CLINICAL FEATURES OF ROTAVIRUS INFECTIONS : INFLUENCE OF CHILD AGE ON CLINICAL MANIFESTATIONS

CARACTERISTIQUES CLINIQUES DES INFECTIONS A ROTAVIRUS : INFLUENCE DE L'AGE DES ENFANTS SUR LES MANIFESTATIONS CLINIQUES

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Résumé :

Objectifs : Décrire les caractéristiques cliniques des infections à Rotavirus et comparer les symptômes observés en fonction de l'âge des enfants.
Malades et méthodes : Les dossiers cliniques de 278 enfants de moins de 5 ans infectés par le Rotavirus ont été consultés rétrospectivement. La présence d'antigènes de Rotavirus du groupe A dans les selles a été détectée par la technique immunoenzymatique. Une corrélation statistique entre les signes cliniques et l'âge des enfants a été recherchée au moyen des tests de corrélation de Pearson.
Résultats : Parmi les 278 enfants positifs à Rotavirus, 93,9% ont présenté une diarrhée, 79,1% des vomissements, 71,6% de la fièvre, 37,4% des signes respiratoires et 33,1% des troubles neurologiques. Une réhydratation intraveineuse requise pour 59,7% des enfants. D'une façon générale, la diarrhée (p = 0,001), les vomissements (p = 0,007), la fièvre (p=0,045), les troubles respiratoires (p = 0,01) et la déshydratation (p < 0,001) étaient significativement plus fréquents chez les nourrissons de 1-24 mois par rapport aux autres enfants infectés.
Conclusion : La sévérité du syndrome clinique induit par les infections à Rotavirus semble être directement influencée par l'âge de l'enfant. Il était intéressant de noter que les nourrissons de 1 à 5 mois ont présenté des formes cliniques souvent aussi sévères que ceux de 6 à 24 mois.

Mots clés : Rotavirus, diarrhée, symptômes, âge.

Abstract:

Objectives : The aim of the present study was to describe clinical features of rotavirus infections in children and to compare the observed symptoms according to the age of the patients.
Patients and methods : Clinical files of 278 rotavirus-positive children under 5 years of age were retrospectively examined. The presence of group A rotavirus antigens in stool samples collected from children was detected by direct sandwich enzyme-linked immuno-sorbent assay. Pearson's correlation tests were used to determine the relationship between each clinical sign noticed and patients' age.
Results : Among the 278 rotavirus-positive children, 93.9% presented with diarrhoea, 79.1% vomiting, 71.6% fever, 37.4% respiratory troubles, and 33.1% neurological signs. Intravenous rehydration was needed for 59.7% of the children. The comparison of clinical signs according to the age showed that diarrhoea (p = 0.001), vomiting (p = 0.007), fever (p = 0.045), respiratory troubles (p = 0.01) and dehydration (p < 0.001) were significantly more frequent in infants of 1 to 24 months old.
Conclusion : The severity of rotavirus illness seems to be directly influenced by child's age. Interestingly, infants of 1 to 5 years old often presented with disease as severe as babies of 6 to 24 months old.

Key words : Rotavirus, diarrhoea, symptoms, age.

INTRODUCTION

Rotaviruses are responsible for high morbidity in developed countries and high mortality in developing countries [1]. Each year, group A rotavirus causes approximately 111 million episodes of gastroenteritis requiring only home care, 25 million clinic visits, 2 million hospitalizations and 440,000 deaths in children under 5 years of age [1, 2].
Rotavirus infections frequently recur in humans from birth to old age. Infections in young children can eventuate in severe, life-threatening diarrhoea, more commonly in primary infection. However infections in older individuals may be asymptomatic or be associated with mild enteric symptoms, probably due to increasing cross-protective immunity as a result of repeated infections, severe infections may also occur in elderly individuals in some settings [3].
In the present study, we described the clinical syndrome associated with rotavirus infection in children, and then compared their clinical symptoms according to their age.

PATIENTS AND METHODS

A total of 2,050 faecal specimen were collected from newborns and children under 5 years of age between January, 2000 and December, 2007. These children were originated from different regions of Tunisia: the North (Tunis and Nabeul), the Centre (Sousse, Monastir, Mahdia and Kairouan), and the South (Sfax) and were either inpatients hospitalized in a paediatric/neonatal unit during an outbreak of rotavirus infections, or outpatients consulting for diarrhoea.
All samples were immediately screened for the presence of group A rotavirus antigens by direct sandwich enzyme-linked immunosorbent assay (IDEIA Rotavirus, Dako®). Tests were conducted and interpreted according to the manufacturer's instructions.
Clinical files of rotavirus-positive children were retrospectively examined, and their age, gender and clinical manifestations of the infection were recorded.
The children were classified into 5 age groups: less than 30 days old, 1 to 5 months old, 6 to 12 months old, 13 to 24 months old, and 25 to 59 months old.
Cases of diarrhoea were defined by the following criteria: (i) presence of three or more liquid stool per day; (ii) loss of the usual pattern of daily evacuations; and (iii) change in the consistency of the stool from solid or semi-solid to liquid, accompanied or not by vomiting, temperature and dehydration [4].
Pearson's correlation tests were used to determine the relationship between each observed clinical sign and the patient's age group and gender. Significance level of $P < 0.05$ was used for all analyses.

RESULTS

Out of the 2,050 total number of samples screened for rotavirus in the present study 438 (21.4%) were positive for rotavirus antigen. Among rotavirus-positive cases, medical records were available for 278 children who finally represented the studied population.
Male predominance was observed among rotavirus-positive filed children : among of 278 infected children, 153 were boys and 125 were girls, a sex ratio was 1.2.
The mean age of these patients was 12.7 months (range, from birth to 59 months). Their distribution according to age and hospitalisation stastus is shown in Table 1.

Table I : Distribution of Rotavirus-positive children according to their age and hospitalisation status.
Tableau I : Répartition des enfants porteurs de Rotavirus en fonction de leur âge et leur statut d'hospitalisation.

Children age	Outpatients	Inpatients	Total N (%)
< 1 month	2 (0.7%)	9 (3.2%)	11 (4.0%)
1-5 months	3 (1.1%)	67 (24.1%)	70 (25.2%)
6-12 months	7 (2.5%)	97 (34.9%)	104 (37.4%)
13-24 months	6 (2.2%)	58 (20.9%)	64 (23.0%)
25-59 months	5 (1.8%)	24 (8.6%)	29 (10.4%)
Total N (%)	23 (8.3%)	255 (91.7%)	278 (100%)

Among the 278 rotavirus-positive filed children, 93.9% presented diarrhoea, 79.1% vomiting, 71.6% fever, 37.4% additional respiratory troubles, 33.1% neurological signs, and 59.7% needed intravenous rehydration. The clinical manifestations detected in the infected children according to their age are presented in Table II. Statistical comparison of the clinical signs between children age groups showed that neonates usually presented milder syndrome, as diarrhoea ($P<0.001$), vomiting ($P<0.001$), fever ($P=0.008$), respiratory troubles ($P=0.048$) and dehydration ($P=0.025$) were significantly less frequent in newborns less than 1 month old than in older children. More precisely, diarrhoea ($P=0.001$), vomiting ($P=0.007$), fever ($P=0.045$), respiratory troubles ($P=0.01$) and dehydration ($P<0.001$) were significantly more frequent in infants of 1 to 24 months old than in children younger or older. No significant difference was observed in clinical syndrome between boys and girls.

DISCUSSION

Rotavirus infection is the most common cause of acute, dehydrating diarrhoea in children under 5 years of age.
In the present study, the clinical syndrome caused by rotavirus infection was directly influenced by children age. Indeed, neonates presented fewer symptoms than older infants. This observation was already described in infants [5-7] as well as in animal models [8, 9], but not really explained. Nevertheless, many hypotheses were suggested to explain it : (a) the number of rotavirus receptors on the enterocytes surface is very low in neonates, then quickly increases in infants, and decreases along their growth [10], (b) the intestinal lumen concentration of enzymes (such as trypsin, which is necessary for rotavirus infectivity) is very low in newborns and increases in older children [10], (c) maternal antibodies transmitted transplacentally or through breast-feeding may protect neonates against severe rotavirus infections [11-13], (d) some specific strains of Rotavirus ("nursery strains") have been reported to be avirulent and exclusively isolated from asymptomatic neonates [14].
Globally, in the present study, Rotavirus disease was more severe in infants of 1 to 24 months old than in children younger

Table II : Clinical features of Rotavirus infection according to patients' age.
Tableau II : Caractéristiques cliniques de l'infection à Rotavirus en fonction de l'âge des patients.

Clinical sign	Children age					Total N (%)
	<1 month	1-5 months	6-12 months	13-24 months	25-59 months	
Diarrhoea	7 (63.6%)	66 (94.3%)	100 (95.9%)	61 (95.3%)	27 (93.1%)	261 (93.9%)
Fever	4 (36.4%)	49 (70.0%)	77 (75.3%)	50 (78.1%)	19 (65.5%)	199 (71.6%)
Vomiting	3 (27.3%)	52 (74.3%)	91 (87.6%)	52 (78.1%)	22 (75.9%)	220 (69.7%)
Respiratory troubles	1 (9.1%)	30 (42.3%)	47 (47.4%)	19 (29.7%)	7 (24.1%)	104 (37.4%)
Neurological troubles	2 (18.2%)	27 (38.6%)	36 (36.1%)	21 (32.8%)	6 (20.7%)	92 (33.1%)
Dehydration*	3 (27.3%)	43 (61.4%)	68 (70.1%)	42 (65.6%)	10 (34.5%)	166 (59.7%)
Total	11	70	104	64	29	278 (100%)

* Dehydration requiring intravenous rehydration

or older. According to literature data, the peak incidence of serious rotavirus infections is generally quoted as occurred in children before 2 years of age [15, 16]. Indeed, infections in children after 2 years of age may be associated with mild enteric symptoms, possibly due to increasing cross-protective immunity as a result of repeated infections during the two first years of life. Moreover, according to literature data, severe rotavirus infections is generally known to concern children after 6 months of age [15, 16]. Indeed, during the first few months of life, infants are thought to be partially protected by maternal antibodies acquired transplacentally or through breast feeding. Thus, in the present study, it was unexpected to notice that 61.4% of infants aged from one to five months needed intravenous rehydration (Table II). Such a result may be of high importance considering that the Advisory Committee on Immunization Practices currently recommends the initiation of the rotavirus vaccine series at 2 months of age, although the first dose can be given as early as the age of 6 weeks [17, 18]. If infants during the first few months of life are at greater risk for symptomatic rotavirus infection than it has generally been appreciated, routine immunization schedules might be reconsidered in order to extend the benefits of rotavirus vaccine to these vulnerable infants. Of course, the safety, effectiveness, and feasibility of immunizing neonates would have to be established [19].

Most factors associated with virulence remain unknown. The severity of this illness seems to be influenced by host factors, such as age of infection and malnutrition, but also by viral factors, as some genotypes known to be associated with greater severity of illness than others [20-27]. So far, the few studies carried out to attempt correlation between rotavirus genotypes and clinical data as disease severity have generally been inconclusive, or at best, they have shown that differences do not appear to be of major clinical importance [21].

CONCLUSION

Rotavirus vaccines are usually given to infants at about 2 month of age. Infants in the first few months of life may remain vulnerable to serious rotavirus infections. Our findings should prompt a possible rethinking of the optimal rotavirus immunization schedule.

The pathogenesis of rotavirus infections is not completely understood. First, the presentation of infection seems to be conditioned by particular characteristics of each patient: age, susceptibility, primary infection or re-infection, immune state and malnutrition. Furthermore, the relationship between genotype and clinical outcomes seems to be complex and controversed to date. Developments in polymerase chain reaction techniques now make it possible to quantify the viral load during an effective episode by real-time RT-PCR: thus, it appears that children with more severe diarrhoea excrete more virus than children with less severe disease [3]. Further studies of the role of virulence factors in rotavirus infections are needed to explain the pathogenesis of rotavirus infections.

References

1- Parashar UD, Gibson CJ, Bresee JS, Glass RI. Rotavirus and severe childhood diarrhea. Emerg Infect Dis 2006 ; 12 : 304-6.

2- Parashar UD, Hummelman EG, Bresee JS, Miller MA, Glass RI. Global illness and deaths caused by rotavirus disease in children. Emerg Infect Dis 2003 ; 9 : 565–72.

3- Kang G, Iturriza-Gomara M, Wheeler JG, et al. Quantitation of group A rotavirus by real-time reverse-transcription-polymerase chain reaction: correlation with clinical severity in children in South India. J Med Virol 2004; 73 : 118-22.

4- Vasilev BL, Marchenko LG, Gerasun BA, Vasil'eva RI. On clinical manifestations of rotavirus-related gastroenteritis and possible links with its viral phenotype. Kin Med Osk 2000 ; 78 : 35-6.

5- Kapikian AZ, Hoshino Y, Chanock R. Rotaviruses. In: Fields BN, Knipe DM, Howley PM, eds. Fields Virology. 4th ed. Philadelphia: Lippincott-Raven Press 1996 : 1787-1833.

6- Linhares AC, Mascarenhas JAP, Gusmao RHP, Gabbay YP, Fialho AM, Leite JPG. Neonatal rotavirus infection in Belém, Northern Brazil: nosocomial transmission of a P[6] G2 strain. J Med Virol 2002 ; 67 : 418-26.

7- Bahl R, Ray P, Subodh S, et al. Incidence of severe rotavirus diarrhea in New Delhi, India, and G and P types of the infecting rotavirus strains. J Infect Dis 2005 ; 192 : S114-9.

8- Ciarlet M, Gilger MA, Barone C, McArthur M, Estes MK, Conner ME. Rotavirus disease, but not infection and development of intestinal histopathological lesions, is restricted in rabbits. Virology 1998 ; 251: 343-60.

9- Ciarlet M, Conner ME, Finegold MJ, Estes MK. Group A rotavirus infection and age-dependent diarrheal disease in rats: a new animal model to study the pathophysiology of rotavirus infection. J Virol 2002 ; 76 : 41-57.

10- Riepenhoff-Talty M, Lee PC, Carmody PJ, Barrett HJ, Ogra PL. Age-dependent rotavirus enterocyte interactions. Proc Soc Exp Biol Med 1982 ; 170 : 146-54.

11- Duffy LC, Byers TE, Riepenhoff-Talty M, La Scolea LJ, Zielezny M, Ogra PL. The effects of infant feeding on rotavirus-induced gastroenteritis: a prospective study. Am J Public Health 1986 ; 76 : 259-63.

12- Elias MM. Distribution and titres of rotavirus antibodies in different age groups. J Hyg 1977 ; 79 : 365-72.

13- Misra S, Sabui TK, Basu S. A prospective study of rotavirus diarrhea in children under 1 year of age. Clin Pediatr 2007 ; 46 : 683-8.

14- Linhares AC, Mascarenhas JAP, Gusmao RHP, Gabbay YP, Fialho AM, Leite JPG. Neonatal rotavirus infection in Belém, Northern Brazil: nosocomial transmission of a P[6] G2 strain. J Med Virol 2002 ; 67 : 418-26.

15- Dormitzer PR. Rotaviruses. In: Mandel, GL, Bennett, JE, and Dolin R. Principles and Practice of Infectious Diseases, Sixth edition. Elsevier, Churchill-Livingstone. Philadelphia 2005 : 1902-13.

16- Ward RL, Bernstein DI, Staat MA. Rotaviruses. In: Feigin RD, Cherry JD, Demmler-Harrison GJ, Kaplan SL. Textbook of Pediatric Infectious Diseases, Sixth edition 2009 : 2245-70.

17- Centers for Disease Control. Prevention of rotavirus gastroenteritis among infants and children. MMWR 2006 ; 55 : 1-13.

18- Centers for Disease Control. Rotavirus vaccination coverage and adherence to the advisory committee on immunization practices (ACIP)-recommended vaccination schedule – United States, February 2006-May 2007. MMWR 2008 ; 57 : 398-401.

19- Clark HF, Marcello AE, Lawley D, Reilly M, DiNubile MJ. Unexpectedly high burden of rotavirus gastroenteritis in very young infants. BMC Pediatrics 2010 ; 10 : 40.

20- Ball JM, Tian P, Zeng CQY, Morris AP, Estes MK. Age-dependent diarrhea induced by a rotaviral nonstructural glycoprotein. Science 1996 ; 272 : 101-4.

21- Cascio A, Vizzi E, Alaimo C, Arista S. Rotavirus gastroenteritis in Italian children: Can severity of symptoms be related to the infecting virus? Clin Infect Dis 2001 ; 32 : 1126-32.

22- Polanco-Marin G, Gonzalez-Losa MR, Rodriguez-Angulo E, Manzano-Cabrera L, Camara-Mejia J, Puerto-Solis M. Clinical manifestations of the rotavirus infection and his relation with the electrophoretypes and serotypes detected during 1998 and 1999 in Merida, Yucatan, Mexico. J Clin Virol 2003; 27 : 242-6.

23- Nakagomi O, Nakagomi T, Arisawa K. A lack of significant association between the electrophoretype or G-serotype of the infecting strain and disease severity of rotavirus gastroenteritis. Arch Virol 2006 ; 151 : 1947-60.

24- Mota-Hernandez F, Calva JJ, Gutierrez-Camacho C, et al. Rotavirus diarrhea severity is related to the VP4 type in Mexican children. J Clin Microbiol 2003; 41 : 3158-62.

25- Linhares AC, Verstraeten T, Wolleswinkel-van den Bosch J, Clemens R, Breuer T. Rotavirus serotype G9 is associated with more-severe disease in Latin America. Clin Infect Dis 2006 ; 43 : 312-4.

26- Jang SJ, Kang JO, Moon DS, et al. Comparison of clinical characteristics of patients with rotavirus gastroenteritis relative to the infecting rotavirus G-P genotype. Korean J Lab Med 2006 ; 26 : 86-92.

27- Bern C, Unicomb L, Gentsch JR, et al. Rotavirus diarrhea in Bengladeshi children: correlation of disease severity with serotypes. J Clin Microbiol 1992; 30 : 3234-8.