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Study of Clinical Characteristics and Clinical Complications of *Norovirus gastroenteritis* in Admitted Children to the Hospital

Alireza Nateghian[1], Fereshteh Moshfegh[1*] and Zabihollah Shoja[2]

[1]Department of Pediatrics, Iran University of Medical Sciences, Tehran, Iran.
[2]Department of Virology, Pasteur Institute of Iran, Tehran, Iran.

Authors' contributions

This work was carried out in collaboration among all authors. All the authors were involved during the investigation process in all stages of this study including a primary data collection, analysis and the documentation of the collection. All authors read and approved the final manuscript.

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ABSTRACT

Aim: The current study aimed to detect *Norovirus* infections based on the use of sensitive and specific Multiplex PCR and to evaluate their clinical symptoms among children.
Methods: A cross-sectional study was performed among patients with acute gastroenteritis (99 subjects) admitted to Ali Asghar Hospital, Tehran, Iran, between 2014 and 2015. Fecal specimens were examined for *Norovirus* using Multiplex PCR. Clinical characteristics and severity of diarrhea were provided as a comparison of two groups (*norovirus*-positive and -negative children) using Chi-squared and independent Samples t-test.
Results: The prevalence of *Norovirus* infection was determined as 18%, among all samples genotyped, all genogroup was determined as GII and the GI was not identified in any of the samples. The age of *non-Norovirus* patients (16 months) was found to be significantly higher than that of *Norovirus*-positive patients (9 months) (P = 0.001). Based on the data presented herein, patients with *Norovirus* infection were diagnosed with fever in more than 50% of them followed by diarrhea (90%), vomiting (over 80%), and abnormalities (over 80%). however, no clear difference was found as comparison of both groups. The serum potassium level in non-*Norovirus* patients was

**Corresponding author: E-mail: fereshteh_moshfegh@yahoo.com;*

found to be increased as compared to *Norovirus* positive patients (0.011) and the presence of hypoxia (Po2) in patients with *Norovirus* infection suffering from diarrhea was markedly higher when comparing with non-*Norovirus* types (P = 0.014). Moreover, MCV levels in *Norovirus* positive patients were significantly lower as compared to subjects with non-*Norovirus* diarrhea (p = 0.045).
Conclusions: Our data suggested that this genotyping of *Norovirus*, due to their higher rate of attack, is likely to cause a severe viral outbreak. The most important result of this study is the change in the level of potassium in patients with heart problems.

Keywords: Norovirus; PCR; children; clinical symptoms; genotype.

1. INTRODUCTION

Acute gastroenteritis is one of the most common symptoms of gastrointestinal infections which are most commonly seen in children younger than 5 years of age. Previous studies have shown that annual mortality from acute gastroenteritis has decreased from 4.6 million in 1982 [1] to 3.3 million in 1992 [2] and eventually it has dropped to 2.5 million in 2000 [3]. Despite the decrease in mortality, the prevalence of acute gastroenteritis in children less than 5 years old has not decreased in recent years. Bacteria, parasites and viruses can cause acute gastroenteritis in children, but viruses are one of the most important agents that have been isolated from children with acute gastroenteritis [2,3]. Although, rotavirus is an important causes of acute gastroenteritis in children less than 5 years before the introduction of rotavirus vaccine. However, *Norovirus* account for 70% to 90% of the acute viral gastroenteritis in societies, where rotavirus vaccine has been applied. According to CDC reports, human *Norovirus* accounts for more than 21 million cases per year, accounting for more than 90% of all non-bacterial gastroenteritis per year, as well as acute foodborne gastroenteritis [4].

In general, *Norovirus* is responsible for 12% of hospitalization of children under the age of 5 years with acute gastroenteritis. *Norovirus* infection is associated with a range of clinical symptoms [5,6]. The prepatent period is generally between 24 and 48 hours. The onset of symptoms occurs suddenly and most patients have both signs of diarrhea and vomiting, although one of these symptoms can be present alone [7]. In addition, the most frequently reported adverse events were generalized myalgia, restlessness, and headache. Fever (38.3 to 38.9°C) occurs in about half of the cases. Although patients usually experience discomfort, the severity of the illness is usually not very high, where the disease generally lasts for 48 to 72 hours.

According to a study by Patel et al. 2009, PCR-RT was reported as a high-precision standard for detecting *Norovirus* infection. Real Time PCR is employed to detect *Norovirus* in the epidemiological studies and various EIA methods have been proposed [8]. The more severe manifestations of the disease have been reported in children less than 1 year old, the elderly and those with underlying disorders that are infected in hospital outbreaks [9-11]. It is worth noting that the risk of dyspepsia, constipation and reflux may be increased in patients with acute gastroenteritis [12] .However, further studies are needed on the post-infectious complications.

Although very few studies have been conducted to determine *Norovirus* infection in Iranian patients with gastroenteritis, the studies reported a prevalence of 4 to 20%, which is lower than many countries, especially neighboring countries [13]. Given the limited studies on *Norovirus* infection, especially in pediatric patients, accurate understanding of the clinical course and complications of *Norovirus* in pediatric patients is essential for therapeutic planning.

The present study was aimed to examine the clinical course and the complications of *Norovirus*-induced gastrointestinal infections in children admitted to Ali Asghar Children's Hospital, Tehran, Iran.

2. MATERIALS AND METHODS

2.1 Data Collection

This cross-sectional study was conducted among patients (99 subjects) admitted to Ali Asghar Hospital with acute gastroenteritis between 2014 and 2015. The sample size was calculated according to the following formula

$$n = \frac{(z_{1-\frac{\alpha}{2}})^2 \times \sigma^2}{d^2}$$

To evaluate the presence of *Norovirus*, fecal specimens were collected according to the standard instructions in closed containers. Then, under cold chain condition, the samples were transferred to the virology lab at the Pasteur Institute of Iran and immediately stored at -20°C [14].

Exclusion criteria: It included bandemia, toxic manifestation, the presence of more than 5 white or red blood cells in the stool sample and bloody diarrhea.

Inclusion criteria: 1) Having two times vomiting episodes per day, 2) Two-three times diarrhea per day, 3) Having common symptoms in a 24-hour period, which symptoms have not happened after taking laxative. The disease Data, disappearance symptom, the presence of vomiting or diarrhea and complications were recorded in the questionnaire. Furthermore, the data were collected from the results of the questionnaire and laboratory tests. Finally, they were analyzed using SPSS software version 20.

Samples were tested for viral pathogenesis using in-house *Norovirus* ELISA in a laboratory followed by RT-PCR and electron microscopy. Then, patients with confirmed neurovirus infection were enrolled in the study [15,16].

Patients were finally assigned to the two groups of subjects: 1. Children suffering from *norovirus*-induced viral diarrhea. 2. Children suffering from gastroenteritis without *Norovirus* infection.

For these purposes, 99 stool samples were collected from children under five years of age. After extraction of RNA, neurovirus detection was performed using real time RT-PCR, specific primers and probe that target the binding domain between ORF1 and ORF2 in the *Norovirus* genome. It should be noted that all stages of the test were performed according to Superscript III Platinum One-step RT RT-PCR Kit (Thermo Fisher Scientific).

2.2 Statistical Analysis

Data were assessed in SPSS 20. To analyze parametric variables, independent Samples t-test was applied, while binary and nominal variables were evaluated by using chi-squared test. P-values below 0.05 were considered significant when comparing two groups.

3. RESULTS

As shown in Table 1, there was no significant difference between the two groups in terms of gender (P = 0.6), According to serum potasium, the rate of infection in children with *Norovirus* gastroenteritis was significantly lower than that of children without *Norovirus* (P = 0.11) (Fig. 1).

Furthermore, MCV levels were significantly lower in children with *Norovirus* gastroenteritis than in children with *norovirus*-negative diarrhea (P = 0.014; P = 0.045). Based on the results presented herein, the *Norovirus* positive patients was not affected by all factors (other lab data and clinical manifestations that are explained in the table) except the three factors mentioned (Table 2).

The Findings demonstrated that mean corpuscular volume (MCV) and serum potasium were affected by *Norovirus* infection. On the other hand, there was no any relationship between *Norovirus* and hospitalizations during the months (P = 0.635).

Table 1. Frequency of patients in the two groups studied based on sex

Frequency group	Sex		Age average
	Male	Female	
Positive *Norovirus* (18 cases)	%66/7(12 cases)	%33/3(6 cases)	9/36±3/25
Negative *Norovirus* (81 cases)	%60/5(49 cases)	%39/5(32 cases)	15/49±13/97
P-value	0/6		0/001

Table 2. Comparison of the mean of Po2 and MCV in two groups

Factors groups	Po2	MCV
Positive *Norovirus*	49/80± 17/95	74/82± 40/69
Negative *Norovirus*	71/35± 36/87	77/55± 5/40
P-value	0/014	0/045

Table 3. Frequency of complications in patients with gastrointestinal infections in two groups

Group		Positive *Norovirus*	Negative *Norovirus*	P-value
Fever	Yes	14	72	0/2
	No	4	9	
Diarrhea	Yes	18	74	0/3
	No	0	7	
Vomiting	Yes	13	54	0/6
	No	5	27	
Respiratory symptoms	Yes	6	27	1
	No	12	54	
Decrease appetite	Yes	13	73	0/057
	No	73	8	
The beginning of the disease symptoms	Gradual	13	54	
	Suddenly	5	27	
Previous antibiotic consumption	Yes	6	33	0/53
	No	12	47	
	No response	0	1	
Fidgetiness	Yes	12	60	0/5
	No	6	21	
Headache	Yes	1	7	
	No	2	25	0/5
	No response	15	49	
Cramp and abdominal pain	Yes	11	47	
	No	7	30	
	No response	0	4	0/9
History of contact with the patient	Yes	7	18	0/1
	No	11	63	
Weight Loss	Yes	4	8	
	No	14	72	0/2
	No response	0	1	
Weight Loss	Yes	8	23	
	No	10	57	0/1
	No response	0	1	
Underlying disease	Yes	6	16	
	No	11	65	0/2
	No response	1	0	
Food allergy	Yes	3	12	0/3
	No	15	67	
	No response	0	2	
Diagnosis of food allergy	Test	1	3	0/2
	Clinical	2	8	
	No response	0	1	
Generalised miallergic	Yes	1	13	1/000
	No	2	22	
	No response	15	46	

Ten subjects (55/5%) with *Norovirus* infection exhibited low-grade febrile and 4 subjects (22/2%) high-suffered from high-grade febrile. Nevertheless, no relation was found between *Norovirus* and fever (P = 0.635).

It is noteworthy, diarrhea were reported in 44.4% (8 cases) of *Norovirus* positive patients (5 to 10 times), while 41.9% (34 cases) of *Norovirus* negative patients reported diarrhea 5-10 times. The volume of diarrhea (mild, moderate, severe) was also reported to be moderate in both groups

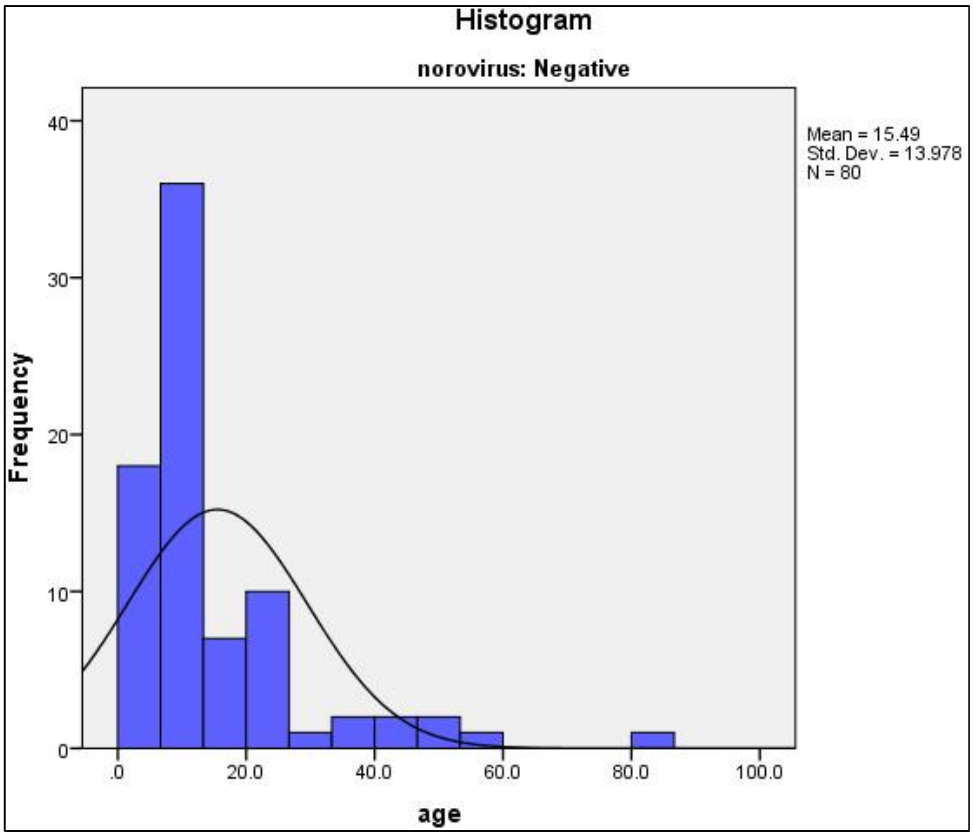

Fig. 1. Sexual frequency distribution of children without *Norovirus* infection

Table 4. Comparison of antibiotic use in patients admitted to hospital

Taking antibiotics group	Yes	No
Positive *Norovirus*	8	10
Negative *Norovirus*	47	33
P-value	0/2	

(55.6% [10 cases] of *Norovirus* positive patients and 41.9% [31 cases] of *Norovirus* negative patients. Furthermore, the type of diarrhoea in the majority of patients in both groups was more loose/watery stools (100% [18 subjects] of the *Norovirus* positive group and 90/1% [73 cases] of *Norovirus* negative patients). Most *Norovirus* positive patients recovered 2-4 days after the start of vomiting (38/9%); however, vomiting symptoms in patients who suffered from gastroenteritis without *Norovirus* infection lasted less than 2 days (29/99 people). Fever, vomiting and diarrhea were the most prevalent signs of the disease in both groups (27.8% of the patients with *Norovirus* infection [5 subjects] and 25.9% of subjects [21 subjects] with gastroenteritis without *Norovirus* infection). The present data show that there was no relationship between the presence of *Norovirus* and restlessness (P = 1.000). The frequency of complications in patients suffering from gastrointestinal infections is summarized in Table 3.

Table 5. Occurrence of complications in patients admitted to hospital

Taking antibiotics group	Yes	No
Positive *Norovirus*	1	17
Negative *Norovirus*	5	74
P-value	1/000	

As shown in Table 4, no significant relationship was found between *Norovirus* infection and previous antibiotic use (P = 0.53). Based on data presented herein, cefixime was the most prescribed antibiotic (38.5%, 15 cases), followed by amoxicillin (9 patients, 23.1%). It is noteworthy that presence of complications is indicated in Table 4.

Table 6. General condition of patients at the time of discharge in two groups

Condition Group	Complete recovery without antibiotics	Complete recovery with antibiotics	Relative recovery with antibiotics	Relative recovery without antibiotics
Positive *Norovirus*	3 cases (%16/7)	2 cases (%11/1)	6 cases (%33/3)	7 cases (%38/9)
Negative *Norovirus*	19 cases (%23/5)	12 cases (%14/8)	30 cases (%37)	19 cases (%23/5)
Total	22cases (%22/2)	14 cases (%14/1)	36 cases (%36/4)	26 cases (%26/3)

Overall, mild dehydration was detected in 8 of 18 *Norovirus*-positive subjects (44/4%), The mild dehydration was also detected in 50.6% (41/81) of *Norovirus*-negative subjects. Moderate dehydration was seen in 50% (9/18) of patients with *Norovirus* gastroenteritis. However, severe hydration was observed in only one person.

Of the 18 individuals that were positive for *norovirus*, 5 (5/18 cases: 27/7%) showed had heart disease. However, among the 81 samples from other group that were negative for *norovirus*, FTT (failure to thrive, below the 3% of growth chart) (30%) (25/81) was the most frequently detected underlying disease. Among the 18 samples from subjects in our study that were positive for *Norovirus*, the respiratory symptoms identified in 7 patients including dry cough (4 cases) and wheezing (3 cases).

Among all enrolled children that were negative for *Norovirus*, 19 had respiratory symptoms including wheezing (7 subjects), dry cough (9 subjects), and productive cough (8 subjects). *Norovirus*-induced icter was not seen in any of the patients. There were no significant differences according to hospital admission between any of the complications and *Norovirus* infection (P =1.000).

Among all participated children that were negative for *Norovirus*, the most common adverse events were secondary bacterial infections (2 cases) followed by otitis media (1 patient), sinusitis (1 patient) and cardiac arrest (1 case), while there was a rare case of complication in the *Norovirus*-positive patients, which included one-sided pleural effusion.

Among all treated children with *Norovirus* infection (18 cases), 3 (16.6%) showed complete recovery without antibiotic use, 2 (11.1%) recovered completely with antibiotic therapy, followed by relative improvement with antibiotic (in 33.3%, 6 cases); in the remaining 38.8% of recovered patients, 7 cases exhibited relative treatment without antibiotic (Table 5).

Among all treated children without *Norovirus* infection (80 cases), complete and relative recovery with antibiotic at the time of discharge were (12/80, 14.8%) and (30/80, 37%), respectively and also, complete and relative recovery without antibiotic at the time of discharge were (19/80, 23.45%) and (19/80, 23.45%), respectively (Table 6).

4. DISCUSSION

The *Norovirus* infection in the world has been shown to have a heavy economic burden [1-3], therefore, the importance of *Norovirus* has been highlighted in both developed and developing societies. Therefore, identification of these viruses as an important cause of gastroenteritis in all age groups, especially children, is of great importance. Nevertheless, the present study was designed to detect *Norovirus* infections based on sensitive and specific methods, and to evaluate their clinical symptoms among children. In the present study, the prevalence of genomic *Norovirus* infection was higher (18%) than previous studies reported in Iran [13], although among all samples genotyped, all genotype was determined as GII and the GI genotype has not been identified in any of the samples. The present study reported a higher prevalence compared to developing countries; with high mortality rates. Also, the GII gene group genogroup was the most frequently detected type which is in line with previous investigations [17,18].

Based on the data presented herein, the prevalence of *Norovirus* was higher than previous studies in Iran (19), which seems to suggest that using the real-time RT-CPR method isapplied this method as a very sensitive method,

it is likely that some positive samples were not detected in past investigations and therefore reported a lower prevalence. Few studies have reported *Norovirus* infections in Iran as a group of viruses, which reported a prevalence of 4% to 20% [13]. There was no correlation between the occurrence of *Norovirus*-induced diarrhea and the month of admission (P = 0.635). The age of non-*Norovirus* patients (16 months) was significantly higher than that of *Norovirus*-positive patients (9 months), (P = 0.001). The results of a domestic study that was conducted in two educational hospitals in the past decade are partly similar to the current study, where *Norovirus* has been found in 11.3% of patients suffering from acute diarrhea with an average age of 4 ± 2.8 years. In comparison, the highest frequency was observed in December [19]. Other studies have indicated that *Norovirus*es account for 12% of acute gastroenteritis in children younger than 5 years old, while 18 cases of our recorded diarrhea was associated with this virus [5,6]. A study in Zambia has identified *Norovirus* in 52/454 (11.5%) tested cases, while *Norovirus* cases (18 cases) were more common among 99 patients with viral diarrhea compared with aforementioned study.

Based on the data presented in an integrated virological and epidemiological study of *Norovirus* outbreaks from 13 European countries, it has been shown that the higher prevalence rate of this virus has also been reported more often in countries with higher population density and higher rates of diarrhea and vomiting [20]. Like the study of Zambia, in the current study, fever, diarrhea and vomiting were the most common complications in *Norovirus*-associated diseases. Nevertheless, there was no clear difference with *Norovirus* negative subjects in this regard [21]. Previous use of antibiotics and sex between two types of *Norovirus* infections and non- *Norovirus* infections did not show a significant difference in the present study. As other studies indicated, laboratory tests were generally normal, which is more or less in agreement with our findings. The serum potassium level in non- *Norovirus* patients was higher than *Norovirus* positive patients (0.011). MCV levels in *Norovirus* positive patients were significantly lower as compared to children with non- *Norovirus* diarrhea (p=0.045). However, no significant difference was found between the two groups in other laboratory tests. In other studies, the level of white blood cell (WBC) has not changed or increased slightly and despite the occurrence of dehydration, blood urea nitrogen (BUN) and serum creatinine concentrations, are usually unchanged.

A study by Lopman, et al. 2005 was conducted in the Netherlands in a university hospital among patients with underlying disorders (80 patients and 60 nurses), where GII was the most frequently detected type. On the other hand, *Norovirus* infection in patients with diseases such as cardiovascular disease, kidney transplantation, and immunodeficiency has led to a reduction in serum potassium, an increase in C - reactive protein (CRP), and an increase in creatine phosphokinase (CPK) level. They also reported that *Norovirus*es prolonged diarrhea in patients with a higher age (In the present study, GII genotype was the most frequently detected typegenotype. On the other hand, among all enrolled *Norovirus*- positive patients with diarrhea symptoms, congenital cardiovascular diseases such as small ventricular septal defect (VSD), patent ductus arteriosus (PDA), and atrial septal defect (ASD) were the most frequently detected disease. Among these groups, serum potassium levels were also lower compared to other *Norovirus*-positive patients without underling disease and other viral infections. Therefore, it can be concluded that this genotype, due to its higher rate of attack, causes severe sever outbreaks, leading to hospitalization.

Regarding the lower serum potassium levels in these patients, especially in cardiac patients, monitoring patients with heart disease referred to hospitals with diarrhea is very important for the level of potassium and other issues (electrolytes, type of virus, etc.) and requires very fast and accurate monitoring in these patients; therefore, Multiplex PCR is required for rapid detection of *Norovirus*es and accurate monitoring.

Since our study was not a cohort study and patients were randomly enrolled in the study and we did not have any backgrounds for heart disease, we can design a study in which serum potassium levels be monitored from the first day to the elimination of congenital heart defect in children and garlic and to evaluate gastroenteritis trend. Accordingly, the results will be evaluated with the control group.

It has been shown that dyspepsia risk, constipation and reflux may be increased in patients with acute gastroenteritis during neurovascular outbreaks [12], but further studies are needed on postinfectious types. The range of

clinical symptoms of *Norovirus* infection in patients suffering from diarrhea was very diverse in the current study like other studies [5,6]. Fever, vomiting, diarrhea were the most common symptom in both groups. *Norovirus* infection was not associated with fever and generalized myalgia (P = 0.635; P = 1.000). Reductions in appetite were mostly seen in *Norovirus* negative patients (P = 0.057), but there were no significant differences between the two groups. Other studies have shown that the onset of symptoms is suddenly occurred and most patients experienced both symptoms of diarrhea and vomiting alone or in combination [7]. In both types of diarrhea, the highest frequency of diarrhea was 5 to 10 times (moderate), where diarrhea was watery. Moderate dehydration was seen in 50% of *Norovirus* infections.

Among all *Norovirus* negative children FTT (30%) (25/81) was the most frequently detected underlying disease, 33.3% of the *Norovirus* positive children showed heart disease as underling illness that were similar to other sources [15,17], among all enrolled children with *Norovirus* infections, heart disease (33.3%)(6/18) was the most common underlying disease that was consist with other investigations (10, 11). According to available evidence, *Norovirus* infection was more common in children with underlying disorders, such as heart disease, kidney transplantation and immunosuppressive drugs, which should be hospitalized and monitored continuously [11]. A study evaluated outcome of *Norovirus* in transplant recipients, in which patients with *Norovirus* infection exhibited symptoms of prolonged infection. *Norovirus* can also cause more severe and prolonged gastrointestinal disease among transplant recipients with chronic and relapsing diarrhea [22].

It has been previously indicated that *Norovirus* infections in patients with cardiovascular disease, immunosuppression and kidney transplantation could be associated with severe consequences of reduced potassium levels, elevated levels of creatine phosphokinase and C-reactive protein. On the other hand, the duration of diarrhea can be increased in the elderly [23]. Therefore, strict preventional measures such as proper hand washing, lack of contact with patients suffering from acute gastroenteritis and avoidance for crowded environments can be applied for minimizing the risk of nosocomial outbreaks. In the current study, the presence of complications did not play a significant role in the admission of *Norovirus* positive patients (P = 1.000), but other studies revealed that infection in hospitalized patients may lead to more severe forms of disease than those in the community [10].

The study has shown that approximately 70% of children with *Norovirus* infections were in contact with other individuals. Therefore, consistent with previous studies, neuroviral infections are highly contagious. The highest rate of *Norovirus* infection has been detected in the 6-8 month old group with an average of 70% in cold months (autumn and winter), [13]. In the present study, due to the fact that the distribution of collected samples is not suitable for one year, seasonal distributions throughout the year are not very judgmental, although the seasonal and age pattern of neurovirus infection in Iran seems to be similar to reports from other parts of the world [17].

Norovirus- induced gastroenteritis is generally mild and self-limiting, although it also has disability and dehydration during the course of the disease (24 to 48 hours). Based on studies, clinical manifestations of *Norovirus* infections in all age groups has been included fever (37 to 45%), diarrhea (66-81%), vomiting (65-69%), abdominal pain (30-68%), Headache (22% to 81%), muscle aches (26 to 58%), and anorexia (90%), [24]. These findings appear to be in line with clinical manifestations of *Norovirus* infection in previous studies. It is also interesting to note that breastfeeding analysis in children with known viruses showed that more than 72/2% (13/18) of children fed breast milk, which can be concluded from the reports that maternal antibodies against *Norovirus* are not sufficiently preactive; moreover, it is likely to be very low due to the variety of antigens. Another possibility is that mothers may not have been infected with *Norovirus* in the recent years [25].

Children who are admitted to the hospital due to acute gastroenteritis or diarrhea may be exposed to antibiotics based on bacterial or viral infections or on the basis of clinical examinations in the first stage and bacterial culture tests. In this study, the analysis of the use of antibiotics at the time of admission in children with *Norovirus* infection revealed that less than 7% of children had antibiotic use. This suggests that clinical experts, along with tests, have been successful in differentiating between *Norovirus* gastrointestinal illness and bacterial gastroenteritis. The results showed that almost 18% of the acute viral diarrhea in children was caused by *norovirus*es,

and it occurred more often in the cold season. The diagnosis of *Norovirus* gastroenteritis does not sufficiently address the clinical symptoms, because the clinical manifestations of the infection are similar to other viral diarrhea. By using new methods such as PCR-RT, the chance of detecting *Norovirus* could be increased. Understanding the clinical course of the *Norovirus* infection is essential in preventing the transmission of this virus to other people in the community, especially those with underlying illnesses.

5. CONCLUSION

According to the findings, the present study demonstrated that the GII was considered as a common genetic type, where was the main cause of acute *Norovirus* gastroenteritis in children less than 5 years old. Therefore, identification of *Norovirus* genotypes is of great importance because genetic analysis can provide useful information about the recombination as well as their evolution status, which may help in the development of epidemiological studies and even vaccine design in the future.

CONSENT

As per international standard, written consent of parents of patients has been collected and preserved by the author(s).

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards, and was approved by Iran University of Medical Sciences Institutional Review Board (Protocol number 2016/2758, April 2016.4.23).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Snyder JD, Merson MH. The magnitude of the global problem of acute diarrhoeal disease: A review of active surveillance data. Bull World Health Organ. 1982;60 (4):605-13.
2. Bern C, Martines J, de Z, I, Glass RI. The magnitude of the global problem of diarrhoeal disease: A ten-year update. Bull World Health Organ. 1992;70(6):705-14.
3. Kosek M, Bern C, Guerrant RL. The global burden of diarrhoeal disease, as estimated from studies published between 1992 and 2000. Bull World Health Organ. 2003;81 (3):197-204.
4. Dicaprio E, Ma Y, Hughes J, Li J. Epidemiology, prevention, and control of the number one foodborne illness: Human *norovirus*. Infect Dis Clin North Am. 2013; 27(3):651-74.
5. Dolin R, Treanor JJ, Madore HP. Novel agents of viral enteritis in humans. J Infect Dis. 1987;155:365.
6. Estes MK, Prasad BV, Atmar RL. *Norovirus*es everywhere: Has something changed? Curr Opin Infect Dis. 2006; 19:467.
7. Division of viral diseases, National Center for immunization and respiratory diseases, centers for disease control and prevention. updated *Norovirus* outbreak management and disease prevention guidelines. MMWR Recomm Rep. 2011;60:1.
8. Patel Manish M, Halla Aron J, Jan Parashar V, Umesh D. *Norovirus*es: A comprehensive review. J Clin Virol 2009; 44:1–8.
9. Goller JL, Dimitriadis A, Tan A, et al. Long-term features of *Norovirus* gastroenteritis in the elderly. J Hosp Infect. 2004;58:286.
10. Lopman BA, Reacher MH, Vipond IB, et al. Clinical manifestation of *Norovirus* gastroenteritis in health care settings. Clin Infect Dis. 2004;39:318.
11. Mattner F, Sohr D, Heim A, et al. Risk groups for clinical complications of *Norovirus* infections: An outbreak investigation. Clin Microbiol Infect. 2006; 12:69.
12. Porter CK, Faix DJ, Shiau D, et al. Postinfectious gastrointestinal disorders following *Norovirus* outbreaks. Clin Infect Dis. 2012;55:915.
13. Jalilian S, Samarbaf-Zadeh AR, Mozhgani SHR, Makvandi M, Parsa-nahad M, Pirmoradi R, et al. Relative frequency of *Norovirus* infection in children suffering from gastroenteritis and referred to Aboozar Hospital, Ahvaz, Iran. Jundishapur J Microbiol. 2012;5(1):355-8.

14. PHLS standard operating procedure: investigation of faecal specimens for bacterial pathogens; 2003.
Available:http://www.phls.org.uk/dir/hq/sops/bsoppdf/bsop30i3.pdf
(Accessed on: 15 January 2004)
15. Green SM, Lambden PR, Deng Y, et al. Polymerase chain reaction detection of small round-structured viruses from two related hospital outbreaks of gastroenteritis using inosine-containing primers. J Med Virol. 1995;45:197-202.
16. Vipond IB, Pelosi E, Williams J, et al. A diagnostic EIA for detection of the prevalent SRSV strain in United Kingdom outbreaks of gastroenteritis. J Med Virol. 2000;61:132-7.
17. Wollants E, De Coster S, Van Ranst M, Maes P.A decade of *Norovirus* genetic diversity in Belgium. Infect Genet Evol. 2015;30:37-44.
18. Hoa Tran TN, Trainor E, Nakagomi T, Cunliffe NA, Nakagomi O. Molecular epidemiology of *Norovirus*es associated with acute sporadic gastroenteritis in children: Global distribution of genogroups, genotypes and GII.4 variants. J Clin Virol. 2013;56(3):185-93.
19. Roomani S, Mohebbi SR, Hosseini SM, Azimzadeh P, Vahedۥ M, Jadali F, et al . Prevalence of *Norovirus* infection and determination of the dominant genogroup in children with acute gastroenteritis in Tehran, 2008-2009. Research in Medicine. 2011;35(1):68-73.
20. Kroneman A, Verhoef L, Harris J, Vennema H, Duizer E, van Duynhoven Y, et al. Analysis of integrated virological and epidemiological reports of *Norovirus* outbreaks collected within the foodborne viruses in Europe network from 1 July 2001 to 30 June 2006. J Clin Microbiol. 2008;46(9):2959-65.
21. Howard LM, Mwape I, Siwingwa M, Simuyandi M, Guffey MB, Stringer JS, Chi BH, Edwards KM, Chilengi R. *Norovirus* infections in young children in Lusaka Province, Zambia: Clinical characteristics and molecular epidemiology. BMC Infectious Diseases. 2017;23;17(1):92.
22. Avery RK, et al. Severe chronic *Norovirus* diarrheal disease in transplant recipients: Clinical features of an under-recognized syndrome. Transpl Infect Dis. 2017;19: e12674.
23. Mattner F, Sohr D, Heim A, Gastmeier P, Vennema H, Koopmans M. Risk groups for clinical complications of *Norovirus* infections: an outbreak investigation. Clin Microbiol Infect. 2006;12(1):69-74.
24. Robilotti E, Deresinski S, Pinsky BA. *Norovirus*. Clin Microbiol Rev. 2015;28(1): 134-64.
25. Bucardo F, Lindgren PE, Svensson L, Nordgren J. Low prevalence of rotavirus and high prevalence of *Norovirus* in hospital and community wastewater after introduction of rotavirus vaccine in Nicaragua. PLoS One. 2011;6(10): e25962.

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