Travelers' Diarrhea in Children at Risk

An Observational Study From a Spanish Database

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Background: Gastrointestinal symptoms are a common cause of consultation about children traveling to or coming from developing countries. The aim of this study was to identify the risk factors associated with gastrointestinal syndrome in children who travel.

Methods: A prospective observational analytical and multicenter study was performed within +Redivi, a Spanish Tropical Medicine network on imported infections, from January 2009 to December 2013. All participants aged 16 years and younger were included in the analysis. Ethical approval was obtained from all the participating centers.

Results: A total of 606 children ≤16 years of age were registered in the +Redivi database during the study period. Median age was 8.7 years (interquartile range, 4.4–12.4 years), 65.8% (399/606) were immigrants, 90% were >2 years old and 54% were male. Median travel duration, excluding immigrants, was 50 days (interquartile range, 30–150 days). Children with gastrointestinal symptoms represented 13.5% (82/606) of total consultations. A significant association was found in bivariate analysis between gastrointestinal disorder and age <2 years ($P < 0.01$) and travel duration ($P = 0.046$). Immigrants had less gastrointestinal disorders than tourists ($P < 0.05$). The most prevalent infection was protozoan in 23.4% (142/606), and *Giardia intestinalis* was the most common pathogen in 10.1% (61/606) of total children. Independent risk factors for gastrointestinal symptoms were tourist and traveler child visiting friends and relatives ($P = 0.03$), travel duration <90 days ($P = 0.008$) and bacterial cause ($P < 0.001$).

Conclusions: Traveling children who developed a gastrointestinal syndrome represented 13.5% of the total pediatric consultations in +Redivi. Independent risk factors were tourist or traveler visiting friends and relatives, travel duration <90 days and bacterial infection. *G. intestinalis* was the most common infectious agent causing a gastrointestinal disorder in the traveler children.

Key Words: gastrointestinal symptoms, traveler children, pediatrics, tropical medicine.

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International tourist arrivals worldwide reached 1138 million in 2014, a 4.7% increase over the previous year, and the fifth consecutive year of above average growth since the 2009 economic crisis, according to the latest UNWTO World Tourism Barometer.[1]

Estimates of the number of children traveling abroad are limited, and although tourism remains the most frequent reason for traveling, a substantial increase in children accompanying their parents or familiar members on trips for visiting friends or relatives (VFRs) has been reported lastly.[2–4] Also, the risk is lower for tourist children than that for pediatric VFRs travelers, and it might be related to the length of the trip,[5] to the exposition to >1 pathogen, to have closer contact to local population and to the evidence that VFRs travelers take less frequently pre-travel advice.[6–8]

Diarrhea related to traveling is sometimes associated with other symptoms such as fever being part of a systemic clinical picture, and most of the episodes are self-limiting and dehydration can usually be controlled by oral rehydration therapy. However, severe episodes can lead to a higher likelihood of progressing to complications or death.

Spanish collaboration +Redivi is a network of specialized and nonspecialized centers on tropical medicine and imported infections, which attend immigrants and travelers (including VFRs, expatriates and missionaries among others).

The decision for launching a study about gastrointestinal (GI) symptoms and traveler children was the scarcity of published articles related to this issue. When searching through PubMed database, using ("diarrhea"[All Fields] OR "diarrhea"[MeSH Terms] OR "diarrhea"[All Fields]) AND traveler [All Fields] AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields]), a total of 23 articles were found matching all the possible combinations. Otherwise, when searching for diarrhea in adult travelers, there is a huge diversity of articles talking about diagnosis, treatment and vaccines.

The aim of this study was to describe the demographic and epidemiologic characteristics of children ≤16 years with GI symptoms consulting in the post-travel visit to the Spanish +Redivi centers, to identify possible risk factors for them and to compare them with children consulting for other reasons.

METHODS

Data Collection

This was an observational study based on a prospective cohort selected from the Spanish network on Infectious Diseases Imported by Travelers and Immigrants (+Redivi). This network comprises 21 medical centers (1 primary care center and 20 hospitals, both specialized and nonspecialized in travel medicine) in different regions of Spain. The network shares a common database for online data registry on imported infections, where demographic, clinical and travel-related data are collected according to a standardized protocol. Data are obtained from every patient (traveler or migrant) attending the center who comes either for travel-/

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migration-related infections or for a health examination. These data cannot be linked back to an individual patient as these are codified when registered in the database, and only each center can link the information of the database to their individual patient. Episodes are registered with different codes in the database although the patient had had a previous and different episode registered in the database.

The population included in +Redivi comprises immigrants from any country and returned travelers, defined as any person who crossed an international border before seeking medical advice for a presumed travel-related disease or for screening for asymptomatic infections. The network also includes well-established migrants, or their descendants, who come to consultation after traveling to VFRs in their countries of origin. Data about travel country destination, travel duration and type of traveler were mandatory to be registered in the database, as well as clinical, epidemiological and disease process data, according to a standardized fill form.

The types of traveler are as follows: (i) those first arrived to our country for permanent or temporal residence were classified as immigrants, (ii) those autochthonous children traveling abroad for pleasure as tourists, (iii) those foreign-born who were traveling to their country of origin as VFR immigrants and (iv) those autochthonous children belonging to a foreign family who were traveling to the country of family origin as VFR travelers. It is important to distinguish VFR as a high-risk traveler because it is ethnically and racially distinct from the majority population of the country of residence (a higher-income country), who returns to his or her home country (lower-income country) to visit friends or relatives. Family members, such as the spouse or children, who were born in the country of residence are included in the VFR category.

The analysis carried out in this article was performed as a subanalysis of the information collected in the database, from January 2009 to December 2013 both inclusive and for children ≤16 years old.

Statistical Analysis

Frequency and percentage were used to summarize data. We performed continuous variables as median and interquartile range ($P_{25–75}$). The association between categorical variables was evaluated using the χ^2 test when the sample was large enough (>30) or the Fisher exact test for small samples. The variables that had a significant *P* value in the univariate analysis were included for further multivariate analysis to be identified as an independent risk factor associated with GI symptoms. *P* values were considered significant at a level of 0.05, 2-tailed. The potential interaction between independent variables was analyzed by means of multivariate models.

Among those children affected by GI symptoms, the adjusted odds ratio (OR) and 95% confidence interval (95% CI) were calculated to compare individuals with those children consulting for other reasons. *P* values ≤0.05 were considered statistically significant.

Variables included in the study were date of visit, birth date, gender, country of birth, travel destination country, country of residence, type of traveler (tourist, immigrant, VFR immigrant and VFR travelers), pre-travel advice, travel duration (total days of travel), reasons for consultation and final diagnosis. In Spain, pre-travel advice can be sought in specific clinics for pre-travel advice that are accountable to the Health Ministry or in specialized centers for tropical medicine. The variables disclosed whether the patient was attended or not in any of those centers before the travel.

Statistical analysis was performed with Stata 13.1 package (StatCorp LP, College Station, TX). The study was approved by the Ethics Committee of Clinical Research (CEIC) of the coordinator center and by each of the research participating centers of the Spanish database +Redivi. Those registered in the database records respect the confidentiality procedures established in the Data Protection Act.

RESULTS

Baseline Data of Children Registered in +Redivi Database

A total of 606 children were registered in the Spanish +Redivi database from January 2009 to December 2013. Children who reported GI symptoms as a primary or secondary reason for consultation represented 13.5% (82/606) of total consultations in +Redivi, representing the third frequent cause of visits at medical centers of the +Redivi network.

The other most common reasons for consultation were health examination after traveling or for immigrant screening (41.4%), altered laboratory results (26.9%) and fever (12.5%). Demographic characteristics were the following: 54% (327/606) were male; most of them were immigrants, 65.8% (399/606); 90% were >2 years old and median age of all children was 8.7 years (interquartile range, 4.4–12.4 years). An analysis comparing age and geographic areas showed that children <2 years old are likely associated with traveling to/from Europe and Sub-Saharan Africa than Asia, Indian subcontinent or Caribbean/Latin America. Overall median travel duration was 50 days (interquartile range, 30–150 days), and pre-travel advice was given to only 30.9% of the targeted children. A significant trend was observed for seeking pre-travel advice between VFR immigrants (21.4%) and tourists (41.2%). Apart from immigrants, other types of travelers were VFR immigrants 6.93% (42/606), VFR travelers 21.6% (131/606) and tourists 5.6% (34/606). Related to immunosuppression, 0.7% (4/606) was HIV-infected children. High risk for traveling was considered for most of the VFR immigrant, VFR traveler and tourist children.

The most prevalent infection was protozoan in 23.4% (142/606), and *Giardia intestinalis* was the most common pathogen in 10.1% (61/606) of total children.

Eosinophilia was observed in 31.7% (192/606) of the registered children, mainly associated with helminthic infection with an OR of 3.38 (95% CI: 2.14–5.34).

Children With GI Symptoms

Seventy-seven percent (10/13) of bacterial infections showed GI symptoms as the primary reason for consultation, much higher than protozoan 22.5% (32/142) or helminthes 15.5% (15/97). Otherwise, diagnosis for children with GI symptoms was associated with protozoan infections in 39% (32/82) of the cases, helminthes in 18.3% (15/82) and bacterial infections in 12.2% (10/82) of them. However, 30.5% (25/82) of patients were not associated with any pathogen. Immigrants had less GI disorders compared with tourists ($P < 0.05$) (Table 1).

G. intestinalis was only associated with GI symptoms in 27.9% (17/61) of the cases of giardiasis. A significant association was found in bivariate analysis between having a GI disorder and age <2 years ($P < 0.005$) and travel duration ($P < 0.05$).

Bivariate analysis between type of patient and GI symptoms showed risk associated with tourist (OR: 0.70; 95% CI: 0.35–1.38) when compared with other types of travelers, but its precision was too low to consider it significant.

Bivariate analysis between geographic area of birth and GI symptoms showed a trend association with $P < 0.001$, being those children born in Europe or industrialized countries at higher risk for GI symptoms (25%; 95% CI: 0.19–0.33) than those from other continents (Africa 11%, Asia 17% and America 6%) (Table 1).

Protozoan infection was 2-fold higher if traveling to Sub-Saharan Africa (OR: 2.00; 95% CI: 1.33–3.00), but it was not associated with other geographic areas. No association was established between giardiasis and any geographic area (Table 1).

In a multivariate analysis, the independent risk factors associated with GI symptoms were travel duration <90 days versus

TABLE 1. Demographic, Travel-related and Diagnosis Data Related to Destination or Origin Geographic Area

Variable	All regions	Europe and North America	Sub-Saharan Africa	North Africa	Latin America and Caribbean	Indian Subcontinent and Asia
No of travelers	606 (100%)	10 (1.65%)	184 (30.36%)	22 (3.63%)	220 (36.3%)	170 (28.05%)
Age (years)						
Median	8.7	9.1	5.9	12.02	10.2	8.4
IQR	4.4–12.4	2.7–12.6	2.7–10.5	7.5–13.1	6.8–13.4	4.1–12.0
Travel duration (days)						
Median	50	30	60	45	34	60
IQR	30–150	30–30	22–120	15–60	30–78.5	30–240
Reason for travel (%)						
Tourism	34 (5.6)	2 (20)	10 (5.4)	0	15 (6.8)	7 (4)
VFR traveler	131 (21.6)	0	52 (28.3)	6 (27.3)	34 (15.5)	39 (23)
VFR immigrant	42 (6.9)	0	9 (4.9)	1 (4.6)	15 (6.9)	17 (10)
Immigrant	399 (65.9)	8 (80)	113 (61.4)	15 (68.2)	156 (70.9)	107 (63)
Pre-travel advice (%)	31	0	49.3	0	20.3	25.4
Diagnosis						
Protozoan	142 (23.4)	4 (40)	70 (38)	2 (9.1)	32 (14.6)	34 (20)
Helminthes	97 (16)	0 (0)	30 (16.3)	8 (36.4)	22 (10)	37 (21.8)
Bacterial	13 (2.2)	0 (0)	5 (2.7)	0 (0)	6 (2.7)	2 (1.2)
Unknown	354 (58.4)	6 (60)	79 (43)	12 (54.5)	160 (72.7)	97 (57)
Giardiasis	61 (10.1)	0 (0)	17 (9.2)	0 (0)	21 (9.6)	23 (13.5)

IQR indicates interquartile range.

>90 days ($P = 0.008$), tourist and VFR traveler child versus immigrant and VFR immigrant ($P = 0.03$) and the bacterial infection ($P < 0.001$). The rest of variables were not associated with risk factors after adjusting for potential confounders.

DISCUSSION

This study provides the first prospective observational analysis of potential risk factors associated with childhood GI symptoms in traveler children.

Children included in the study having GI symptoms represented 13.5% of total consultations, much lower than other studies addressed to adults.[9,10] It has been demonstrated that 8% of travelers to the developing world required medical care during or after travel, and more than a quarter of those who seek medical assistance presented with GI symptoms.[11–13] Also, diarrhea, abdominal pain and fever were the most frequent post-travel complaints in a study of a group of children whose family visited a travel clinic for pre-travel advice.[14]

Regarding the type of traveler, we defined VFR children as a high-risk group of travelers such as have been described in other studies.[15,16] They tend to be younger and stay longer in high risk and at times in remote areas of developing countries.[15] Children frequently become ill during or after travel. In a study of the Global TravEpiNet during the period 2009 to 2011, being a VFR traveler was an independent predictor of declining a recommended vaccine.[16] A perception of low risk, a lack of access to a travel clinic or someone knowledgeable in travel medicine and a lack of financial resources to purchase vaccines and prophylactic medications are among the reasons why most lack appropriate pre-travel advice, antimalarial prophylaxis or vaccinations.[4] Many of them stay in family homes, which may increase their risk for acquiring certain diseases such as enteric infections. Regarding the age and type of traveler, the study showed that 46% of VFR children were <5 years of age,[17] the same as shown in our study where lower median age was associated with VFR travelers (median age = 4.1 years old; $P < 0.001$) from other type of travelers.

We did not find association between geographic area and specific pathogen. However, a significant trend ($P < 0.001$) showed higher risk of GI symptoms in children born in Europe or in industrialized countries (25%; 95% CI: 0.19–0.33) than those coming from other continents (Africa 11%, Asia 17% and America 6%). Unlike what was observed in our study, other studies demonstrated that traveler to/coming back from all regions, except Southeast Asia, presented with parasite-induced diarrhea more often than with bacterial diarrhea.[11] Regarding parasitic causes, giardiasis was reported disproportionately among travelers returning from south central Asia,[11] similar to our study results.

A GeoSentinel Surveillance Network study on 25,867 returned travelers over a 10-year period (from 1996 to 2005) analyzed data from travelers who sought medical attention showing microbiologically confirmed GI disease in only 30% (7442) of the travelers[18] less than our results (41.6%). Multivariate analysis demonstrated that GI symptoms were associated significantly with younger age group and those traveling for the reason of tourism,[18] and our results only showed tourist and VFR traveler as independent risk factors for them. It seems plausible because younger children are likely to be in contact with soil-transmitted helminthes; and tourists are traveling outside their living area where host factors can have a role to develop GI symptoms.

Also, they demonstrated that traveling for longer periods (>28 days) was associated with lower risk (OR: 0.93; $P = 0.04$),[18] as we observed in our study for travel duration >90 days after adjusting it for other confounding factors. Some bias might have an implication on these results because those children traveling longer time are less likely to seek post-travel health advice due to the spontaneous time limitation for the majority of GI syndromes.

Regarding the causes, 65% of patients with GI symptoms had a parasitic infection, 31% bacterial and 3% viral,[11] very similar to our results where parasitic infection (57.3%) is the most likely cause associated with GI symptoms. Other studies show bacterial infections as the most prevalent cause of GI symptoms.[19] Laboratories of different centers attending post-travel diseases also use different techniques to study these infections. This fact could justify some of these controversial results. There is no standard protocol to be used in this clinical framework. Coccidian parasites are increasingly recognized as causes of travelers' diarrhea, but their percentages may have been underestimated in the GeoSentinel survey[18] because the diagnosis of these organisms requires specific staining techniques that are not routine in many laboratories. Moreover, there is a limitation factor in our study related to the laboratory studies because not all the laboratories are screening parasites with the same method of diagnosis and there is a lack of a standardized

protocol for searching causes of travelers' diarrhea. Similarly, viral pathogens, such as rotavirus and norovirus, are not routinely tested for at health centers and their percentages could have been underestimated; however, these agents usually cause a short-term illness that typically resolves before travelers seek medical attention.[18]

Another study showed that most travelers' diarrhea in children was caused by bacteria, but in children <2 years old viral etiologies may be more common.[20] The self-limited evolution of viral infections could be the reason why we found very low number of children infected with virus in our study. The likelihood of seeking health advice after the travel is unlikely when the cure of infection is spontaneous as happening with viral or bacterial (*Escherichia coli*) infections. In another study among traveler children in Zurich (Switzerland), diarrhea was more common in those returning from Western Balkan Countries and North Africa.[21] This study showed that the returned children, who are sick enough to go to the emergency room, presented with a broad spectrum of travel-associated morbidities, mainly diarrheal illness (39%), and 3.6% of children with severe travel-associated diseases requiring hospitalization were mainly VFR or immigrant children.[21]

We are used to test for *Giardia* antigen because it can increase the yield in the diagnosis of this common parasitic cause of persistent diarrhea and may need to be tested repeatedly. As described, *Giardia* antigen is a test used for any child or adult with GI symptoms returning after travel as a routine for diagnosis.[22]

Regarding bacterial infection as the source of GI symptoms, infants and young children may experience prolonged episodes of diarrhea when infected with bacterial organisms that commonly cause acute, self-limited diarrhea in older individuals; for this age group, stool cultures may be useful in the evaluation of persistent diarrhea.[20]

Helminthic infections (roundworms) were unlikely in our study (15.5%) because the median travel duration was only 50 days in our cohort of children. It has been evidenced that they are more common in children who have prolonged stays in the tropics or children traveling as VFRs.[23]

Independent risk factors for GI symptoms in our study were being tourist or VFR traveler, travel duration <90 days and bacterial infection. *G. intestinalis* was the most common infectious agent causing a GI disorder in the traveler children.

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