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Virology Question and Answer Scheme (VIROQAS)

Severe gastroenteritis with secondary fever in a 10-month-old boy

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Case presentation

A 10-month-old boy presented in our emergency department in a severely reduced general condition, apathetic and sleepy. He had non-bloody diarrhea and had been vomiting for two days prior to admission. As medication he did receive dimenhydrinate, which did not improve his symptoms. His mother also had diarrhea at the same time. Beginning at the evening before admission to our hospital he refused eating and drinking. At 3 am on the day of admission his mother found him in a stuporous state, not reacting properly. Consequently he was brought to the hospital. Until that day the patient had developed regularly and was otherwise well. In the emergency room he did not react much to stimulation and often fell asleep. The examination revealed a heavily inflated abdomen. There was no pain during palpation, no enlargement of liver and spleen, no resistance.

The blood results showed reduced blood glucose (25 mg/dl), very low sodium (125 mmol/l) and mildly reduced potassium (3.48 mmol/l). The white blood cells were increased (WBC 23.420/μl) of which 62% were segmented neutrophils and 3% band neutrophils, the marker of infection C-reactive protein (CrP) was marginally increased (5.6 mg/l). The liver enzymes were significantly raised (GOT 323 U/l, GPT 183 U/l, GGT 12 U/l) and the blood coagulation was compromised (Quick 50%, INR 1.41, PTT 27 s). The creatinine was within normal range (0.37 mg/dl). Further blood results revealed high creatinine kinase (972 U/l) and high cortisol (857 nmol/l). Further endocrinological workup revealed no abnormalities. Kidney and the thyroid function values as well as immunoglobulin IgA, IgG and IgM were within normal range. The initial venous blood gas analysis was mainly within normal range: pH 7.36, pCO2 33.1 mmHg, pO2 46.6 mmHg, bicarbonate 18.4 mmol/l, base excess −5.9 mmol/l. Investigation of metabolic parameters revealed normal ammonium, lactate, acylcarnitines in dried blood and organic acids in the urine. In the initial analysis the urine showed ketonuria and mild proteinuria. After intravenous hydration therapy on the first day the patient's general condition improved and the boy became less apathetic. During the following days vomiting and diarrhea still persisted on a high level and the patient needed high substitution of sodium, potassium and magnesium. At the fourth day of hospitalization the patient became septic. The infection markers in the blood, as well as the cortisol increased (CrP 29.5 mg/l, up to 109.3 mg/l the fifth day, cortisol 1212 nmol/l), whereas the platelets decreased from 444,000/μl to 198,000/μl. We started an intravenous antibiotic therapy beginning with Cefuroxim and Tobramycin. During the antibiotic therapy the general condition improved again.

The patient was discharged of the hospital after 12 days. Five days later the child had to be readmitted, because of increasing frequency of diarrhea and vomiting, while refusing oral nutrition. Apart from a slightly decreased glucose level of 69 mg/dl the blood results were normal. An intravenous rehydration was started. After two days the diarrhea and vomiting decreased and the boy restarted eating and drinking again. He had also developed an otitis media, which was treated symptomatically with xylometazoline and paracetamol. The patient could be discharged from the hospital after three days.

What further tests are indicated?

What is your interpretation of these results?

See evidence-based opinion overleaf.

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Evidence-based opinion

What further tests are indicated?

The examination of the feces during the first hospitalization revealed that the specimen was negative for Salmonella, Shigella, Campylobacter, as well as for rotavirus at that time. The blood cultures taken before starting the antibiotic therapy revealed *Escherichia coli* and *Klebsiella pneumoniae*. Both bacteria reacted sensitive for the given antibiotics in the *in vitro* testing. Furthermore, norovirus genogroup II with a viral load of 9.22×10^8 copies/g stool (Ct value 16.95) was detected as presumably causative agent by real time PCR (Cepheid SmartCycler® Norovirus, Genzyme Virotech GmbH, Rüsselsheim, Germany; Stratagene Mx3005 (Stratagene, La Jolla, CA). Direct sequencing of the capsid gene fragment revealed genotype II.4 variant 2008 (GenBank accession number GQ303445). The analysis of the feces during the second hospitalization was negative for norovirus PCR, but positive for rotavirus antigen (Ag-ELISA ProSpecT®, Rotavirus EZ Microplate Assay, Remel, Lenexa, USA).

What is your interpretation of these results?

Rotavirus and norovirus are beside adenovirus, astrovirus, coronavirus and parechovirus the 2 most common viral agents that cause infantile acute gastroenteritis (AGE).[1,2] Norovirus infections have historically been described as mild and self-limiting. This virus circulates in community environments, and evidence indicates that it is involved in cases of AGE in infants and adults.[2] Norovirus can be genetically divided into 5 genogroups (GI–GV), of which GI, GII, and GIV cause AGE in humans.[3] Norovirus GII has caused global AGE epidemics, and the genotype GII.4 has been predominantly associated with large outbreaks of AGE.[4] The potential severity of norovirus gastroenteritis is still underestimated.

To our knowledge this is the first case of gastroenteritis caused by norovirus that presented initially with a severe clinical picture and a clinical course which was complicated by a secondary bacterial septicaemia. This sepsis may be due to bacterial translocation from the damaged intestine due to severe norovirus gastroenteritis. Several cases of secondary bacterial sepsis after rotavirus gastroenteritis have been published so far. Most of these children had an increase of temperature several days after the beginning of diarrhea.[5,6] The sepsis was caused mostly by Gram-negative bacteria like *Enterobacter cloacae* and *Klebsiella pneumoniae*, which are normal commensals of the intestine, translocated into the blood due to the damaged intestine. The secondary gastroenteritis due to rotavirus in our case underlines the importance of this virus as a nosocomial pathogens causing significant morbidity in hospitalized children.[1]

Recently, also translocation of norovirus from the intestine into the blood has been described by Takanashi et al.[7] Rotavirus is already known to cause viremia and extraintestinal manifestation.[8–10] The viremia starts at the beginning of the infection and lasts for three days in average. Circulation of norovirus in the blood of our patient may have contributed to the severity of the initial clinical presentation. However, norovirus in the blood of our patient has not been determined. According to a recent report, immunocompetent pediatric patients had a median duration of 16 days of norovirus shedding in stool specimens.[11] This is line with findings in our case during the second hospitalization period where norovirus PCR in the stools was negative 17 days after initial testing.

General complications of norovirus infection, which especially occurs in winter seasons, are fever, dehydration, acidosis, low sodium, low potassium, hypoglycemia and headache.[12–14] Furthermore, norovirus is known to cause peripheral edema caused by hypoalbuminaemia.[14] Rarely, it is associated with CNS symptoms as convulsions and encephalopathy with altered consciousness.[15,16] Our patient suffered from dehydration, low sodium, reduced potassium, hypoglycemia, elevated cortisol levels and creatinine kinase levels, raised liver enzymes, and impaired blood coagulation, which elaborates the diversity of clinical symptoms. In a recent Spanish prospective study it has been shown that norovirus gastroenteritis affects mainly children under 2 years of age and compared to rotavirus is slightly less severe and fever is less frequent.[17]

The genotype GII.4 found in our case is the most prevalent genotype throughout several epidemic seasons during the past 15 years worldwide (1995/96, 2002/2003, 2004/2005, 2006/2007).[3] The GII.4 strain is known to evolve rapidly by mutation and selection resulting in successive emergence of new variants (indicated by the first year of detection as 1996, 2002, 2004, 2006a, and 2006b). In Germany, 63–76% of the norovirus outbreaks were caused by II.4 variants 2006a and 2006b during the last three epidemic winter seasons (2006/2007, 2007/2008, and 2008/2009).[18,19] Last year, the emergence of a new variant (II.4 variant 2008) has been reported by several members of the Food-borne Viruses in Europe network (FBVE) (personal communication).[20] The case described here is the first report of an infection caused by the new GII.4 variant in Germany. Recently, a new variant of Norovirus GII.4/2007 and inter-genotype recombinant strains of NVGII causing acute watery diarrhea among children in Kolkata, India, has been described.[21] Since there are not yet sufficient clinical data to ascertain whether the new subtype in our case is more infectious or predestines to a severe clinical course, further clinical and molecular epidemiological studies are needed.

Conflict of interest

The authors declare that they have no conflict of interest.

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