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A case-control study of risk factors for rotavirus infections in adults, Denmark, 2005–2009

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SUMMARY

Rotavirus (RV) infections affect young children, but can also occur in adults. We sought to identify risk factors for RV infections in adults aged ⩾18 years in Denmark, and to describe illness and genotyping characteristics. From March 2005 to February 2009, we recruited consecutive cases of laboratory-confirmed RV infection and compared them with healthy controls matched by age, gender and municipality of residence. We collected information on illness characteristics and exposures using postal questionnaires. We calculated univariable and multivariable matched odds ratios (mOR) with conditional logistic regression. The study comprised 65 cases and 246 controls. Illness exceeded 10 days in 31% of cases; 22% were hospitalized. Cases were more likely than controls to suffer serious underlying health conditions [mOR 5·6, 95% confidence interval (CI) 1·7–18], and to report having had close contact with persons with gastrointestinal symptoms (mOR 9·4, 95% CI 3·6–24), in particular young children aged <3 years and adults aged >18 years. Close contact with young children or adults with gastrointestinal symptoms is the main risk factor for RV infection in adults in Denmark. RV vaccination assessments should consider that RV vaccination in children may indirectly reduce the burden of disease in adults.

Key words: Adults, epidemiology, genotype, matched case-control study, risk factor, rotavirus infection.

INTRODUCTION

Rotaviruses (RV) are the most common cause of severe dehydrating diarrhoea in children worldwide. A global review estimated that RV was detected in almost 40% of children hospitalized with diarrhoea [1]. The frequency of fatal outcome following infection varies greatly between countries and it was estimated that 82% of deaths in children occur in low-income countries, mainly because of poor access to adequate treatment [2, 3]. By the age of 2 years, most children will have had a RV infection and thereby developed immunity [4]. However, RV reinfections may occur throughout life suggesting that protective immunity against the pathogen is partial. In most settings, the infection is regarded predominantly as a disease of young children, with less being known about its

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epidemiology and clinical features in adults, in part because adults are infrequently examined for RV. Few studies investigating the aetiology of acute gastroenteritis in adults indicated that they acquire RV infections although estimation of disease burden varies broadly depending on the country and study setting. One review of RV infection in adults indicated that the proportion of RV detection in adults with acute gastroenteritis ranged from 3% to 63% [5]. Two prospective cohort studies detected RV in 15% of adults hospitalized with community-acquired acute gastroenteritis in a university hospital in Germany, and in 18% of adults with acute gastroenteritis admitted to three emergency departments in major medical centres in the USA [6, 7].

The predominant route of transmission is person-to-person. In Denmark, a prospective observational study in children aged <5 years with RV gastroenteritis indicated that in 43% of infectious episodes studied, at least one other family member, including adults, also experienced gastrointestinal symptoms [8]. In countries with a temperate climate the number of cases in children peaks in the winter and early spring with almost no cases reported the rest of the year, while infections in adults seem to occur throughout the year [9]. This observation has given rise to the hypothesis that adults could be the reservoir for transmission during the rest of the year. To examine the determinants associated with infections in adults that might play a role in RV transmission, we describe adult cases registered in Denmark over a 4-year period in terms of illness and genotype distribution and investigate the risk factors for RV disease.

METHODS

Study design

We performed a case-control study from March 2005 to February 2009. Consecutively identified RV cases and controls were invited to participate in the study throughout the study period. Cases were all patients aged $\geqslant$18 years with a positive finding of rotavirus A in a stool sample, submitted for gastroenteritis diagnostic testing, including testing for RV, at Statens Serum Institut (SSI), from general practitioners or hospitals from all parts of Denmark. Simultaneously, we identified eight potential control subjects matched for gender, nearest date of birth and municipality of residence from the Danish Civil Registry, which includes all legal residents in Denmark.

Ethical standards

Stool samples were tested for RV as part of a diagnostic package for microbiological diagnostics as requested by treating clinicians of patients with gastrointestinal symptoms. No additional biological specimens were taken and no additional tests were done specifically for the purpose of the study. The treating clinician communicated the test results to patients without interference from the study design. Participation in the study was voluntary and data were treated confidentially. Data from the Central Population Register (CPR) were used and all study data were stored in a database on a password-protected server drive with limited access. Clearance from the Danish data protection agency (Datatilsynet) was obtained for this procedure.

Data collection

We used a standard questionnaire and collected information for cases and controls on general socio-demographic characteristics (age, sex, municipality of residence), household characteristics, close contact with children and adults with gastrointestinal symptoms, food consumption (a series of specific food items and place of food consumption), travel history, water-related activities (lake, river, swimming pool), contact with animals, mode of transport, and hygiene habits, and we collected information on characteristics of the illness (symptoms, duration of illness, underlying illness, hospitalization) only for cases. We sent the questionnaire by mail to cases within a few days following diagnostic confirmation – and on the same day to their corresponding controls – throughout the study period. Cases completed the questionnaire regarding exposures in the 5 days prior to disease onset. Controls were instructed to use the period within a few days (range 5 days) preceding a fixed date, namely the date of collection of the first stool specimen of the matched case.

Microbiological investigation

Stool samples were examined using the routine diagnostic test at SSI, a RV antigen detection ELISA (Oxoid A/S, Denmark). This diagnostic ELISA test was used during 2006–2008, and in 2009 a real-time PCR [10] using RNA extracted from a 10% stool suspension using the total nucleic acids kit on a MagNA Pure LC robot (Roche Diagnostics A/S, Denmark) was introduced. RNA extractions were stored at

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−80 °C prior to genotyping. The G and P types were determined by multiplex PCR following the algorithm and genotyping methods described on the EuroRotaNet website (http://www.eurorota.net/). For some samples, additional sequence analysis was necessary to determine the genotype. PCR products were purified using the High Pure PCR Purification kit (Roche Diagnostics A/S) and sequenced using the PCR primers on an ABI automated sequencer using BigDye v. 1.1 (Applied Biosystems, Denmark) chemistry. The genotypes were assigned by BLAST analysis and/or phylogenetic analysis with known reference sequences [11].

Descriptive and analytical epidemiology

We described cases by demographic, illness and genotyping characteristics. We analysed effects of exposures by calculating matched odds ratios (mOR) in univariable and multivariable analysis in a conditional logistic regression. We considered exposures with a P value <0·20 in the univariable analysis for multivariable analysis and eliminated them in a backward selection with $P = 0{\cdot}05$ as the cut-off point. Alternatively, forward selection was used with the same cut-off references. When one or more of the negatively associated variables [OR <1 and 95% confidence interval (CI) upper limit <1] were included (e.g. food variables), final inclusion of these variables depended on the model-building approach. For this reason, we decided to limit our analysis to the main-effects model. We analysed data using Stata v. 10.1 (Stata Corp., USA). We calculated the attributable proportion (AP) in the exposed, and the population attributable fraction (PAF) using the following formulas specifically applying to a case-control study:

$$\mathrm{AP} = (\mathrm{OR} - 1)/\mathrm{OR} \text{ and } \mathrm{PAF} = \mathrm{Pe}^{*}\mathrm{AP},$$

where Pe is the proportion of cases that have the exposure under study.

A total of 804 questionnaires were sent to 100 cases and 704 controls. The overall response rate was 56% with 68 completed questionnaires returned from cases (response rate 68%) and 379 questionnaires from controls (response rate 54%). For the analytical epidemiological analysis, 65 cases and 246 matching controls (mean number of controls per case: 3·8; number of controls per case, range 1–7) were included, as the remaining participants were not part of matching case-control sets and three cases did not have any matched controls.

RESULTS

Descriptive epidemiology

The median age of cases was 45 years (range 20–90 years) and for controls it was 48 years (range 20–90 years). The male:female ratio was 0·6 in cases and 0·5 in controls. Nearly all patients reported diarrhoea (97%) and four patients had bloody diarrhoea. Other symptoms reported by the patients were weakness (81%), nausea (74%), stomach cramps (60%), vomiting (56%), headache (54%), joint pain (37%), fever (34%), having a cold and/or sneezing (19%) and cough (15%). The median duration of the illness was 5·5 days, and 31% of patients reported a duration exceeding 10 days. Ten (15%) patients reported an underlying health condition and five had a malignant disease or diabetes. Fifteen (22%) patients were hospitalized for a median duration of 3 days. The illness caused 38 (56%) of the patients to stay at home from work for a median duration of 5 days (range 1–10 days).

Microbiological characterization

The genotype could be determined in 51 out of 57 samples tested. The predominant genotypes were G1P[8], G9P[8], G2P[4] and G2P[8] detected in 35%, 19%, 7% and 5% of the samples, respectively (Table 1). Six samples could not be typed and one contained two different genotypes G3 + G8P[8]. In hospitalized cases, the predominant genotypes were G1P[8] (5/15) and G9P[8] (3/15). With regard to persons who reported travel, the main genotypes identified were G1P[8] (4/15) and G9P[8] (3/15).

Risk factor analysis

In univariable analysis, cases were more likely than controls to report having been in close contact with other persons with gastrointestinal symptoms (Table 2). When asked a series of questions regarding the circumstances of how and with whom this contact occurred, several significant associations were identified. Close contact with symptomatic children aged <3 years showed a strong association with being a case (OR 12·8, 95% CI 4·7–35). However, contact with symptomatic adults (age >17 years) was also a risk factor (OR 4·9, 95% CI 2·2–11). An association with illness was also found for specific exposures such as being part of the same household as a symptomatic person (OR 6·1, 95% CI 2·6–14), having

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Table 1. *Distribution of rotavirus genotypes in stool specimens of adults, Denmark, 2005–2009 (n = 57)*

Genotypes	*n*	(%)
G1P[8]	20	(34·5)
G9P[8]	11	(19·0)
Negative	6	(10·5)
G2P[4]	4	(7·0)
G2P[8]	3	(5·2)
G8P[14]	2	(3·4)
G1PU	2	(3·4)
G3P[8]	2	(3·4)
G4P[8]	2	(3·4)
G1P[4]	1	(1·7)
G3PU	1	(1·7)
G3*	1	(1·7)
G4P[6]	1	(1·7)
G8P[8]*	1	(1·7)
G12P[8]	1	(1·7)
Total	**58**	**(100·0)**

* G8P[8] and G3 detected in the same patient's specimen.

eaten together (OR 6·7, 95% CI 3·2–14) or sharing toilet facilities with a symptomatic person (OR 4·8, 95% CI 2·2–10). Changing symptomatic persons' diapers (OR 9·9, 95% CI 3·9–25), taking care of ill persons (OR 11, 95% CI 4·3–28) or cleaning the vomit of a symptomatic person were also identified as risk factors (OR 10, 95% CI 3·7–27). Cases reported underlying chronic illness more often than controls (OR 3·8, 95% CI 1·4–10) and in particular diabetes and malignant disease were reported in cases. Fewer cases than controls reported petting animals (OR 0·5, 95% CI 0·3–0·9). Foreign travel was weakly associated with being a case (OR 2·1, 95% CI 1·0–4·8), whereas travel within Denmark was not (OR 0·9, 95% CI 0·2–3·1). A series of questions addressed food intake, both specific foods and place of consumption. Controls were more likely than cases to report several of these exposures. For instance, more controls than cases reported consumption of sandwiches, cold chicken, cold pork, warm pork, pasta and eggs as well as eating food prepared at home (Table 2).

In multivariable analysis, the two main risk factors from the univariable analysis, i.e. close contact with symptomatic persons and underlying illness, remained associated with an increased risk of RV infection. More specifically, the adjusted mOR for close contact with symptomatic persons was 10·6 (95% CI 4·4–26) and the mOR for underlying illness was 7·4 (95% CI 2·3–24). Further, the adjusted mOR for close contact with sick children aged <3 years was 36 (95% CI 7·0–184) and for contact with sick adults (>17 years), it was 8·8 (95% CI 2·4–32). Close contact with symptomatic older children and teenagers (aged 3–17 years) were not reported more often by cases than controls. In contrast to the univariable analysis results, foreign travel was not a risk factor for RV infection and petting animals was borderline significant (OR 0·5, 95% CI 0·2–1·0). We calculated the AP in adults exposed to symptomatic children aged <3 years as 92%, giving a PAF of 24%, and calculated the AP in adults exposed to symptomatic adults as 80% giving a PAF of 21%.

DISCUSSION

In Denmark, RV infection is not a notifiable disease and testing for RV is usually performed only for children as the infection is reputed to predominantly affect children. A national prospective study indicated that 39% of acute gastroenteritis-associated hospitalizations of Danish children aged <5 years were caused by RV [12] demonstrating that RV causes a substantial burden of hospitalizations in children. Despite high RV infection-associated hospitalizations, fatal outcomes are rare as free access to adequate healthcare enables rapid treatment. A serological survey in the UK indicating that IgM antibodies against RV increased with age and reports of RV outbreaks in adults point to an under-recognized burden of RV infections in adults [13–15]. Although nearly all adults have developed antibodies against RV throughout life, our main study results suggest that adults remain susceptible to the infection with an increased risk when they have close contact with young symptomatic children and with symptomatic adults. The PAF results of our study suggest that RV infections in adults could be prevented in 25% and 21% of cases, respectively, if they were not exposed to symptomatic young children (aged <3 years) or to symptomatic adults. Similar to our study findings, prospective cohort family studies investigating person-to-person transmission indicated that parents of RV-infected children were at higher risk of becoming infected compared to parents of healthy children [16–19]. With the same perspective, a vaccination impact assessment highlighted that vaccination of young children against RV would confer indirect protection to older adults and children [20, 21].

Our study also indicates that adults have a higher risk of infection when they have close contact with adults presenting gastrointestinal symptoms, suggesting that adults may also serve as a reservoir for RV.

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Table 2. *Selected determinants for rotavirus infection in adults, results of univariable and multivariable analysis, Denmark, 2005–2009*

	Cases and controls exposure							
	Cases exposed *n* (%)	Controls exposed *n* (%)	Univariable analysis			Multivariable analysis		
			OR	95% CI	*P* value	mOR	95% CI	*P* value
Contact with persons with gastrointestinal symptoms	33 (60·0)	32 (17·3)	9·2	4·1–20·7	<0·001	10·6	4·4–26·0	0·000
If yes, were the persons:								
<3 years	17 (25·8)	6 (2·5)	12·8	4·7–35·2	<0·001	*36*	*7·0–184·5*	*0·000*
3–17 years	7 (10·6)	11 (4·5)	2·6	0·9–7·1	0·065	–	–	–
>17 years	17 (25·8)	18 (7·4)	4·9	2·2–11·1	<0·001	*8·8*	*2·4–32·8*	*0·001*
Living in the same household	18 (26·9)	15 (6·1)	6·1	2·6–14·4	<0·001	–	–	–
Eating together	27 (40·3)	25 (10·2)	6·7	3·2–14·1	<0·001	–	–	–
Sharing toilet facilities	20 (29·4)	21 (8·6)	4·79	2·2–10·6	<0·001	–	–	–
Changing diapers	19 (28·8)	10 (4·1)	9·89	3·9–25·3	<0·001	–	–	–
Caring	19 (27·9)	9 (3·7)	10·95	4·3–27·8	<0·001	–	–	–
Cleaning vomit	13 (19·1)	1 (0·4)	10·9	3·7–27	1,000	–	–	–
Underlying health condition	10 (15·4)	12 (5·0)	3·8	1·4–9·9	0·007	7·4	2·3–23·7	0·001
Petting animal	26 (38·8)	134 (55·6)	0·5	0·3–0·9	0·02	0·5	0·2–1·0	0·039
Animal (pet) at home	20 (31·8)	79 (34·7)	1·12	0·6–2·0	0·756	–	–	–
Travel history abroad	13 (81·3)	23 (63·9)	1·9	0·5–7·7	0·359	–	–	–
Place of food consumption								
Outside home	11 (16·9)	7 (2·9)	6,0	2·0–18·4	0·002	–	–	–
Takeaway	20 (32·3)	76 (35·5)	0·8	0·4–1·5	0·414	–	–	–
Takeaway canteen	2 (3·1)	6 (3·0)	1,0	0·2–5·2	0·993	–	–	–
Private	19 (30·2)	80 (37·6)	0·7	0·4–1·3	0·244	–	–	–
Canteen	17 (27·4)	72 (34·0)	0·7	0·3–1·3	0·238	–	–	–
Nursing home	3 (4·8)	3 (1·5)	2·2	0·4–11·3	0·346	–	–	–
Restaurant	20 (31·8)	72 (33·5)	0·86	0·5–1·7	0·694	–	–	–
Snack stand	15 (24·2)	58 (27·1)	0·72	0·4–1·5	0·385	–	–	–
Train, plane, ferry	7 (11·3)	18 (8·6)	1·4	0·5–4·1	0·56	–	–	–
Type of food items and water consumed								
Salad	56 (84·9)	218 (92·8)	0·49	0·2–1·2	0·119	–	–	–
Fresh fruit	58 (90·6)	221 (94·6)	0·56	0·2–1·7	0·306	–	–	–
Sandwich	38 (59·4)	186 (81·6)	0·27	0·2–0·6	<0·001	–	–	–
Cold chicken	12 (20·3)	89 (40·6)	0·42	0·2–0·8	0·011	–	–	–
Hot chicken	28 (45·9)	129 (57·3)	0·5	0·3–1·0	0·052	–	–	–
Cold pork	35 (53·9)	172 (76·4)	0·35	0·2–0·7	0·001	–	–	–
Hot pork	30 (50·9)	148 (66·4)	0·5	0·3–0·9	0·013	–	–	–
Tartar	3 (4·6)	8 (3·5)	1·3	0·3–5·4	0·701	–	–	–
Pasta	28 (47·5)	147 (65·0)	0·45	0·3–0·9	0·015	–	–	–
Rawfish	5 (7·8)	43 (18·9)	0·38	0·1–1·0	0·049	–	–	–
Shellfish	21 (33·3)	77 (34·5)	0·9	0·5–1·7	0·744	–	–	–
Pasteurized milk	40 (61·5)	152 (67·6)	0·84	0·5–1·4	0·476	–	–	–
Unpasteurized milk	5 (8·3)	41 (18·8)	0·41	0·1–1·1	0·072	–	–	–
Cheese	16 (27·6)	44 (21·9)	1·4	0·7–2·7	0·397	–	–	–
Prepared eggs	39 (65·0)	185 (81·1)	0·36	0·2–0·8	0·005	–	–	–
Raw eggs	5 (7·7)	30 (12·9)	0·7	0·2–1·8	0·38	–	–	–
Ice cream	23 (38·3)	95 (44·4)	0·68	0·4–1·4	0·31	–	–	–
Previous day's meal	34 (54·8)	145 (64·4)	0·66	0·4–1·3	0·209	–	–	–
Drink tap water at home	50 (79·4)	212 (92·6)	0·27	0·1–0·8	0·007	–	–	–
Drink tap water outside home	29 (58·0)	140 (66·7)	0·57	0·3–1·2	0·152	–	–	–

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This study result, and the hypothesis that adults could represent a viral reservoir, are consistent with the results of a clinical and virological study reporting that both children and adults excreted the pathogen in their stools [22]. By contrast, our study results do not point to an increased risk of transmission from children and teenagers aged 3–17 years with gastrointestinal symptoms, suggesting that exposure to adults mainly comes from young children or other adults, whereas exposure from older children and teenagers is less important. This could be due to better hygiene in those age groups or because they shed less RV due to a stronger immunity than in younger and older age groups. Foreign travel was only borderline significant in our study whereas previous studies reported that foreign travel is associated with higher risk of RV infection [23]. It cannot be excluded that a larger sample size would have enabled us to identify a significant association as we only had a few cases reporting foreign travel. Our study also indicates that adults with underlying health conditions have an increased risk of being diagnosed with RV. This finding is concordant with other study results showing, for instance, that immunodeficiency predisposes to RV infections and can generate a chronic RV infection with frequent diarrhoea [24–28]. Regarding clinical features of the infection in adults, our results, in line with other study results, indicate a broad spectrum of symptoms with more than half of the cases reporting diarrhoea, weakness, nausea, stomach cramps, vomiting or headache. Following reports of suspected interspecies transmission of animal RV to humans in Slovenia and Bulgaria [29, 30], we also explored the hypothesis of zoonotic transmission. We identified two cases of suspected zoonotic transmission in our cases. However, this seems to happen infrequently, as we did not find an increased risk of RV infection associated with exposure to animals. Transmission from animals to humans might occur on rare occasions but not enough to be a risk factor detectable in an epidemiological study investigating sources of infection in adults. Consumption of almost all specific food items was reported more frequently by controls than cases. We do not have any straightforward explanation for this unexpected observation, which could be due to recall bias. Another explanation could be that cases are less prone to eat some food items a couple of days before onset of illness if minor signs of discomfort precede the date of overt gastroenteritis. For this reason we decided to exclude those variables in the multivariable analysis. The genotype distribution in our study was comparable to the published pan-European collaborative strain surveillance network results between 2006 and 2009 [31], with two cases of suspected zoonotic transmission with the same genotype, G8P[14], reported in Denmark in 2006.

Our study has some limitations that might influence our results. It relied on testing stool specimens sent for routine microbiological diagnostics, most likely from patients with suspected infection with enteric bacteria. These patients may have had rather severe gastroenteritis and are not likely to be representative of all adults with gastroenteritis in the Danish population. Recruitment of cases was restricted to certain regions of Denmark, for which SSI was the provider of primary microbiological diagnostic tests at the time of the study. Therefore caution should be exercised when extrapolating our results to the whole Danish population.

CONCLUSION

In conclusion, adults are more likely to become infected with RV through close contact with young sick children and also with adults presenting gastrointestinal symptoms. Therefore, both child-to-adult and adult-to-adult transmission should be considered in future evaluations of RV disease dynamics including vaccination impact assessments.

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DECLARATION OF INTEREST

None.

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