Rotavirus is frequent among adults hospitalised for acute gastroenteritis

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ABSTRACT

INTRODUCTION: Rotavirus infection is the most common aetiology of acute gastroenteritis (AGE) among young children. In adults, diagnostics focus mainly on bacterial causes, though recent studies suggest that rotavirus is a frequent agent. The aim of this study was to examine the proportion of rotavirus in adults hospitalised with AGE and to identify possible predictors.

METHODS: During a 24-month period from 1 May 2010 adults (> 15 years) with AGE admitted to one of four hospitals in the Central Denmark Region were examined for rotavirus with VIKIA Rota-Adeno rapid test in addition to routine culture for bacterial pathogens.

RESULTS: A total of 265 adult patients were included. 9.4% tested positive for rotavirus. Enteropathogenic bacteria were found in 24.5% of the cases. In the majority of cases (62.3%), no pathogen was found. Overall, rotavirus was the second-most frequent pathogen, exceeded only by *Campylobacter* spp. Immunosuppression and a C-reactive protein (CRP) below 50 mg/l (0-8 mg/l) were associated with rotavirus. The seasonality of rotavirus differed markedly from that of bacterial gastroenteritis.

CONCLUSION: Rotavirus is the second-most frequently identified pathogen in adults hospitalised with AGE. Close contact to children or travel activity does not predict rotavirus gastroenteritis, but immunosuppression and a CRP below 50 mg/l do. The seasonality of rotavirus differs from that of bacterial gastroenteritis, making rotavirus the most frequently identified cause of AGE in adults admitted to hospital in the colder months.

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TRIAL REGISTRATION: not relevant.

Rotavirus infection is universal and rotavirus is the most common aetiology of acute gastroenteritis (AGE) among infants and young children. Rotavirus as a cause of AGE among adults has traditionally been neglected. When adults are admitted to a hospital with AGE, faeces samples are routinely cultured for enteropathogenic bacteria, and empirical antibiotic treatment is initiated in elderly patients and severe cases. Normally, viral agents are left undiagnosed or not disclosed systematically. Hence, the importance of rotavirus as cause of AGE among adults is not well described. Recent studies have indicated that rotavirus may be a more frequent cause of AGE in adults than previously assumed, with proportions ranging from 2.9 to 22% in hospitalised patients and from 2.6 to 18% in patients who are attending hospital consultation or being admitted to hospital [1-6]. Limitations of these studies included varying population uptakes with one study including only patients aged 65 years or more [6], small sample sizes [4, 5] and a varying panel of pathogens tested besides rotavirus. The aim of this study was to determine the proportion of rotavirus in AGE among adults by testing for rotavirus in AGE patients who were admitted to hospital, and to identify possible predictors for rotavirus gastroenteritis.

METHODS

During a period of 24 months (from May 2010 to April 2012) we screened adults (> 15 years) who were hospitalised with AGE as their primary diagnosis for rotavirus in four hospitals in the Central Denmark Region with a total population of 800,000 people. Patients were included upon admission or upon tranferral from another department if AGE was their primary diagnosis. Furthermore, patients who developed AGE during their hospitalisation were also included. No data exist on the total number of AGE as primary diagnosis at admission, and a few patients might have been missed depending on the doctor-on-call's awareness of ongoing studies, but we expect no bias in the inclusion due to this as inclusion took place before any diagnostic procedures were performed. Three departments of internal medicine in three different tertiary hospitals (Silkeborg Regional Hospital, Viborg Regional Hospital and Herning Regional Hospital) covering three out of five tertiary hospitals in the region and one infectious disease department at Aarhus University Hospital participated in the study. The population uptake of the various parts of the region is homogeneous.

AGE was defined as three or more loose stools within 24 hours, symptoms for less than seven days and a minimum of one of the following symptoms: fever, nausea, vomiting, abdominal pain, cramps, tenesmus, blood or mucus in the stools.

Descriptive information about the patient, recent

ORIGINAL ARTICLE

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travel history, children in the household, clinical symptoms, microbiological findings, comorbidity and final diagnosis were collected in questionnaires at admission to the hospital and at discharge. Nosocomial infection was defined as onset of AGE ≥ 3 days after admission. Patients who were HIV positive, received immunomodulating therapy or chemotherapy (e.g. due to malignancies, rheumatic, inflammatory bowel or chronic respiratory diseases) were considered immunosuppressed.

Faecal samples were obtained and cultured for enteropathogenic bacteria at the local department of microbiology according to the routine procedures for patients with AGE. Additionally, the faecal samples were analysed with VIKIA Rota-Adeno rapid (bioMérieux) [7] at the Department of Microbiology, Viborg Region Hospital (Viborg, Silkeborg and Herning) and at the Laboratory of Parasitology, Aarhus University Hospital (Aarhus). The sensitivity and specificity of the VIKIA Rota-Adeno rapid are listed as 100% (95% confidence interval (CI): 96.3-100) and 100% (95% CI: 98.6-100), respectively [8].

The statistical analyses were made in STATA14 using Fisher's exact test, two-sample t-test for means. Multivariable logistic regression including variables with a p-value < 0.1 in the multivariate was used to compute odds ratios (OR) with 95% CI. C-reactive protein (CRP) was included in the multivariate analysis as a binomial variable.

Trial registration: not relevant.

RESULTS

A total of 268 episodes were eligible for inclusion in the study. Three patients were excluded: one had been included twice due to readmission why one episode was excluded, one patient did not have diarrhoea and one was excluded due to lack of delivery of a faecal sample, leaving a total of 265 patients.

Faecal samples from 25 patients (9.4%) tested posi-

TABLE 1

Microbiologic aetiology of acute gastroenteritis.

Aetiology	Cases, n (%)
Campylobacter jejuni/C. coli	31 (11.7)
Rotavirus	25 (9.4)
Clostridium difficile	25 (9.4)
Norovirus	7 (2.6)
Salmonella spp.[a]	8 (3.0)
Adenovirus	5 (1.9)
Giardia lamblia	2 (0.8)
VTEC	1 (0.4)
Total cases with positive microbiology[b]	97/265 (37)

VTEC = verotoxin-producing *Escherichia coli*.
a) *Salmonella* Enteritidis (n = 4), *Salmonella* Typhimurium (n = 4).
b) 6 cases had > 1 pathogen found.

TABLE 2

Demographics of patients with acute gastroenteritis.

	Rotavirus			Logistic multivariate regression	
	positive (N = 25)	negative (N = 240)	p-value[a]	odds ratio (95% CI)	p-value[a]
Age, yrs, mean (95% CI)	61.0 (52.7-69.2)	59.8 (57.1-62.5)	0.799[b]	-	-
Age, n (%)			0.384		
17-35 yrs	3 (12)	49 (20)		–	–
36-64 yrs	11 (44)	74 (31)		–	–
65-99 yrs	11 (44)	117 (49)		–	–
Female sex, n (%)	11 (44)	132 (55)	0.302	–	–
Nosocomial infection, n (%)	1 (4)	56 (24)	0.021	0.18 (0.02-1.28)	0.086
Chronic disease, n (%)	22 (88)	167 (70)	0.063	2.02 (0.44-9.40)	0.369
Immunosuppression, n (%)	12 (46)	50 (21)	0.010	2.38 (1.03-5.49)	0.042
Recent international travel history, n (%)	2 (8)	34 (14)	0.546	–	–
Children in the home, n (%)	1 (4)	46 (21)	0.090	0.29 (0.04-2.22)	0.234
Clinical features					
Fever, n (%)	16 (64)	139 (59)	0.673	–	–
CRP-value, mg/l, mean (95% CI)[c]	36 (7-64)	94 (80-107)	–	–	–
CRP < 50 mg/l, n (%)	18 (78)	98 (44)	0.002	2.65 (1.03-6.85)	0.044
Blood in stool, n (%)	1 (4)	32 (13)	0.330	–	–
Mucus in stool, n (%)	2 (8)	38 (16)	0.546	–	–
Vomiting, n (%)	11 (50)	97 (41)	0.499	–	–

CI = confidence interval; CRP = C-reactive protein.
a) Fisher's exact test.
b) 2-sample t-test for means.
c) Normal < 8 mg/l, 20 missing values of CRP, equally distributed between rotavirus and non-rotavirus.

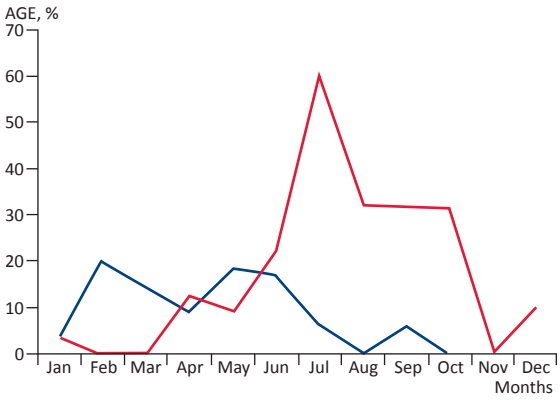
tive for rotavirus. Enteropathogenic bacteria were isolated from 65 patients (24.5%). The microbiological findings are shown in **Table 1**. Five patients had two pathogens tested and one had three pathogens tested: Rotavirus was a part of the aetiological agent in three cases together with adenovirus, *Giardia lamblia* and *Clostridium difficile*. Two patients tested positive for both *C. difficile* and adenovirus. In one patient, rotavirus, adenovirus and *Campylobacter* spp. were detected. In 62.3% of cases, no pathogen was found (165/265).

Demographic patient information is shown in **Table 2**. Immunosuppression was a significant factor in being infected with rotavirus. Nosocomial infection, AGE with onset after ≥ 3 days of hospitalisation, was inversely associated with being infected with rotavirus. A significant part of rotavirus patients compared with non-rotavirus patients with AGE had a CRP under 50 mg/l (p = 0.002). In the multivariate analysis, patients with rotavirus were significantly more immunosuppressed than patients with bacterial pathogens (OR = 2.38; 95% CI: 1.03-5.49) and a CRP < 50 mg/l (OR = 2.65; 95% CI:1.03-6.85) was found more frequently.

Vomiting, fever, blood or mucus in the stools could not be used to distinguish rotavirus from bacterial gastroenteritis.

The seasonality of rotavirus and bacterial gastroenteritis showed different patterns, see **Figure 1**. The prevalence of rotavirus peaked from February to June with 15.1% (18/119) of samples testing positive for rotavirus, whereas from July to January only 2.5% (3/118) positive cases were identified. In February, rotavirus was the primary pathogen, twice as common as all bacterial causes. Bacterial gastroenteritis showed a converse seasonal trend; from June to October 34.8% (32/92) of the samples were positive and from November to May only 4.8% (7/145) were positive for enteropathogenic bacteria. Infections with *C. difficile* were excluded in this analysis as this pathogen is generally considered an antibiotics-related infection that is not due to interpersonal transmission in the community.

FIGURE 1



Annual distribution of rotavirus gastroenteritis (–) and enteropathogenic bacterial gastroenteritis (–), respectively[a].

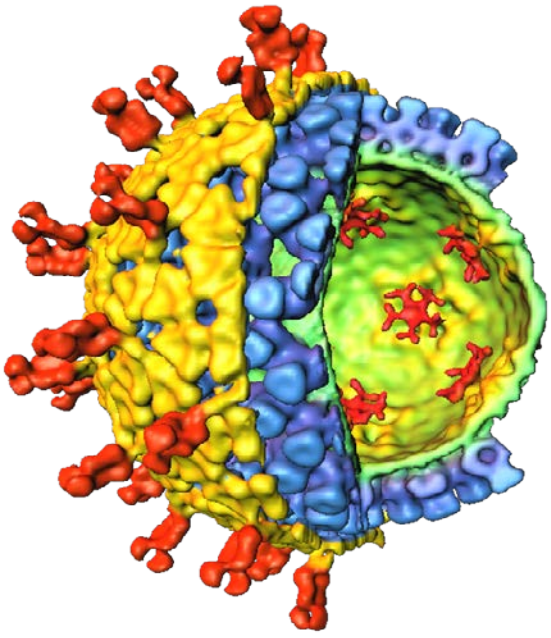
AGE = acute gastroenteritis
a) Episodes comprising *Clostridium difficile* infection only and/or > 1 pathogen were excluded. Specifically, four rotavirus and one *Campylobacter* infection were excluded (no. 28).

DISCUSSION

In this study, we demonstrated that rotavirus was the second-most frequent cause of AGE in adults with 9.4% of patients testing positive for rotavirus. This adds to the growing body of evidence that rotavirus is an important pathogen in AGE also in adults. In more recent studies, rotavirus has consistently been one of the most frequently identified pathogens in adults with AGE. The prevalence falls in the 2.5-22% range [1-6]. The present study is representative for AGE in hospitalised patients. Due to the nature of rotavirus infection, it could be expected that a larger part of the milder cases of AGE run their course in home settings; hence, the total burden of rotavirus may be underestimated when only hospitalised patients are included.

In temperate zones such as USA and Denmark, the incidence of rotavirus infections in children peaks in March [9, 10]. Unsurprisingly, the same pattern was observed in adults with rotavirus being the most frequent cause of AGE in the cooler months. The seasonality was notable in this study and comparable with the seasonality demonstrated by Anderson et al [2]. In both our study and that of Anderson et al, bacterial enteropathogens and rotavirus infections display a reverse trend [2].

We looked at different indicators for rotavirus gastroenteritis. Surprisingly, no significant association with children in the household was found, although rotavirus is well described as a paediatric disease. The lack of association between rotavirus and exposure to children has been reported previously by Anderson et al [2]. In contrast, a recent study demonstrated that vaccination of children against rotavirus significantly reduces AGE caused by rotavirus among adults [11]. The transferred effect of children's vaccinations on adult AGE with rotavirus seems rational, but the effect of the vaccination on hospitalisations of adults with AGE might not be very pronounced as no association was found in the two studies from hospital settings. In 2009, the WHO recommended that rotavirus vaccination should be introduced in the childhood vaccination programme in the European Region [12]. Based on a recent health technology assessment report, it was decided not to implement rotavirus vaccination in Denmark. However, this report did not take herd immunity and the risk of parents being infected by their children into consideration [13]. Rotavirus gastroenteritis is not more prevalent in developing countries than in developed countries [14]. In accord-



Computer-aided reconstruction of a rotavirus. Courtesy of Sanofi Pasteur MSD. Source: Photo kindly provided by MSD.

ance herewith, we did not find that recent travel was a predictor of rotavirus gastroenteritis.

Clinical symptoms, e.g. fever, vomiting, blood or mucus in the faeces, could not distinguish between rotavirus and bacterial AGE, but CRP was significantly lower in patients with rotavirus. Immunosuppression was correlated with a greater risk of rotavirus. Immunosuppressed patients are generally at risk of infections and therefore the association with rotavirus is not surprising [2, 15]. It seems possible that this group of patients also carries and thereby sheds rotavirus for a prolonged period of time; hence, it is possible that we overestimated the role of rotavirus in AGE in this group of patients. In the present study, only patients with AGE were included, but to clarify the period during which the rotavirus test remains positive in these patients, it could be interesting to perform consecutive testing regardless of symptoms.

In conclusion, we demonstrate that rotavirus is the second-most frequently identified pathogen in adults admitted to hospital with AGE in Denmark. Thus, our data add to the accumulating evidence showing that rotavirus plays an important role in the aetiology of AGE, also in adults. Rotavirus patients have a lower CRP than other patients with AGE. Immunosuppression was shown to be a risk factor for rotavirus infection, while children in the household and travelling were not. Furthermore, our data emphasise the seasonality of rotavirus gastroenteritis in adults and show that it peaks in the cooler months like in children.

Several rapid diagnostic tests for detection of rotavirus are available, making the diagnostics of rotavirus quick and easy. Establishing the diagnosis rapidly could potentially prevent unnecessary use of empirical antibiotic treatment, save additional diagnostic procedures and help taking decisions on hygienic precautions. This may be beneficial for both the patient and the economy of the healthcare system. We therefore suggest that adults hospitalised with AGE be routinely tested for rotavirus, at least in the rotavirus season from January to June.

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CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk

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