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ORIGINAL ARTICLE

The Significance of Serum and Fecal Levels of Interleukin-6 and Interleukin-8 in Hospitalized Children with Acute Rotavirus and Norovirus Gastroenteritis

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Key Words
interleukin-6;
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Background: Rotavirus and norovirus are the most common known causes of viral gastroenteritis in children. This study examined the association between serum interleukin 6 (IL-6) and interleukin 8 (IL-8) levels and disease severity in the acute phase of rotavirus and norovirus gastroenteritis in children, and it also explored the role of fecal cytokine levels in children with viral and bacterial gastroenteritis.

Methods: This prospective study enrolled patients aged 4 months to 14 years admitted with acute gastroenteritis in a tertiary care center. Peripheral blood samples were collected for IL-6 and IL-8 assays within the first 3 days of diarrhea. Stool samples were obtained from the patients in the first 24 hours after admission.

Results: Serum IL-6 and IL-8 were measured in children with viral ($n = 66$) and bacterial ($n = 23$) infections, and in healthy controls ($n = 10$). In the acute phase of gastroenteritis, a moderately positive correlation was found between serum IL-6 levels and disease severity ($r_s = 0.41$, $p < 0.01$). Serum IL-8 levels correlated with the duration of fever ($r_s = 0.28$, $p = 0.03$). Fecal IL-6 levels correlated with the maximum number of daily bowel movements ($r_s = 0.35$,

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$p < 0.05$). Rotavirus infection induced significantly higher serum IL-8 levels than norovirus infection ($p < 0.05$). Receiver operating characteristic (ROC) curve analysis showed that absolute neutrophil count (ANC), maximum body temperature (BT), and Vesikari score were significant predictors in discriminating rotavirus from norovirus gastroenteritis.
Conclusion: IL-6 and IL-8 are involved in the pathogenesis of acute gastroenteritis in both rotavirus and norovirus. An ANC of less than 9000/mm^3, maximum BT of less than 38.2°C, and Vesikari score of less than 14 at the end of the course are potential predictors of norovirus infection in children compared with rotavirus gastroenteritis.

1. Introduction

Acute gastroenteritis is one of the major causes of morbidity and mortality in children worldwide. It is an infection of the gastrointestinal tract caused by a wide range of enteric pathogens, including bacteria, viruses, and parasites.[1,2] Rotavirus, norovirus, enteric adenovirus, and astrovirus are the most common causes of viral gastroenteritis in children.[1,3–7] As the burden of illness due to bacterial pathogens has decreased with improvements in hygiene and sanitation, viruses have become the leading etiologic agents in severe diarrhea requiring hospital admissions, although most cases are self-limiting.[8] However, it is often difficult to differentiate between viral and bacterial infections by clinical features alone because of similar presenting symptoms.[9,10] Moreover, rotavirus and norovirus are the two most common viral agents causing acute gastroenteritis in children,[2,3] with rotavirus infection accounting for 40% of all outpatient visits for acute gastroenteritis in young children.[8] Recent studies have indicated that norovirus can also cause as severe an illness as rotavirus.[3] More than 90% of the outbreaks of gastroenteritis in which the cause could not previously be identified are now attributed to this virus in the United States.[4] These findings suggest that norovirus is a more important viral agent than other enteric viruses.

Interleukin-6 (IL-6), a pleiotropic cytokine produced by lymphoid and nonlymphoid cells, has a broad range of functions including immune responses, acute-phase reactions, and hematopoiesis.[11–13] Interleukin-8 (IL-8), a member of the chemotactic cytokine family, plays an important role in recruiting inflammatory cells such as neutrophils and lymphocytes to an inflammatory site.[14] Their local and systemic effects have been described in hosts with mucosal infections.[15] However, previous studies on IL-6 and IL-8 in the pathogenesis of gastroenteritis have mainly focused on rotavirus and bacterial infections.[9,10,16,17]

The aim of this study was to examine the association of serum and fecal levels of IL-6 and IL-8 and clinical features in children with acute gastroenteritis, and also to explore the significance of these cytokines during the acute phase of norovirus infection.

2. Methods

This prospective survey enrolled patients aged 4 months to 14 years who were admitted to Chung Shan Medical University Hospital between March 2009 and February 2010 for gastroenteritis. The inclusion criterion was acute gastroenteritis, which was defined as the passage of loose or watery stools three or more times in a 24-hour period while excluding noninfectious causes such as medications (e.g., antibiotics, laxatives) or procedures (e.g., enemas, endoscopy).[18] We carefully reviewed each patient's medical history and excluded those with other bowel disorders (e.g., irritable bowel syndrome, Crohn's disease, or allergic colitis) and diarrhea lasting more than 7 days.

The clinical symptoms of gastroenteritis were recorded, including body temperature (BT) and maximum number of vomiting and diarrhea episodes within a 24-hour period. Fever was defined as a body temperature of more than 38°C (100.4°F). The severity of illness was assessed using the 20-point Vesikari scoring system,[19,20] which is based on BT, the severity of diarrhea, vomiting, dehydration, and treatment. Rehydration therapy followed by early reintroduction of age-appropriate feeding was the standard treatment. Age-matched healthy controls were recruited from the general pediatric clinics. The hospital's Institutional Review Board approved this study, and the parents or guardians of all the participants provided informed consent.

2.1. Laboratory analysis

Stool samples were collected from the patients in the first 24 hours after admission, and stored at −80°C until viral testing. All stool samples were also sent for bacterial cultures and microscopically examined for ova and parasites. To isolate bacterial pathogens, xylose lysine deoxycholate (XLD) agar, blood agar plate (BAP), and *Clostridium difficile* Selective Agar (CDSA; Becton Dickinson, Sparks, MD, USA) were inoculated. Rotavirus, norovirus, adenovirus, and astrovirus were detected by commercial enzyme immunoassay (EIA) kits (Ridascreen; R-Biopharm AG, Darmstadt, Germany) according to the manufacturer's instructions. Serum C-reactive protein (CRP) levels were determined by nephelometry on a BN ProSpec analyzer (Dade Behring, Marburg, Germany), while serum white blood cell (WBC) counts were determined using an automated hematology analyzer XE-5000 (Sysmex Corporation, Kobe, Japan). The absolute neutrophil counts (ANCs) were calculated by the following formula: ANC/mm^3 = WBC count × (% bands + % neutrophils) × 0.01.