Report of data on children with non-*typhi* Salmonella gastroenteritis in a three-year period

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SUMMARY

The purpose of this study was to evaluate the clinical and laboratory data of children with acute gastroenteritis caused by non-typhoid *Salmonella spp*. infections. Clinical (demographic data, symptoms and findings) and laboratory data (stool microscopy, rapid antigen tests, culture, multiplex polymerase chain reaction and blood test results) of children with acute gastroenteritis caused by non-typhoid *Salmonella spp.* between January 2010 and October 2012 were evaluated. Differences between the groups for categorical variables were estimated with a chi-square or Fisher exact test; for continuous variables with two independent samples a *t* test was used. P values < 0.05 were considered statistically significant.

Sixty-seven children, 39 (58.2%) males and 28 (41.8%) females aged between 1 - 16 years (mean ± SD: 4.64 ± 2.91), were diagnosed with acute bacterial gastroenteritis caused by non-typhoid *Salmonella spp*. The main serotypes are *Salmonella enteritidis* (85%) and *Salmonella typhimurium* (7.5%). The presenting symptoms were diarrhoea (95.5%), fever (61.1%), vomiting (34.3%), abdominal pain (32.8%), loss of appetite (7.4%) and malaise (7.4%). Fever and dehydration (moderate and/or severe) were detected in 11 (16.4%) patients. The mean leukocyte count was 10.930/µL [95% confidence interval (CI), SD: ±5.710/µL], neutrophil count was 7.880/µL (95% CI, SD: ±4.960/µL), CRP was 64.16 mg/L (95% CI, SD: ±76.24 mg/L), and erythrocyte sedimentation rate was 34.72 mm/hour (95% CI, SD: ±13.64 mm/h). Stool microscopy was positive for leukocytes in 18 patients (26.8%). The definitive diagnosis was made with positive stool culture (n=65) and/or PCR test (n=4). Viral antigen positivity was detected in 10 patients (14.9%), evaluated as viral co-infection and false positive results. Antibiotic therapy and hospitalization were required in 26 (38.8%) and 23 (34.3%) patients, respectively. *Salmonella* carriage was detected in one patient (1.5%). Bloody diarrhoea, leukocytes in stool with an increased erythrocyte sedimentation rate and a CRP level without overt leukocytosis may indicate *Salmonella* infection. Viral antigens may cause false positive results in fast antigen tests in cases where clinical and laboratory findings indicate bacterial aetiology. Stool culture is a reference method in diagnosis whereas some agents may be detected via molecular techniques (polymerase chain reaction) in spite of negative culture. Multiplex polymerase chain reaction may be used to detect *Salmonella spp*. and may reveal false positivity for viruses as well as the detection of other bacteria.

Keywords: child, gastroenteritis, polymerase chain reaction, *Salmonella*, stool culture.

INTRODUCTION

Salmonella species are gram negative, facultative anaerobic and motile bacilli belonging to the *Enterobacteriaceae* family. *Salmonella* may cause five different clinical situations including acute gastroenteritis, enteric fever, septicaemia, metastatic infection and chronic carrier state [1, 2]. The illness caused by *Salmonella* serotype *typhi* is called "typhoid fever" and the one caused by *Salmonella* serotype *paratyphi* A, *Salmonella* serotype *paratyphi* B (*Salmonella schottmuelleri*), *Salmonella* serotype *paratyphi* C (*Salmonella hirschfield*) is called "paratyphoid fever". Enteric fever is the general name for the diseases referred as typhoid and paraty-

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phoid fever. The main serotypes among non-typhi *Salmonella spp.* are *Salmonella enteriditis, Salmonella typhimurium*, and other non-typeable *Salmonella spp.* [1-4]. Transmission of the infection is through the fecal-oral route via contaminated water and foods. This is the reason of endemicity in underdeveloped and developing countries where the sewage systems can mix with drinking water and the infrastructure and public health services are inadequate [3,4]. The *Salmonella* infection most commonly presents itself as gastroenteritis, also called as minor salmonellosis, and usually lasts 3-7 days [5]. Temporary bacteraemia can be seen in a small number of patients (1-4%) and some of the patients need to be hospitalized due to dehydration [5]. A mild increase in C-reactive protein (CRP), the erythrocyte sedimentation rate (ESR) and leukocytosis can be seen [5].
The purpose of this study is to evaluate clinical and laboratory data of patients diagnosed as minor salmonellosis with co-infections and/or false positivity of viral agents.

PATIENTS AND METHODS

The records of children who were diagnosed as minor salmonellosis (n=67) at Yeditepe University Hospital were retrospectively investigated. Their demographic (age and gender) features, clinical complaints, signs and findings, laboratory data [stool microscopy, fast viral antigen tests, stool culture, multiplex polymerase chain reaction (mPCR) test, and other sepsis markers] and methods of treatment were evaluated. Underlying risk factors (nursing school/school, intake of suspected food/water, patient contact and domestic infection) were determined.
Enteric *Salmonella* infections were diagnosed by positive stool culture for Salmonella types and/or by the mPCR. A *Salmonella* carrier state was detected after Salmonella species had been detected in the stool for at least one year.
Patients' complaints, symptoms and physical examination findings at admission, laboratory results (complete blood count, blood biochemistry, CRP and ESR) of those treated with intravenous fluids and/or admitted due to dehydration because of high fever were evaluated. The leukocyte counts in accordance with their ages and presence of leukopenia or leukocytosis were determined. The upper ranges of CRP and ESR were accepted as 2.8 mg/L and 20 mm/h, respectively. The results of antigen tests performed with the immunochromatographic method in order to detect possible infectious agents [bacteria, virus (rotavirus, adenovirus, and norovirus) and amoeba (*Entamoeba histolytica*)] were evaluated in terms of false positives or co-infections (Certest-Spain, r-Biopharma-Germany). For the isolation of *Salmonella* from faeces, Columbia Agar with 5% Sheep Blood, Eosin methylene blue agar (EMB) as selective and differential medium, and Selenite-F Broth as enrichment medium were used. After 8, 12 and 24 hours, highly selective *Salmonella-Shigella* agar mediums were plated with different subcultures. The biochemical reactions of lactose negative colonies reproducing in EMB and SS agar were evaluated and suspected colonies of Salmonella underwent further biochemical identification (API ID32 GN., bioMérieux, France). To determine the specific nucleic acid sequences of *Salmonella* strains, an mPCR test (Diarrhea ACE, Seeplex, Korea) was performed on the stool sample (gastroenteritis agents whose specific nucleic acid sequences can be determined are as follows: rotavirus, norovirus GI, norovirus GII, adenovirus, astrovirus, *Salmonella spp., Shigella spp., Vibrio spp., Campylobacter spp.,* toxin B-producing *Clostridium difficile*, *Clostridium perfringens, Yersinia enterocolitica, Aeromonas spp., E. coli* O157:H7, Vero-cytotoxin-producing *E. coli*). Stool culture was performed on 67 patients while a mPCR test was performed on 12 patients.
The statistical evaluation of all collected data was done with SPSS v.20 software. Descriptive analyses were performed as mean and standard deviation for constant variables and frequency and percentage for categorical variables. A chi-square test or Fisher's definite probability test was performed to determine whether there was difference between the groups for categorical variables. In addition, two independent samples t-tests were performed to determine the difference in terms of constant variables. The significance value was $p<0.05$.

RESULTS

Minor salmonellosis was detected in 67 children in three years (5.2%). The rate of minor salmo-

Table 1 - Year-based differences of number of patients with minor salmonellosis.

Years	*Patients requiring stool cultures No.*	*Patients with high suspicion for enteric bacterial agents No. (%)*	*Minor salmonellosis No. (%)*	*Statistical significance (p)*
2010	505	74 (14.6)	27 (5.3)	
2011	480	65 (13.5)	27 (5.6)	> 0.05
2012	290	35 (12.0)	13 (4.5)	
Total	1275	174 (13.6)	67 (5.2)	

nellosis did not differ according to years (p>0.05) (Table 1).

Salmonella species were detected mostly during summer; 64% of patients were admitted between June and October (Figure 1). Patients' ages were between 1 and 16 years (4.64±2.91; 95% confidence interval) and 62.6% were under the age of five years. Thirty-nine of the patients were male (58.2%) and 28 were female (41.8%). Upon the evaluation of etiological risk factors, it was determined that nine patients (13.5%) had a history of suspicious food or water intake, six patients (8.9%) were attending to day-care centers or schools, and five cases were domestic infections. Forty-seven patients (70.1%) had no risk factors. No patient was immunocompromised.

The most common complaints were diarrhoea (95.5%), fever (61.1%), vomiting (34.3%), abdominal pain (32.8%), fatigue (5.9%) and loss of appetite (7.4%), and seven patients (10.4%) had bloody diarrhoea. Thirty patients (44.7%) had a temperature ≥38°C. Thirty-five patients (52.2%) had no dehydration, 21 patients had mild and 11 patients (16.4%) had moderate or severe dehydration. Four patients (5.9%) had hepatomegaly and/or splenomegaly (Table 2). Extraintestinal manifestations (*e.g.* osteomyelitis) were absent in our patients.

The mean blood leukocyte count was 10.930/mm^3 [95% confidence interval (CI), SD: ±5.710/mm^3], neutrophil count was 7.880/mm^3 (95% CI, SD: ±4.960/ mm^3), CRP was 64.16 mg/L (95% CI, SD: ± 6.24 mg/L), and ESR was 34.72 mm/hour (95% CI, SD: ±13.64 mm/h) (Table 3). Leukocytosis was seen in eight patients (21.6%) and leukopenia in seven patients (18.9%). CRP was increased in 34 patients. 18 patients had a high ESR (81.8%) (Table 4).

Stool microscopy was positive for leukocytes in 18 patients (26.8%). The definite diagnosis was made with positive stool culture (n=65, 97%) and mPCR test (n=4, 6%). In two patients, *Salmonella* was detected both in stool mPCR and in stool culture. In 10 patients (14.9%), viral antigen positivity was detected, which led to suspicion of co-infection or a false positive result. The main serotype among our patients with non-typhi *Salmonella spp.* was *Salmonella enteriditis* (Table 5).

Twenty-three patients (34.3%) were hospitalized for treatment. The duration of hospitalization ranged between 1 and 10 days (mean: 3.3 days).

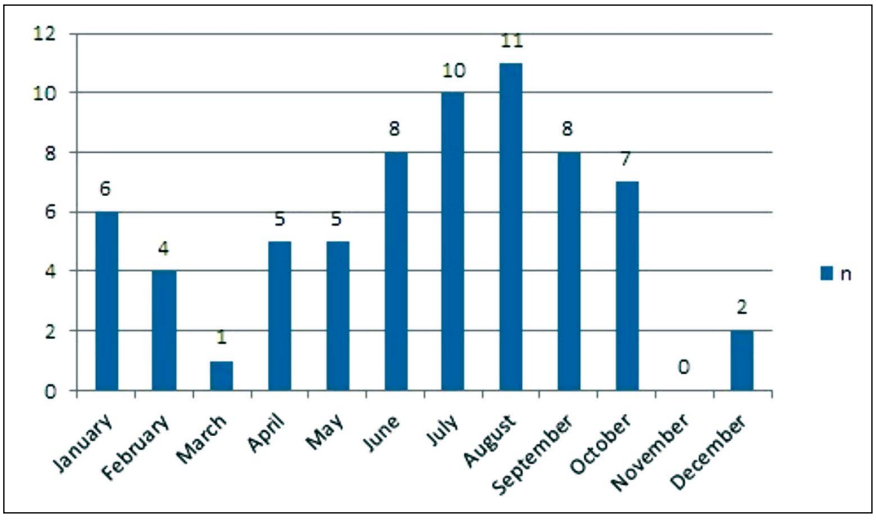

Figure 1 - Monthly distribution of patients.

Table 2 - Distribution of symptoms and findings.

Symptoms	*No.*	*%*
Diarrhoea	64	95.5
Fever	41	61.1
- Bloody diarrhoea	7	10.4
Vomiting	23	34.3
Abdominal pain	22	32.8
Fatigue	4	5.9
Loss of appetite	5	7.4
Findings		
Fever (≥ 38°C)	30	44.7
Dehydration	32	47.7
Dehydration level		
- Mild	21	65.6
- Moderate	7	21.9
- Severe	4	12.5
Hepato-splenomegaly	4	5.9

Antimicrobial therapy was administered to 26 patients (38.8%). The clinical and laboratory findings of patients treated with antibiotics are shown in Table 6. *Salmonella* carriage was detected in one patient (1.5%).

Despite the positive fast antigen tests for rotavirus and adenovirus which led to suspicion of a viral co-infection, no other agent except *Salmonella* was detected in the mPCR tests of these patients; therefore, those results were accepted as false positives.

DISCUSSION

Non-typhoidal *Salmonella* infection causes 155.000 deaths with 93.8 million diarrhoea cases per year (6). Among the gastroenteritis patients in various parts of the world, the detection of *Salmonella* is between 2.66 and 15.2% [7-9]. In our study, the rate of *Salmonella* detection was 5.2%. In other publications from our country, this ratio is between 1 and 2.5% [10, 11]. Different rates of detection are not only dependent on local epidemiological dynamics but may also relate to the analytical and diagnostic performances of microbiological methods used for diagnosis.

Minor salmonellosis is seen as endemic in our country. Nationwide studies show that the number of patients with enteric fever increases in the summer and fall, reaching a peak between July and October and decreases during winter [4]. The non-typhoidal *Salmonella* was shown to increase in Africa at the beginning of rainy seasons [12]. In the series of Gordon et al. with 176 patients, the disease was mostly seen between June and October (64%). In Portugal, where the climate is very close to our country, 76% of patients were admitted between June and October [7]. In our study, we determined that 64% of *Salmonella* cases were detected between June and October. In the study

Table 3 - Patients' laboratory results.

Laboratory results	*Min - Max*	*Mean ± Standard deviation*
Leukocyte (/mm^3)	2.100 - 23.500	10.930 ± 5.71
Neutrophil (/mm^3)	1.500 - 19.400	7.880 ± 4.96
CRP (mg/L)	0.1 - 427.6	64.16 ± 76.24
ESR (mm/h)	5 - 57	34.72 ± 13.64

CRP: C-reactive protein, ESR: erythrocyte sedimentation rate.

Table 4 - Patients' sepsis markers.

Markers	*No.*	*%*
Leukocytosis	8	21.6
Leukopenia	7	18.9
Neutrophilia	13	35.1
Neutropenia	1	2.7
CRP ≤ 2.8 mg/L	3	8.1
CRP 2.9 - 15 mg/L	7	18.9
CRP 16 - 50 mg/L	11	29.7
CRP > 50 mg/L	16	43.2
ESR (>20 mm/h)	4	18.2

CRP: C-reactive protein, ESR: erythrocyte sedimentation rate.

Table 5 - Serotyping of non-typhi *Salmonella* spp.

Serotypes of non-typhi *Salmonella spp.*	*No.*	*%*
Salmonella enteritidis	68	85
Salmonella typhimurium	6	7.5
Non-typeable *Salmonella spp.*	6	7.5

Table 6 - Demographic and clinical characteristics of patients who were treated with antibiotics.

		Antimicrobial therapy (No.)		*P*
		(+)	*(-)*	
Age	0 - 12 months	1	6	0.259
	13 months - 5 years	13	22	
	>5 years	12	13	
Fever ≥ 38°C		19	7	0.000*
Abdominal pain		6	16	0.176
Bloody diarrhea		6	1	0.012*
Dehydration levels	Mild	12	9	0.793
	Moderate	4	3	
	Severe	3	1	
Hepato-splenomegaly		4	0	0.020*
Leukocytes in stool		9	9	0.254
Hospitalization		19	4	0.000*
Leukocytosis		6	2	0.246
Neutrophilia		9	4	0.300
CRP (mg/L)	< 2.8	1	2	0.265
	2.8 - 15	3	4	
	16 – 50	5	6	
	>50	12	4	
ESR (mm/h)	>20	3	1	0.594
Elevated ALT		3	0	0.250
Elevated AST		3	1	0.626

*: P < 0.05
ALT: alanine transaminase, AST: aspartate transaminase, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate.

of Yurdakök et al, *Salmonella* gastroenteritis was mostly seen between the months of June and October [10].

The *Salmonella* infection can be seen in anyone who has had contact with infected water and food, without age discrimination. Non-typhoidal *Salmonella* infections are seen more often in children younger than five years, adults between the ages of 20 - 40 years and in those older than 70 years [13-15]. Our patients were between the ages of 1 and 16 years, 62.6% of them being under the age of five. In a study conducted in Portugal, 82% of the patients were under the age of 15 years [7]. This age discrimination may be due to increased contact with infected materials.

Non-thyphoidal *Salmonella* infections are generally related to eggs, meat and dairy products [16]. Ingestion of suspected food/water in our patients was 13.5%. In a study done in Vietnam, 8% of patients had a history of contact with other patients with gastroenteritis. In 8.9% of our patients, there was history of contact with patients having similar complaints in nursing schools/schools and 7.5% had a domestic infection [8].

The presenting symptoms of patients were diarrhoea, fever, vomiting and abdominal pain. In a study done by Crotti et al., 59.7% of patients with minor salmonellosis presented with fever, 76.1% with abdominal pain and 28.4% with vomiting [17]. In our study, 30 patients (44.7%) had a fever higher than 38°C. In the study done by Palumba et al., all patients had fever [18]. In the study done by Yurdakök et al. dehydration was detected in 14% of the patients [10]. Moderate to severe dehydration was detected in 16.4% of our patients.

In 37 patients whose other laboratory tests were evaluated, the mean leukocyte, neutrophil, CRP and ESR were 10.930/µL, 7.880/µL, 64.16 mg/L, and 34.72 mm/h respectively. Leukocytosis was seen in 8 patients (21.6%) and leukopenia in seven

patients (18.9%). In the study of Almeida et al. the leukocyte counts were between 1500 and 34300/µL (mean: 9800), neutrophil counts were between 1000 and 31500/µL (mean: 6500) and CRP levels were between 5 and 389 mg/L (mean: 75) and 14.8% of patients had leukocytosis (>15.000/µL) [7].

The stools of patients with minor salmonellosis are generally blood-free [19]. Seven of our patients (10.4%) had bloody diarrhoea. The blood in the stools of these patients was thought to be due to *Salmonella* because no other bloody diarrhoea causing agent was found. In a study from Turkey, 27% of patients had bloody diarrhoea [10]. In our study, the stool microscopy was positive for leukocytes in 18 patients (26.8%). In the study by Crotti et al. 50.7% of patients had leukocytes in the stool and 7.5% had bloody diarrhoea [17].

Non-typhoidal *Salmonella* infection usually causes self-limiting gastroenteritis in humans [20, 21]. The severity of symptoms, bloody diarrhoea, dehydration and inability to feed may cause hospitalization of these patients. In the Portuguese study, 20.2% of children were hospitalized and the duration ranged between 2 - 15 days [7]. In a study performed in Croatia, 23% of the patients were hospitalized for a mean duration of 7 days [22]. Hospitalization was required in 34.3% of our patients. The duration of hospitalization ranged between 1-10 days (mean: 3.3 days).

Bacteraemia, sepsis, septic shock, immune suppression, sickle cell anaemia, and infants (age <3 months), are indications for antibiotic therapy. Twenty-six patients were treated with antibiotics in our study; high fever (n=19), bloody diarrhoea (n=6), hepato-splenomegaly (n=4), leukocytosis (n=6), high CRP levels (>50 mg/L) and increased ESR (n=3) were the primary indications for antibiotic therapy. In the study done by Almeida et al., 11.2% of patients were treated with antibiotics for occult bacteraemia (n=7), age <3 months (n = 4), bloody diarrhoea (n=4) and immunosuppression/corticotherapy (n=4), *Salmonella* bacteraemia (n=1), septic shock (n=1) and sepsis (n=1) [7]. Chronic carrier state is defined as *Salmonella* residing in stool/urine for more than a year [23]. In patients with minor salmonellosis, chronic carrier state rates are between 0.2 and 0.6% whereas this rate goes up to 1-4% in enteric fever [3, 4]. In our study, one out of 67 patients was determined to be a carrier (1.5%). In the study done by Ban et al., chronic carrier state was determined to be 0.2% [22].

CONCLUSIONS

Minor salmonellosis may cause diarrhoea (may be bloody in some patients), fever, increased ESR and CRP values without prominent leukocytosis in our patients. *Salmonella* should be investigated in patients with diarrhoea (bloody or not), leukocytes in stool >5 Hpf, fever, increased sedimentation rate and CRP values without prominent leukocytosis. Stool culture is the gold standard in diagnosis of minor salmonellosis; also, PCR is another investigational method for these bacteria. In patients with acute gastroenteritis, increased levels of sepsis markers in blood, and leukocytes in stool increase the suspicion about minor salmonellosis. Sometimes bloody diarrhoea is seen in acute gastroenteritis along with high fever and stool culture is of great importance in the detection of bacteria. In patients with suspicion of bacterial disease because of symptoms and laboratory findings despite positive rapid viral antigen tests, the stool culture and/or PCR test results should be evaluated for definite diagnosis to exclude false positivity in rapid viral antigen tests. PCR may be useful for diagnosis of infectious diseases in patients with prior antibiotic use, or other technical difficulties for culture methods. These factors may prove the increasing important role of molecular laboratory methods in definite diagnosis of infections.

Abbreviations: (CI), Confidence interval; (CRP), C-reactive protein, (EMB), Eosin methylene blue; (ESR), erythrocyte sedimentation rate; (Hpf), High power field; (mPCR), Multiplex polymerase chain reaction; (SD), Standard deviation

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