SCIENTIFIC EMINENCE GROUP

Research Article

Open Access

World Journal of Immunology and Respiratory Medicine

jirm@scientificeminence.com

Comparison of Clinical Features of Childhood Rotavirus and Norovirus Gastroenteritis in Tunisia

Mouna HZ[1*], Hanène M[2], I Trabelsi[1], IB Salem[3] and Manel BM[1]

[1]*Research Unit, Genomic, Biotechnology and Antiviral Strategies (UR17ES30), Higher Institute of Biotechnology of Monastir. University of Monastir, TU-5000 Monastir, Tunisia.*

[2]*Department of Pharmaceutical Sciences, Faculty of Pharmacy, University of Monastir.*

[3]*Laboratory of Environmental and Food Analyses (VIROTEK LAB) Sousse, Tunisia.*

*** Corresponding Author**

Mouna HZ, Research Unit, Genomic, Biotechnology and Antiviral Strategies (UR17ES30), Higher Institute of Biotechnology of Monastir. University of Monastir, TU-5000 Monastir, Tunisia, Tel: 97769624, E-mail: mouna20781@yahoo.fr

Citation

Mouna HZ, Hanène M, I Trabelsi, IB Salem, Manel BM (2021) Comparison of Clinical Features of Childhood Rotavirus and Norovirus Gastroenteritis in Tunisia. World J Immunol Respir Med 1(1):102

Publication Datess

Received date: August 28, 2021

Accepted date: September 28, 2021

Published date: September 29, 2021

Abstract

Acute gastroenteritis is one of the most common infectious diseases in humans and continues to be one of the leading causes of morbidity and mortality worldwide. Rotavirus (RV) and norovirus (NoV) have been recognized as the main agents responsible for this disease. This study compared the prevalence and clinical features of childhood RV and NoV gastroenteritis in Tunisia. Fecal specimens and clinical data were collected from 435 children (238 inpatients and 197 outpatients) under 13 years of age with acute diarrhea at Monastir region, Tunisia. Patients with underlying diseases associated with diarrhea or those diagnosed with bacterial gastroenteritis were excluded. Virus RNA was extracted, amplified, electrophoresed, sequenced and phylogenetically analyzed to determine the prevalent genotypes. Chi-square and Fisher's exact test were used to compare characteristics of clinical manifestation in each group. Of the 435 specimens, 120 (27.6%) were positive for RV and 60 (13.8%) were positive for NoV. Among the 435 children with diarrhea, fever was detected in 245 (56.3%) cases, vomiting in 279 (64.1%) cases, abdominal pain in 35 (8.1%) cases, bloody stool in 11 (2.5%) cases, anemia in 101 (42.4%) cases, ear, nose and throat disorders in 50 (19.3%) cases and cough in 32 (12.4%) cases. Compared with NoV, patients with RV gastroenteritis had a significantly higher percentage of vomiting (75.2 vs. 47.2%, $P = 0.005$), and cough (12.4 vs. 0%, $P = 0.019$). In contrast, the duration of diarrhea was significantly higher in children infected with NoV than in those infected with RV (9.87 ± 6.64 vs. 7.30 ± 3.82 days, $P = 0.010$). The severity of the diarrhea was evaluated for hospitalized infants. No significant differences were observed between RV and NoV infections with regard to the clinical severity of the disease, especially for dehydration.

Keywords: Rotavirus; Norovirus; Gastroenteritis; Clinical features; Children

Introduction

Gastrointestinal diseases are one of the most frequent and preventable health problems worldwide, presenting high rates of morbidity and mortality especially in developing countries. Many viral strains cause acute gastroenteritis in humans. Rotavirus (RV) and norovirus (NoV) are the most common causes. Group A rotaviruses (RVs), family *Reoviridae*, are a major cause of acute diarrhea worldwide in infants [1], while NoVs, family *Caliciviridae*, are recognized as the most important cause of nonbacterial gastroenteritis outbreaks in school-age children and adults worldwide [2, 3]. Transmission of these viruses can occur through direct contact with shedding persons, contaminated food, sewage-contaminated water, contaminated aerosols and environmental contamination [4]. Clinical studies on the clinical characteristics and differences between the common pathogens are rare. The clinical manifestations of viral gastroenteritis include diarrhea, vomiting, fever, anorexia, headache, abdominal cramps, and myalgia. None of these single symptoms clearly distinguishes viral gastroenteritis from diarrheal illness due to RV or NoV. The age of the child, associated findings, appearance of the stool, seasonal peaks, and history of exposure may provide clues for distinguishing viral from other pathogens. In general, bacterial infections have been reported to be associated with increased age and blood and mucus in the stool – characteristics usually associated with non-viral diseases.

The purpose of this paper is to describe the clinical picture of gastroenteritis in inpatients and outpatients and to compare the symptoms and signs of RV infections with those of NoV infections.

Materials and Methods

Population, Clinical Definitions and Specimen Collection

A total of 435 patients met the criteria for a diagnosis of acute gastroenteritis-that is, three or more loose stools for at least one day and for no longer than 14 days and/or vomiting and fever. A total of 239 boys and 196 girls with gastroenteritis aged 18 days to 13 years were studied. Patients with chronic diarrhea were excluded. According to the severity of the illness 238 patients were admitted to Monastir University Hospital and 197 remained outpatients and consulting several dispensaries in the region ofMonastir.

On admission the parents were asked in detail about clinical symptoms before the hospital was contacted, such as the appearance and frequency of stools and the occurrence of vomiting, fever, abdominal pain, and concomitant respiratory symptoms. Severity criteria, such as duration of the diarrhea, number of stools or bouts of vomiting, range of body temperature, degree of dehydration (dehydration was graded as mild, moderate, or severe), capillary refill time (CRT), and the presence of skin blotches, were determined for all hospitalized children.

After collection, the samples were stored frozen (-20°C) at the laboratory.

Laboratory methods

Fecal specimens were thawed, diluted with phosphate-buffered saline to 20% suspensions, centrifuged at 10,000×g for 10 min and the viral RNA was extracted using the NucliSENS® EasyMAG™ platform (bioMérieux, Marcy L'Etoile, France), according to the manufacturer's instructions. The stool samples were screened for the presence of group A RVs and NoVs.

Genogroups of NoV were determined by reverse-transcriptase polymerase chain reaction (RT- PCR). The primer pairs used in this study and methodology were according to our previously published paper [5]. The primer set JV12/JV13 was used to amplify a fragment of the RNA polymerase gene. The primers sets G1SKF/G1SKR and G2SKF/G2SKR were used to detect a fragment of the capsid gene of NoV genogroups I and II, respectively [5]. The NoVs detected in the stool samples were characterized genetically by direct sequencing of the PCR products and phylogenetically analyzed, as previously described [6].

All stool specimens were analyzed for group A RV by enzyme immunoassay (Rotavirus ELISA kit, Premier™ Rotaclone®) and G and P genotypes were determined by multiplex semi-nested PCR methods with type-specific primers on the basis of their outer capsid proteins, as previously described [7].

Nucleotide Sequence Accession Numbers

The sequences of NoVs determined in this study have been deposited in GenBank under accession numbers JQ692877–JQ692937.

Statistical Analyses

Data were statistically analyzed by SPSS® software version 19, as previously described [7]. Chi- square and Fisher's exact tests were used to determine the significance of difference observed between two different viruses and two different groups of patients. *P* values <0.05 were considered statistically significant.

Results

Among the 435 children suffering from gastroenteritis, 173 (39.8%) had a positive stool sample for at least one of the two enteric viruses studied. RV and NoV were detected in a total of 120 and 60 stools, respectively. Dual infection with both RV and NoV was found in 7 patients. Among these NoV cases, 10 (16.7%) were genogroup I and 50 (83.3%) were genogroup II. The characterization of RV and NoV genotypes was reported in Hassine-Zaafrane et al. 2011 and Hassine-Zaafrane et al. 2013, respectively. Data on the age, gender, monthly distribution of RV and NoV gastroenteritis and distribution of RV and NoV infections in hospitalized and in non- hospitalized children were previously analyzed [6, 7].

Clinical symptoms and severity of viral diarrhea

With regard, to clinical features such as fever (56.3% incidence), vomiting (64.1%), abdominal pain (8.1%) and bloody diarrhea (2.5%), there were no significant differences between infected and non-infected children or between RV and NoV positive patient results ($P > 0.05$). Comparison of the clinical results showed no significant differences among the 7 patients with mixed infections and those with mono-infection ($P > 0.05$).

Compared with NoV, patients infected with RV gastroenteritis had a significantly higher percentage of vomiting (75.2 vs. 47.2%, $P = 0.005$), and cough (12.4 vs. 0%, $P = 0.019$). In contrast, the duration of diarrhea was significantly higher in children infected with NoV than in those infected with RV (9.87 ± 6.64 vs. 7.30 ± 3.82 days, $P = 0.010$).

Patients were grouped into the seven following age ranges: < 3 months (n = 30), 3-5 months' age group (n = 66), 6-11 months age group (n = 104), 12-23 months age group (n = 105), 24-35 months age group (n = 40), 36-59 months age group (n = 61) and ≥ 60 months age group (n = 23). The age data are missing for 6 non-hospitalized children.

Comparison of clinical signs according to age groups showed that vomiting and fever were more common in 6-11 months' age group, while abdominal pain developed more frequently in 24-35 months' age group ($P < 0.001$). Extra-intestinal symptoms, such as anemia, respiratory problems, and coughs were not significantly different between the different age groups.

Among children hospitalized for gastroenteritis (n = 238), the correlation between the dehydration stage (stage 1: <5%: mild dehydration, stage 2: 5-10%: moderate dehydration, stage 3: > 10 %: severe dehydration, vital risk) and age of children was studied (Figure 1). Statistical analysis showed a significant difference ($P = 0.035$), indeed age was inversely correlated with the stage of dehydration. The youngest children (age <3 months) were the most dehydrated and stage 3 of dehydration has been detected only in children under 24 months.

Severity criteria, such as duration of diarrhea, number of stools, bouts of vomiting, range of body temperature, degree of dehydration, capillary refill time, and presence of skin blotches, were determined for all hospitalized children. Correlations between the severity of the disease and the presence of each virus in stool samples from hospitalized children are reported in Table 1. There is no significant difference in the severity of the gastroenteritis due to both viruses ($P > 0.05$). Also these signs of severity did not differ significantly between single infection and co- infections. There were no significant differences in symptoms among the two viral infection categories ($P > 0.05$). For RV- and NoV-positive patients, the results with respect to duration of the diarrhea and numbers of stools and bouts of vomiting per 24 hours were not significantly different. The degree of dehydration of children infected by RV was moderate in 31.7% and severe in 8.3% of cases, whereas for those infected by NoV, the degree of dehydration was moderate in 39.1% and severe in 0% of cases. With regard to the severity of the symptoms, including the degree of dehydration and state of shock of the patients as estimated by CRT results and the presence or absence of blotches, there were no significant differences between results for RV and NoV infections or among co-infections ($P > 0.05$).

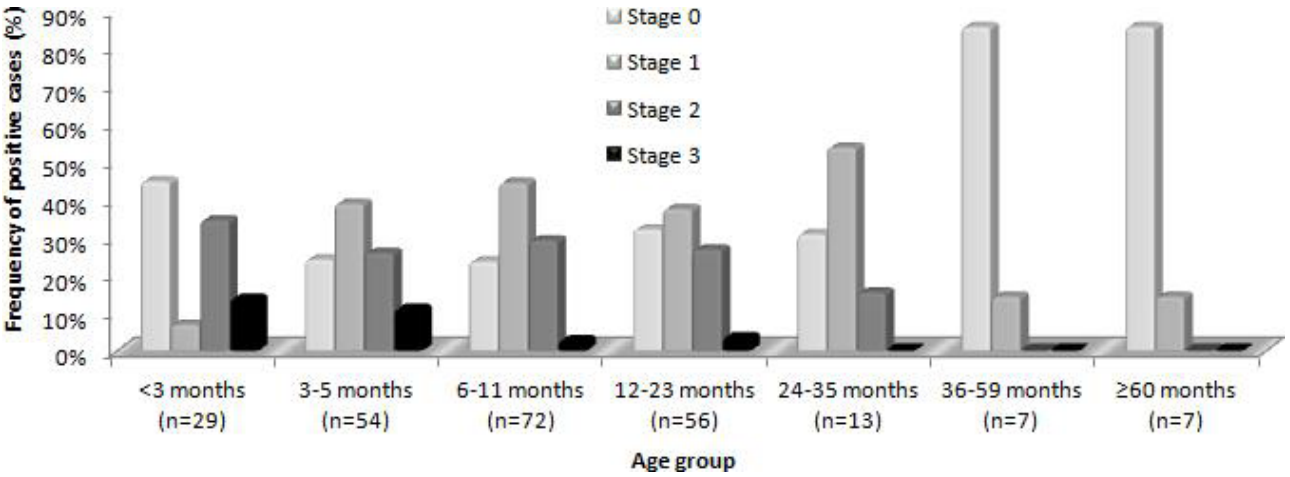

Figure 1: Correlation between degree of dehydration and age of hospitalized children (n = 238). Stage 0: no dehydration; Stage 1 (score 1-3): mild dehydration (<5%); Stage 2 (score 4-8) moderate dehydration (5-10%); Stage 3 (score ≥ 9): severe dehydration (> 10%).

Disease manifestation	*No. (%) of infections*			
	RV (n=60)	*NoV (n=23)*	*Co-infections (n=3)*	*P* [a]
Duration of diarrhea (days)				**0.324**
1-3	6 (10)	1 (4.3)	1 (33.3)	
4-6	21 (35)	7 (30.4)	2 (66.7)	
>6	33 (55)	15 (65.2)	0 (0)	
No. of bouts of diarrhea (stools/24h)				**0.99**
1-3	13 (21.7)	6 (26)	1 (33.3)	
4-5	22 (36.7)	8 (34.8)	1 (33.3)	
≥6	25 (41.7)	9 (39.1)	1 (33.3)	
No. of bouts of vomiting (Episodes/24h)				**0.498**
0	9 (15)	5 (21.7)	0 (0)	
1	1 (1.7)	0 (0)	0 (0)	
2-4	45 (75)	17 (73.9)	3 (100)	
≥5	5 (8.3)	1 (4.3)	0 (0)	
Fever (°C)				**0.258**
<37.5	30 (50)	9 (39.1)	0 (0)	
37.5-38.5	17 (28.3)	9 (39.1)	2 (66.7)	
38.6-39	5 (8.3)	5 (21.7)	1 (33.3)	
>39	8 (13.3)	0 (0)	0 (0)	
Dehydration (%)				**0.19**
0	16 (26.7)	4 (17.4)	1 (33.3)	
< 5	20 (33.3)	10 (43.5)	0 (0)	
5-10	19 (31.7)	9 (39.1)	2 (66.7)	
>10	5 (8.3)	0 (0)	0 (0)	
CRT [b](duration in s)				**0.804**
<3	54 (90)	23 (100)	3 (100)	
3	2 (3.3)	0 (0)	0 (0)	
4	3 (5)	0 (0)	0 (0)	
5	1 (1.7)	0 (0)	0 (0)	
Blotches				**0.121**
0	54 (90)	23 (100)	3 (100)	
1	6 (10)	0 (0)	0 (0)	

[a], χ^2 Test and Fisher exact test; $P \leq 0.05$ considered significant difference between the two viruses; [b], CRT: capillary refill time.

Table1: Correlation between disease severity and etiological viral agent for hospitalized children

Oral, intravenous and mixed rehydration was required in 57.1%, 12.7% and 20.6% of hospitalized children infected with RV, and in 57.7%, 7.7% and 26.9% of NoV mono-infections, respectively. There was no significant difference in the frequency of these types of treatment between RV and NoV ($P = 0.202$). Also, the results representing delays of medical care were no significantly different between RV and NoV infections, with a mean period between the onset of the diarrhea and hospitalization of 3.7 and 4.7 days, respectively ($P = 0.386$).

Signs of severity were compared for the different genotypes of group A RV detected in hospitalized children. The duration of diarrhea ($P = 0.011$), the number of vomiting per day ($P = 0.003$) and the presence of skin blotches ($P < 0.001$) showed a significant difference between the different genotypes. Diarrhea lasting more than 6 days was more common in the case of RV gastroenteritis due to genotypes G3P[8], G4P[8] and G3G4P[8]. The number of vomiting was greater than or equal to 5 episodes per day in the case of infection with genotype G4P[8]. Skin blotches was significantly present in the case of infection with genotype G3P[8] and G4P[8] compared to other genotypes. Concerning the other criteria of gravity, there was no significant differences.

Discussion

Viral gastroenteritis is a common acute infectious disease in all age groups, but especially so in infants and young children. This study contributes to a better understanding of the signs and symptoms of viral gastroenteritis in Tunisian children.

Comparison of clinical signs associated with diarrhea among infected and non-infected children and those whose viral stool test was negative showed no significant difference. These results were discordant with those found in France [8], Italy [9] and India [10] where vomiting have been reported to be more common in children having a viral infection. Similarly, Zuccotti and colleagues found that the presence of severe acute gastroenteritis was more common in children with RV infection (69.2%) than in children without viral infection (41.4%) but there was no difference ($P = 0.718$) between the two groups regarding the duration of hospitalization [11]. In Bangladesh, the percentage of vomiting, diarrhea and abdominal pain in children infected with NoV was higher than in non-infected children [12]. In France, abdominal pain and bloody diarrhea have been described as significantly more common in children with no viral infection [8]. The frequency of respiratory symptoms did not differ statistically between the children infected with a virus and who are not infected. This result is consistent with that found in Finland, which shows that there is no particular association between respiratory signs in children and viral gastroenteritis [13]. However, a recent German study showed that vomiting and respiratory symptoms are more common in the case of viral gastroenteritis than in the case of bacterial gastroenteritis [14]. In fact, these authors have documented the presence of rhinitis in 41, 44, 58 and 9% of patients with RV, NoV, adenovirus and Salmonella infection, respectively. A similar distribution was demonstrated for ear infections and pharyngitis. Comparison of clinical signs according to the two viral infections showed vomiting ($P = 0.005$), anemia ($P = 0.035$) and coughing ($P = 0.019$) were significantly different between the two virus, vomiting and coughing are more common during RV infections and anemia during infections with NoV. Our results were at variance with those reported in Taiwan where vomiting and respiratory symptoms were more frequent in the case of NoV infection without a significant difference between RV and NoV infections [15]. In Tunisia, a previous study showed that respiratory symptoms were found more frequently in the group with RV gastroenteritis [16]. Another study in Chile showed that the intensity of vomiting and fever did not differ between the two types of infection [17]. Similarly, a study in Spain showed that clinical signs and severity of RV or NoV gastroenteritis are similar,

although children with NoV infection are less likely to be dehydrated ($P = 0.05$) in spite of the longer duration of diarrhea observed in these patients [18]. In China, no significant difference was found regarding clinical manifestations of gastroenteritis caused by both viruses [19] (Deng et al., 2009). In other studies vomiting has been reported as statistically most frequent symptom in children infected with RV [20, 21]. In other studies, the RV infections have been reported to cause more fever [8, 15, 22, 23], or more fever and vomiting [24, 25] than NoV and other viruses in children with gastroenteritis. As against, other studies have shown that the high frequency of vomiting was associated with NoV infections and different from other viral or bacterial infections [26, 27]. Moreover, it has been shown that NoV infections can cause severe dehydration and resulting in rare cases the patient's death [26,28].

In our study, we found no statistical difference in clinical signs between mono-infections and mixed infections. To analyze our results, these few mixed infections should be confirmed

serologically because the presence of two viruses associated in one stool does not necessarily mean a co-infection or a more severe clinical infection. This result is consistent with those reported in France [8], England [29] and Chile [17] which showed that the co-infections are not clinically more severe than the mono-infections. In Italy, increased severity was demonstrated in the case of co-infections NoV-RV, NoV-adenovirus, NoV-RV-astrovirus, while the double infection NoV-astrovirus was not more severe than astrovirus or NoV mono-infections [30].

The main complication of gastroenteritis, the most frightening, is dehydration. In our study, dehydration was present in 36.7% of RV gastroenteritis and 31.7% of NoV gastroenteritis and is therefore a serious factor in one third of patients. Comparison of clinical signs according to age groups showed that vomiting and fever ($P < 0.001$) were more common in children aged between 6 and 11 months, which is quite logical, since these children have lost their maternal antibodies and undergo the primary viral infection that is the noisiest clinically. While abdominal pains ($P <$ were statistically more common in children whose age is between 24 and 35 months. In addition, the younger children (age <3 months) are the most dehydrated ($P = 0.035$) and stage 3 of dehydration (severe) has been detected only in children under 24 months. Chouchane and colleagues also demonstrated that dehydration due to diarrhea was observed mainly in infants [31]. This can be explained by the fact that children less than 24 months are more fragile and more quickly dehydrated. These results are consistent with those reported by Iturriza-Gomara and colleagues who showed that the medians of severity scores decreased with increasing age, which probably reflects the impact of immunity does not prevent against the disease but makes it less severe [21].

Comparing the average duration of hospitalization and age of children infected by both viruses showed no significant difference ($P = 0.810$ and $P = 0.121$), whereas in the literature it has been reported that the duration of hospitalization due to RV is significantly longer than that due to NoV [15, 32].

Similarly, among hospitalized children no statistical difference in the severity of symptoms was observed between the two viral infections ($P > 0.05$) for the following clinical signs: duration of diarrhea, number of stools, bouts of vomiting, range of body temperature, degree of dehydration, capillary refill time, and presence of skin blotches. This was also noticed in the case of dual infection. These data show that infection with NoV was equally important that RV infection and can cause severe gastroenteritis. Then usually, RV diarrhea in children was considered more severe than NoV diarrhea, with higher severity scores as has been found in Europe [8, 14, 30, 32, 33], in Taiwan [25], in the United Kingdom [21], in Japan [34] and in Iraq [35]. Similarly, in Tunisia in 2007, the highest score of severity was attributed to RV gastroenteritis [16]. Thus, Turkey has shown that vomiting, dehydration and hospitalizations were significantly more frequent in patients with acute RV gastroenteritis compared with those with diarrhea of another origin [36].

However, in the same way as our results show, studies in Spain and Vietnam have shown that the severity of infections due to NoV is similar to that of infections due to RV [18, 37]. Another study in Brazil also showed that 69% of infections with NoV were detected in hospitalized children who received medical care [38]. In addition, a survey conducted in the United States [39] has established an estimate of the overall hospital morbidity NoV infections in children under 5 years, based on articles published between 1990 and 2008 in 12 developed countries and 7 countries in development. The survey showed that in all studies, NoV was involved in 12% of severe diarrhea in hospitalized children under 5 years. These data suggest that childhood infections with NoV are also severe than those due to RV and require hospitalization of the child. It is increasingly recognized that the severity of diarrhea in hospitalized children dependent on medical care received at home before admission to hospital and the time of their treatment. Indeed, the assumption is that it is also medical education. A Finnish study showed that NoVs were detected among children whose parents were neglecting medical care before admission [34]. Similarly, in our study the severity of infections RV and NoV can be explained by the lack of medical care at home or delay care (3.72 ± 3.11 days for the RV versus 4.70 ± 3.32 days for NoV, $P = 0.386$). In our study two children with diarrhea at RV died, indicating that the RV still remains the major agent of severe diarrhea in children without neglecting the severity and importance of NoV in the etiology of infantile gastroenteritis.

In conclusion, both NoV and RV are common agents in nonbacterial gastroenteritis. This study clearly establishes the importance of NoV as a cause of acute childhood gastroenteritis in Tunisia and genogroup II as the predominant type. The clinical manifestations cannot differentiate NoV from RV infection.

References

1. Parashar UD, Glass RI (2003) Viral causes of gastroenteritis. In: Desselberger U, Gray J, editors. Viral Gastroenteritis. Amsterdam: Elsevier 9-21.

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

3. Koopmans M, van Strien E, Vennema H (2003) Molecular epidemiology of human calcivirus. In: Desselberger U, Gray J, editors. Viral Gastroenteritis. Amsterdam: Elsevier 523-54.

4. Siebenga J, Duizer E, Koopmans M (2010) Norovirus Epidemiology. In Caliciviruses: Molecular and Cellular Virology. Edited by: Hansman GS, Jiang XJ, Green KY. Norfolk: Caister Academic Press 1–24.

5. Sdiri-Loulizi K, Ambert-Balay K, Gharbi-Khelifi H, Sakly N, Hassine M, et al. (2009) Molecular Epidemiology of Norovirus Gastroenteritis Investigated Using Samples Collected from Children in Tunisia during a Four- Year Period: Detection of the Norovirus Variant GGII.4 Hunter as Early as January 2003. J Clin Microbiol 47: 421-9.

6. Hassine-Zaafrane M, Sdiri-Loulizi K, Kaplon J, Ben Salem I, Pothier P, et al. (2013) Prevalence and genetic diversity of norovirus infection in Tunisian children (2007-2010). J Med Virol 85: 1100-10.

7. Hassine-Zaafrane M, Sdiri-Loulizi K, Ben Salem I, Kaplon J, Ayouni S, et al. (2011) The molecular epidemiology of circulating rotaviruses: three-year surveillance in the region of Monastir, Tunisia. BMC Infect Dis 11: 266.

8. Bon F, Fascia P, Dauvergne M, Tenenbaum D, Planson H, et al. (1999) Prevalence of group A rotavirus, human calicivirus, astrovirus, and adenovirus type 40 and 41 infections among children with acute gastroenteritis in Dijon, France. J Clin Microbiol 37: 3055-8

9. Colomba C, De Grazia S, Giammanco GM, Saporito L, Scarlata F, et al. (2006) Viral gastroenteritis in children hospitalised in Sicily, Italy. Eur J Clin Microbiol Infect Dis 25: 570-5.

10. Sowmyanarayanan TV, Ramani S, Sarkar R, Arumugam R, Warier JP, et al. (2012) Severity of rotavirus gastroenteritis in Indian children requiring hospitalization. Vaccine 30 (Suppl 1): A167-72

11. Zuccotti G, Meneghin F, Dilillo D, Romanò L, Bottone R, et al. (2010) Epidemiological and clinical features of rotavirus among children younger than 5 years of age hospitalized with acute gastroenteritis in Northern Italy. BMC Infect Dis 10: 218.

12. Dey SK, Nguyen TA, Phan TG, Nishio O, Mohammad Salim AF, et al. (2007) Molecular and epidemiological trend of norovirus associated gastroenteritis in Dhaka City, Bangladesh. J Clin Virol 40:218-23.

13. Ruuska T, Vesikari T (1990) Rotavirus disease in Finnish children: use of numerical scores for clinical severity of diarrhoeal episodes. Scand J Infect Dis 22: 259-67.

14. Wiegering V, Kaiser J, Tappe D, Weissbrich B, Morbach H, et al. (2011) Gastroenteritis in childhood: a retrospective study of 650 hospitalized pediatric patients. Int J Infect Dis 15: e401-7.

15. Wu TC, Liu HH, Chen YJ, Tang RB, Hwang BT, et al. (2008) Comparison of clinical features of childhood norovirus and rotavirus gastroenteritis in Taiwan. J Chin Med Assoc 71: 566-70.

16. Tinsa F, Brini I, Yahyaoui S, Bousenna O, Bousetta K, et al. (2009) Infectious diarrhoea in children under five years. Tunis Med 87: 599–602.

17. O'Ryan ML, Peña A, Vergara R, Díaz J, Mamani N, et al. (2010) Prospective characterization of norovirus compared with rotavirus acute diarrhea episodes in chilean children. Pediatr Infect Dis J 29: 855–859

18. Roman E, Negredo A, Dalton RM, Wilhelmi I, Sanchez-Fauquier A (2002) Molecular Detection of Human Calicivirus among Spanish Children with Acute Gastroenteritis. J Clin Microbiol 40: 3857–3859

19. Deng L, Jia LY, Qian Y, Chen DM, Zhang Y, et al. (2009) Comparative analysis on clinical manifestations for gastroenteritis caused by norovirus and rotavirus. Zhonghua Liu Xing Bing Xue Za Zhi 30: 398–401

20. Nguyen VM, Nguyen VT, Huynh PL, Dang DT, Nguyen TH, et al. (2001) The epidemiology and disease burden of rotavirus in Vietnam: sentinel surveillance at 6 hospitals. J Infect Dis 183: 1707-12

21. Iturriza Gómara M, Simpson R, Perault AM, Redpath C, Lorgelly P, et al. (2008) Structured surveillance of infantile gastroenteritis in East Anglia, UK: incidence of infection with common viral gastroenteric pathogens. Epidemiol Infect 136: 23-33

22. Olesen B, Neimann J, Bottiger B, Ethelberg S, Schiellerup P, et al. (2005) Etiology of diarrhea in young children in Denmark: a case-control study. J Clin Microbiol 43: 3636-41

23. Yang SY, Hwang KP, Wu FT, Wu HS, Hsiung CA, et al. (2010) Epidemiology and clinical peculiarities of norovirus and rotavirus infection in hospitalized young children with acute diarrhea in Taiwan, 2009. J Microbiol Immunols Infect 43: 506-14.

24. Coffin SE, Elser J, Marchant C, Sawyer M, Pollara B, et al. (2006) Impact of acute rotavirus gastroenteritis on pediatric outpatient practices in the United States. Pediatr Infect Dis J 25: 584–9

25. Chen SY, Chang YC, Lee YS, Chao HC, Tsao KC, et al. (2007) Molecular epidemiology and clinical manifestations of viral gastroenteritis in hospitalized pediatric patients in Northern Taiwan. J Clin Microbiol 45: 2054-7

26. Fretz R, Svoboda P, Schmid H, Baumgartner A (2003) Gastro-entérites aiguës causes par des norovirus: un état des lieux. Bull BA 46: 828–33

27. Lopman BA, Adak GK, Reacher MH, Brown DW (2003) Two epidemiologic patterns of norovirus outbreaks: surveillance in England and Wales, 1992-2000. Emerg Infect Dis 9: 71-7

28. CDC (Centers for Disease Control and Prevention) (2001) "Norwalk-like viruses." Public health consequences and outbreak management. MMWR recomm rep 50(RR09): 1–18

29. Simpson R, Aliyu S, Iturriza-Gomara M, Desselberger U, Gray J (2003) Infantile viral gastroenteritis: on the way to closing the diagnostic gap. J Med Virol 70: 258-62

30. Colomba C, Saporito l, Giammanco GM, De Grazia S, Ramirez S, et al. (2007) Norovirus and Gastroenteritis in Hospitalized Children, Italy. Emerg Infect Dis 13: 1389-91

31. Chouchane S, Fehri H, Chouchane C, Merchaoui Z, Seket B et al. (2005) Hypernatremic dehydration in children: retrospective study of 105 cases. Arch Pediatr 12: 1697-702

32. Lorrot M, Bon F, El Hajje MJ, Aho S, Wolfer M, et al. (2011) Epidemiology and clinical features of gastroenteritis in hospitalised children: prospective survey during a 2 -year period in a Parisian hospital, France. Eur J Clin Microbiol Infect Dis 30:361-8

33. Medici MC, Martinelli M, Abelli LA, Ruggeri FM, Di Bartolo I, et al. (2006) Molecular epidemiology of norovirus infections in sporadic cases of viral gastroenteritis among children in Northern Italy. J Med Virol 78: 1486-92

34. Pang XL, Honma S, Nakata S, Vesikari T (2000) Human caliciviruses in acute gastroenteritis of young children in the community. J Infect Dis181(Suppl 2): S288–94

35. Al-Mashhadani MN, Nakagomi O, Dove W, Ahmed H, Nakagomi T, et al. (2008) Norovirus gastroenteritis among children in Iraqi Kurdistan. J Med Virol 80: 506-9

36. Karadag A, Acikgoz ZC, Avci Z, Catal F, Gocer S, et al. (2005) Childhood diarrhoea in Ankara, Turkey: epidemiological and clinical features of rotavirus-positive versus rotavirus-negative cases. Scand J Infect Dis37: 269-75

37. Nguyen TA, Yagyu F, Okame M, Phan TG, Trinh QD, et al. (2007) Diversity of viruses associated with acute gastroenteritis in children hospitalized with diarrhea in Ho Chi Minh City, Vietnam. J Med Virol 79: 582-90

38. Soares CC, Santos N, Beard RS, Albuquerque MC, Maranhao AG, et al. (2007) Norovirus detection and genotyping for children with gastroenteritis, Brazil. Emerg Infect Dis 13: 1244-6

39. Patel MM, Widdowson MA, Glass RI, Akazawa K, Vinjé J, et al. (2008) Systematic literature review of role of noroviruses in sporadic gastroenteritis. Emerg Infect Dis 14: 1224–3