

Norwalk-like virus as a cause of diarrhea in a pediatric hospital

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Objective: To describe the role of Norwalk-like virus in pediatric diarrhea, since relatively little is known about it in this age group.

Methods: We reviewed all 77 hospitalized cases of diarrhea related to Norwalk-like virus at St Görän's Children's Hospital from 1987 to 1993. Electron microscopy of feces was used routinely, and performed at the former Central Microbiology Laboratory of the Stockholm County Council.

Results: Forty-seven children (61%) had nosocomial diarrhea. Their median age was 9 months. Most nosocomial cases occurred singly or in small clusters during periods when there were also community-acquired cases. However, during the first half of 1992, there was a larger cluster of eight community-acquired and 19 nosocomial cases. Both vomiting and diarrhea were present in the majority of patients. The symptoms were typically mild, and only 14% needed intravenous fluids. Five of 17 children examined repeatedly excreted virus after the symptoms had subsided. We used detection of Norwalk-like virus in fecal samples as an indication of infectiousness and then observed no further nosocomial spread. There was a seasonal variation with a predilection for the winter months.

Conclusion: Norwalk-like virus should also be considered as a cause in cases of nosocomial diarrhea in young children.

Key words: Nosocomial, small round structured viruses, calicivirus, children, infection

INTRODUCTION

Norwalk-like viruses of the small round structured viruses (SRSVs) are important causes of acute vomiting and diarrhea in humans. The first virus in this group to be described, the Norwalk virus, has for long been related to outbreaks of diarrhea in adolescents and adults [1]. It has now become evident that at least some members of the Norwalk-like virus group are also common causes of diarrhea and vomiting in infants and young children [2,3]. Recent demonstrations of high levels of antibody towards Norwalk-like virus in pre-

school children confirm that the very young are infected by the virus [4,5]. Other important causes of vomiting and diarrhea in this age group, besides rotavirus and adenovirus, are SRSVs, such as astroviruses and classical caliciviruses [6,7]. Little is known about the relative importance of Norwalk-like virus compared to these agents.

In this study we review all cases of diarrhea related to Norwalk-like virus in patients hospitalized at St Görän's Children's Hospital during a 7-year-period, and relate their frequency to rotavirus occurrence during the same period. In 1998, the hospital moved to the Karolinska Hospital area and was renamed Astrid Lindgren Children's Hospital.

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PATIENTS AND METHODS

Hospital and wards

St Görän's Children's Hospital was a 250-bed pediatric teaching hospital. The hospital had a catchment area

with a population of 110 000 children, 0–16 years old, from various social and ethnic backgrounds, and was also a tertiary referral center. An admission/infectious disease unit with 15 rooms was provided for isolation. Patients with diarrhea were, if possible, admitted to this unit.

Identification of cases

Diarrhea was defined as an increase in stool frequency to more than three per 24 h and/or a change to a looser consistency of stools. Diarrhea and/or vomiting starting at least 72 h after admission or within 72 h after discharge were defined as nosocomial. Stool samples were sent for virus detection by electron microscopy (EM) in all suspected cases of nosocomial diarrhea, and in approximately 30% of patients with community-acquired diarrhea. The attending physician ordered bacterial examination of stools when clinical data suggested that bacteria could be the cause.

We retrospectively examined the records of all cases with stool samples positive for Norwalk-like virus from 1987 to 1993 for details of symptoms, their duration, other diagnoses and length of hospitalization.

Virologic methods

Stool specimens sent to the virology laboratory of the former Central Microbiology Laboratory of the Stockholm County Council were examined using negative contrast EM. A 10% suspension of feces was prepared. The suspension was not clarified by centrifugation but was left for at least 10 min to let coarse debris settle, before application of a drop on a formvar carbon-coated copper grid for 1 min. The specimen was negatively stained with 2% phosphotungstic acid (pH 6.0) and air-dried. Two grids from each specimen were examined in a JEOL JEM-100C electron microscope at a magnification of 40 000. From October 1988, when SRSVs were suspected, the fecal suspension was pelleted directly on the grid in a Beckman Airfuge by centrifugation for 10 min at 160 000g [8].

In this case, bacteria and debris had been removed by previous centrifugation for 30 min at 20 000g.

Virus particles were classified solely on morphologic criteria, following the principles suggested by Caul and Appleton [9]. Particles with surface spikes and tiny club-like projections were called Norwalk-like. We considered the specimen negative if no virus was detected after 15 min of microscopic examination. From 1987 to 1993, we examined approximately 2400 pediatric stool samples; 1900 community-acquired diarrhea and 500 nosocomial ones.

We did not apply newer techniques, such as the polymerase chain reaction, to achieve a better characterization of these viruses [10]. In our experience, material from frozen SRSVs is difficult to rescue for such analyses. Also, the material was transferred from one laboratory to another, adding another factor of uncertainty.

RESULTS

Patients

Seventy-seven cases were identified during the 7-year period. Their characteristics and symptoms are shown in Table 1. The age and presence of concomitant disease (acute or chronic) did not differ from those in other patients. Both vomiting and diarrhea were present in the majority. The symptoms were typically mild and only 14 (20%) were given intravenous fluids. Hypertonic dehydration was seen in two patients.

Multiple specimens were obtained from 17 patients. As shown in Figure 1, 30% of the children continued to excrete virus after the symptoms had abated. Only one child had a negative EM sample while still symptomatic. Furthermore, none of these children became virus negative during the first week after onset. Two patients (Figure 1, nos 3 and 17) had a symptom-free interval, followed by a new period of vomiting and diarrhea.

Table 1 Patient characteristics and symptoms

Patient characteristics	Community acquired cases (n=30)	Nosocomially acquired cases (n=47)
Median age in months and quartiles	12 (9–18)	9 (6–17)
Number of cases with and (percentage):		
Concomitant diseases	12 (40)	47 (100)
Acute	7 (23)	20 (42)
Chronic	5 (17)	27 (58)
Diarrhea	26 (87)	46 (98)
Vomiting	25 (84)	28 (60)
Fever >38°C	7 (23)	14 (30)
Median duration and range (days)	4 (1–10)	3 (1–9)

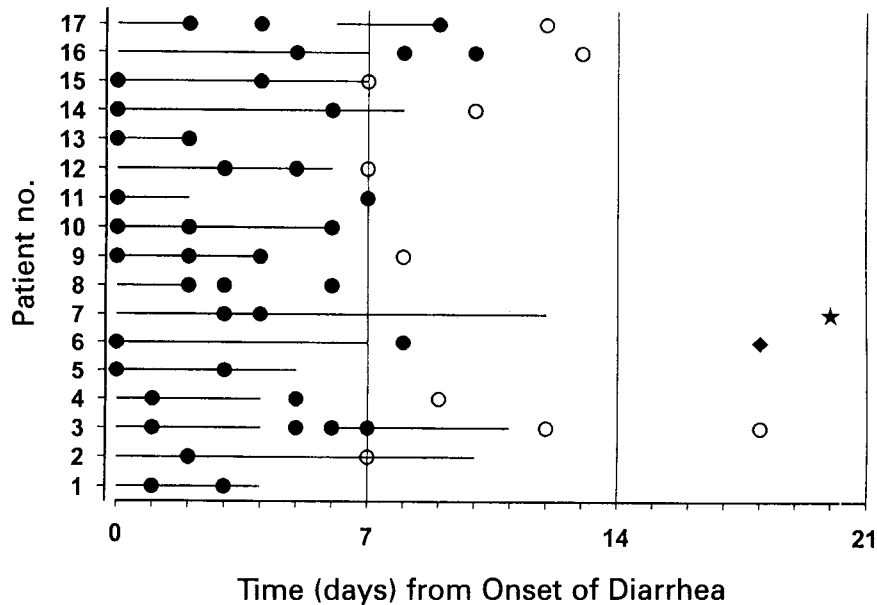


Figure 1 Duration of diarrhea and excretion of Norwalk-like viruses in 17 patients. Lines denote periods with diarrhea. Filled circles, Norwalk-like virus positive; empty circles, Norwalk-like virus negative; star, rotavirus; diamond, adenovirus.

Epidemiologic characteristics

Forty-seven cases (61%) were nosocomial. As a rule, nosocomial cases were seen when the virus was also prevalent in the community (Figure 2). Most cases were single, or just a few simultaneous cases, except during the first half of 1992, when there was a cluster of eight community-acquired and 19 nosocomial cases. In three community-acquired and four nosocomial cases, other pathogens were also found (five rotavirus, one adenovirus, and one salmonella). The seasonal variation of Norwalk virus infections was similar to that of rotavirus, with peaks during the winter (Figure 2).

DISCUSSION

Norwalk-like virus was shown to be a cause of nosocomial and community-acquired diarrhea during winter and spring. One study has reported similar findings [11], while other studies have not demonstrated any seasonal variation [2]. In the first studies of SRSVs as causes of nosocomial diarrhea [12,13], Norwalk-like virus was not specifically identified. However, studies have now shown that viruses then called 'mini-reoviruses' were probably identical to Norwalk-like virus [14].

Norwalk-like virus, unlike rotavirus, was usually found in low numbers in the fecal samples. Often only a few particles could be detected after 15 min of observation. Consequently, several samples containing Norwalk-like virus probably fell below the detection

limit, which with our technique was believed to be about 10^6 virus particles/mL. Our impression was that more virus particles were detected after Airfuge centrifugation.

We have used 72 h after admission as a time limit to classify infections as nosocomial. In adults, the incubation period of Norwalk-like virus is sometimes as short as 24 h [15]. With this shorter time limit, seven of our community-acquired cases would be reclassified as nosocomial. For the larger outbreak in 1992, however, no change of classification would occur. It is possible that the diagnostic vigilance during that long-lasting outbreak led to the detection of more Norwalk-like virus as well as more nosocomial rotavirus cases than usual.

During the first 5 years, we found only single cases or a few cases at the same time, as also reported by Brandt et al [16]. Institutional outbreaks, like the one in our hospital in 1992, have been reported in schools and nursing homes [1,17].

We detected comparatively few community-acquired cases with Norwalk-like virus. This is probably explained by the relatively mild symptoms of infections with Norwalk-like virus, which rarely lead to hospitalization. Nosocomial cases were observed every winter season from 1988. We believe this increase to be real and not merely a result of growing experience and improved methods.

Symptoms following Norwalk virus infection have been well described in adults both from outbreaks and

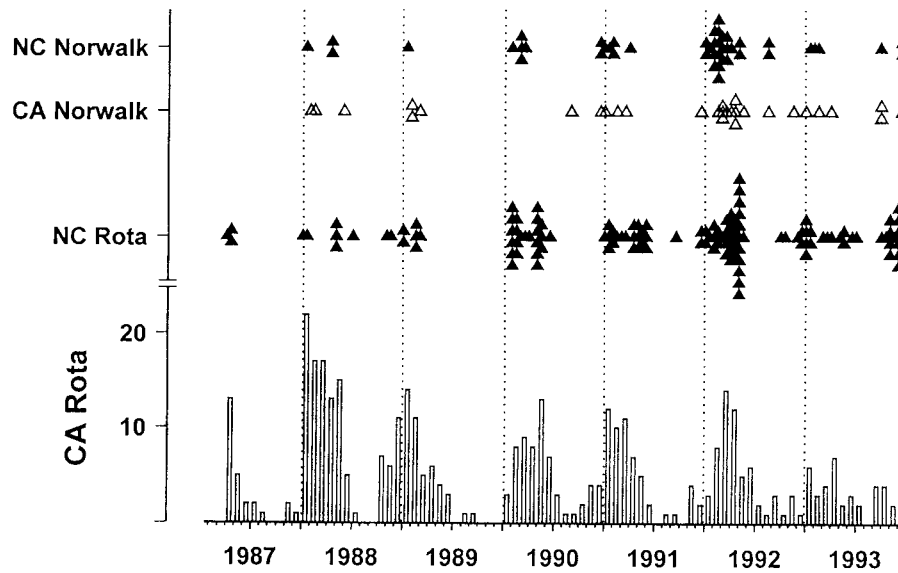


Figure 2 Frequency of cases who excreted Norwalk-like viruses and rotavirus over 7 years. NC, nosocomial; CA, community-acquired.

volunteer studies. The predominance of vomiting was striking in these studies [15]. In our study, diarrhea was as common as vomiting. Such a similarity between the symptoms of Norwalk virus and rotavirus infections was also found in other retrospective studies [4,14]. However, vomiting as a single symptom in our very young patients might have been due to other gastroenteropathies.

In earlier reports, Norwalk-like virus infection was considered to be a brief illness. Viruses were thought to be excreted in detectable amounts for only a couple of days after the onset of symptoms [1]. We have shown here that the duration of Norwalk-like virus excretion, in sufficient amounts for EM detection, is frequently a week or more. We found this to be the case also in infected adults (K-O Hedlund, unpublished observations). It confirms a recent, thorough study on volunteers, where viral antigen was detected 7 days after inoculation [15].

We used virus negativity by EM as a criterion of non-contagiousness, and so far this strategy seems to have achieved its purpose of preventing secondary cases.

Several of the children in our study had chronic underlying diseases. The frequencies were, however, no higher than in other hospitalized children. For astroviruses we have shown that underlying gastrointestinal disease may be a predisposing factor [18], which could not be demonstrated for Norwalk-like virus in this study.

In conclusion, Norwalk-like virus is an important

nosocomial pathogen that causes not only sporadic single cases but also outbreaks in infants and young children.

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