocytes, macrophages and lymphocytes particularly in regions of inflammation (10,28,29). IL-8 is also important in the immune response-related injury in the pathogenesis of acute gastroenteritis (28,30). Therefore, IL-8 has been used as a marker for clinical evaluation in cases of rotavirus infection (29). In particular, serum IL-8 levels were found to be sensitive in differentiating rotavirus gastroenteritis from the other viral gastroenteritis (29). IL-8 is also involved in the onset and increase of acute inflammatory reaction seen in acute pancreatitis (31). For this reason, Digalakis et al. suggested that measurement of IL-8 levels and monitoring the levels during follow-up represent a useful approach for the evaluation of the presence and persistence of acute pancreatitis (31). Recovery in rotavirus gastroenteritis depends on immune response of the patient (32-34). Interferon-gamma (IFN-γ) was shown to be the only cytokine directly inhibiting rotavirus replication and play a key role in infection control (32-35). Infants, children and adults have age-dependent differences in IFN-γ release and IFN-γ production by mature active T cells is a process that continues until the second decade of life (36). In healthy infants, IFN-γ release from T cells was found to be significantly lower compared to adults (36,37). Both phenotypic and functional limitations in immune response have been demonstrated in infants, and immune response was shown to improve with age (37). IFN-γ was also shown to have protective effects against acute pancreatitis, and also highlighted to have an important anti-inflammatory activity in suppression of the proinflammatory consequences of IL-8 expression activated by NF-κB (34,38). Mormile speculated that, through all these immunologic mechanisms, incomplete IFN-γ matura-

tion produced by T cells in an age-dependent manner, results in a more severe course of rotavirus gastroenteritis and development of secondary acute pancreatitis in infants and young children (39). We did not analyze IFN-γ and IL-8 levels in our patient, and prospective studies can more clearly reveal the role of these cytokines in etiopathogenesis.

While hyperamylasemia and hyperlipasemia are rather common findings during acute gastroenteritis, acute pancreatitis is a very rare entity. Acute pancreatitis should be kept in mind during rotavirus gastroenteritis, particularly if the patient presents with epigastric or upper quadrant abdominal pain. Identification of this condition, which generally follows a good course, is still important in terms of treatment approach and patient monitoring.

Informed Consent: Written patient consent was obtained from the patient's family.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - EKÖ, DYÇ; Design - ECÖ, DYÇ; Check - EKÖ, DYÇ, MB; Data Collection and/or Processing - EKÖ, KV; Analysis and/or Interpretation - EKÖ, DYÇ, MB; Literature Review - EKÖ, KV; Writing - EKÖ, MB; Critical Review - DYÇ, MB.

Conflict of Interest: No conflict of interest was declared bye the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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