Risk factors for intussusception in childhood gastroenteritis: a nationwide cross-sectional study in Italy

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ABSTRACT

Background: The aetiology of intussusception is unknown for most of the cases studied, although some associated conditions have been identified. We aimed to clarify the role played by enteric pathogens as potential risk factors for intussusception.
Methods: A retrospective review of the records relating to hospitalizations for gastroenteritis with or without concurrent intussusception in Italian children was conducted among children aged <6 years old during the period 2005-2012. Through a multivariate logistic regression model, the associations, expressed as odds ratios with 95% confidence intervals, were estimated between the presence of gastroenteritis with intussusception and the explanatory variables, such as sex, age, the aetiology of gastroenteritis and whether the subjects lived in the North, South and Islands or Centre Italy.
Results: A total of 174 records related to admissions due to the concomitant manifestation of gastroenteritis and intussusception were extracted and analyzed. The estimate of the adjusted odds ratio confirmed the significant contribution that sex and geographical location made to hospitalizations both for gastroenteritis with concurrent intussusception, and in the associated secondary diagnosis of gastroenteritis, with the exception of the rotavirus, where a different seasonality and a bucking trend were observed. The probability of intussusception became statistically significant lower from 12 months of age to ≤23 months and for age 48-59 months, respect to the first year of life.
Conclusion: Our observational study highlighted males, affected by enteric infections, other than rotavirus and parasitic, living in North and Centre of Italy have an increased risk of developing intussusceptions. In the second and fifth year of life the probability of intussusceptions becomes lower than in the first year. Additional research is needed to confirm these findings and evaluate the pathogenesis which may link such infections with intussusception.

Key words: intussusception, gastroenteritis, hospitalization rates, children, vaccines

INTRODUCTION

Intussusception (IS) is a rare condition where one segment of the intestine invaginates into another [1]. In Italy, the incidence of IS was estimated by Sturkenboom et al. to be 5 x 100000 people, using a paediatricians' medical database and children aged <10 years old as the reference population [2].

Today this condition is mainly investigated in particular in relation to the anti-rotavirus vaccination, which is recognized as a possible risk factor for increased cases of IS [3-5], although opinion on the risk/benefit balance is definitely in favour of vaccination [5-9].

The WHO recommended the epidemiological surveillance of IS, evaluating the basic incidence before the introduction of the vaccination, which led to the implementation of studies that showed a variation of the incidence of IS not linked to vaccination [10]

Enteric pathogens are considered to be possible risk factors for IS [11]. In early childhood almost exclusively idiopathic forms are found, whose aetiology has led to the presumption of the involvement of infectious agents because of the frequent association with the intense reactive hyperplasia of the gut [11].

In particular, viral aetiology seems to prevail over bacterial aetiology: according to some studies, the adenovirus, rotavirus (RV) and enteroviruses are involved respectively in 41%, 10% and 6% of cases of idiopathic IS, although a cause-effect relationship between gastroenteritis (GE) and IS has never been confirmed [11].

Further studies are necessary to clarify the role played by enteric pathogens in IS. To evaluate the factors associated with its development in cases of gastroenteritis, we performed a retrospective review of records relating to hospitalizations for GE in children aged <6 years old in Italy during the period 2005-2012, comparing the cases of GE with concurrent IS (GEIS) to cases of GE without IS in order to analyze the factors associated with GEIS hospitalizations.

METHODS

The retrospective observational study was conducted by analyzing the hospital discharge records (HDRs) provided by the Ministry of Health (National Hospital Discharge Database Development, Ministry of Health, General Directorate of Health Planning, Office VI), related to hospitalizations for GE (unspecified aetiology gastroenteritis of a presumed infectious aetiology, ICD9-CM codes 009–009.3, and a presumed non-infectious aetiology, ICD9-CM code 558.9; gastroenteritis with a specified aetiology: viral gastroenteritis, ICD9-CM codes 008.61–69, among which the gastroenteritis rotavirus, referred to as GERV, was identified by code 008.61, bacterial gastroenteritis, ICD9-CM codes 001–005 and 008–008.5, and parasitic gastroenteritis, ICD9-CM codes 006–007). For all record analyzed additional data such as the sex and the age of the patient, the regional code which carried out the admission and the month of discharge, have been extracted.

Then the sample was stratified into two groups (hospitalizations for GE without IS (absence of 560.0 code: intussusception of the colon or intestine), and hospitalizations for GEIS with ICD9-CM 560.0 code), compared with each other.

Data analysis

Descriptive analyses were used to illustrate the characteristics of the sample. The discrete and nominal variables were described through frequencies and percentages and the difference between hospitalizations for GEIS compared to hospitalizations for GE in the absence of IS was assessed with the χ^2 test or the χ^2 test for trend for ordinal variables. The quantitative variables were expressed in terms of mean and standard deviation (sd), whose significance was assessed with a t-test for independent samples.

The seasonality of the hospitalizations by month for GEIS and for GERV was compared.

The hospitalization rates (HRs) per 100000 children for GEIS were calculated using the Italian resident population aged <6 years old provided by the Italian Institute of Statistics (ISTAT) during the period 2005–2012 [12].These estimated HRs were stratified by gender and by age (0-11 months, 12-23 months, 24-35 months, 36-47 months, 48-59 months and 60-71 months). The average hospitalization rates (AHRs) of the considered period were differentiated by macro-area (Northern, Central and Southern Italy with Italian Islands) and region.

The statistical significance of the temporal trend of HRs was evaluated by the slope of the regression line.

A multivariate logistic regression was used to assess the associations, expressed as odds ratios (ORs) with 95% confidence intervals (95% CI), between the absence/presence of IS during GE, chosen as a dependent variable, and each explanatory variable with significant levels lower than 0.05, such as sex, age classes, the diagnosis present as secondary (SD) and geographical location and adjusted for the effects of other variables.

A p-value of <0.05 was the criterion for statistical significance. The data were processed using the STATA / IC12.0 statistical package.

RESULTS

During the period 2005-2012, 174 HDRs related to admissions due to the concomitant manifestation of GE and IS were extracted, bearing ICD9-CM code 560.0 only as a principal diagnosis. These cases account for 4.30% (174/4042) of all the paediatric hospitalizations for IS occurring during the same period and for the same age groups considered in this study (data not shown in the table).

As shown in Table 1, through a comparison of the cases of GEIS and the cases of GE without IS, a statistically significant differences according to gender emerged (p =0.024), with a male/female ratio among

children hospitalized for GEIS of 1.76 (111/63) versus a ratio of 1.23 (185001/149807) for the remaining portion of the group under investigation.

The average age of the children hospitalized for GEIS was equal to 1.47 ± 1.40, slightly lower than but not significantly different from that of the total surveyed population (1.60 ± 1.46). The distribution by age for GEIS hospitalizations was significantly different (p =0.008) compared to that of GE without IS: in the presence of IS, in fact, more than a third of the hospitalized children were aged 0-11 months (57/174, 32.76%), while for GE in the absence of IS the most represented age group was 12-23 months (102541/334808, 30.63%)

Additionally, the analysis of the SD associated with GE with or without IS highlighted statistically significant differences (p <0.001): the RV aetiology in particular was the second most frequent type of SD in admissions for GE in the absence of IS (40291/168144, 23.96%), but in the presence of GEIS only 16.67% (29/174) of the cases were involved. None of the cases of GEIS were associated with an SD of parasitic GE.

The geographical stratification of GEIS hospitalizations showed statistically significant differences (p <0.001) compared to GE hospitalizations in the absence of IS, with slightly more than half of the hospitalizations for GEIS registered in the North (89/174, 51.15%) as opposed to what was found in the absence of IS (123360/334808, 36.84%).

As highlighted in Figure 1, the seasonal pattern for GERV hospitalizations, peaking in March, did not coincide with that of hospitalizations for GEIS, for which two peaks per year, in May and November, were recorded.

TABLE 1. Characteristics of the sample for the absence/presence of intussusception (IS).

	TOTAL GE N=334982	GE without IS n=334808	GE with IS (GEIS) n=174	p-value
SEX, n (%)				**0.024***
Women	149870	149807 (44.74)	63 (36.21)	
Men	185112	185001 (55.26)	111 (63.79)	
AGE, mean(years)±sd	1.60±1.46	1.60±1.46	1.47±1.40	**0.220****
AGE CLASSES, n (%)				**0.008***
0-11 months	88324	88267 (26.36)	57 (32.76)	
12-23 months	102579	102541 (30.63)	38 (21.84)	
24-35 months	61553	61509 (18.37)	44 (25.29)	
36-47 months	38274	38254 (11.43)	20 (11.49)	
48-59 months	25463	25457 (7.60)	6 (3.45)	
60-71 months	18789	18780 (5.61)	9 (5.17)	
SECONDARY DIAGNOSIS of GASTROENTERITIS (GE), n (%)	168318	168144	174	**<0.001***
Unspecified GE of presumed non-infectious aetiology	29938	29923 (17.80)	15 (8.62)	
Unspecified GE of presumed infectious aetiology	72670	72592 (43.17)	78 (44.83)	
Viral GE (no RV)	21741	21699 (12.91)	42 (24.14)	
GERV	40320	40291 (23.96)	29 (16.67)	
Bacterial GE	2609	2599 (1.55)	10 (5.75)	
Parasitic GE	1040	1040 (0.62)	0 (0.00)	
GEOGRAPHICAL LOCATION, n (%)				**<0.001***
South and Islands	161646	161599 (48.27)	47 (27.01)	
Centre	49887	49849 (14.89)	38 (21.84)	
North	123449	123360 (36.84)	89 (51.15)	

χ^2 test or χ^2 test for trend.

**t-test.*

GE: gastroenteritis; IS: intussusception.

Statistically significant differences are shown in bold (p-value<0.05).

FIGURE 1. The seasonality of hospitalizations for GERV (rotavirus gastroenteritis) versus GEIS (gastroenteritis with concurrent intussusception).

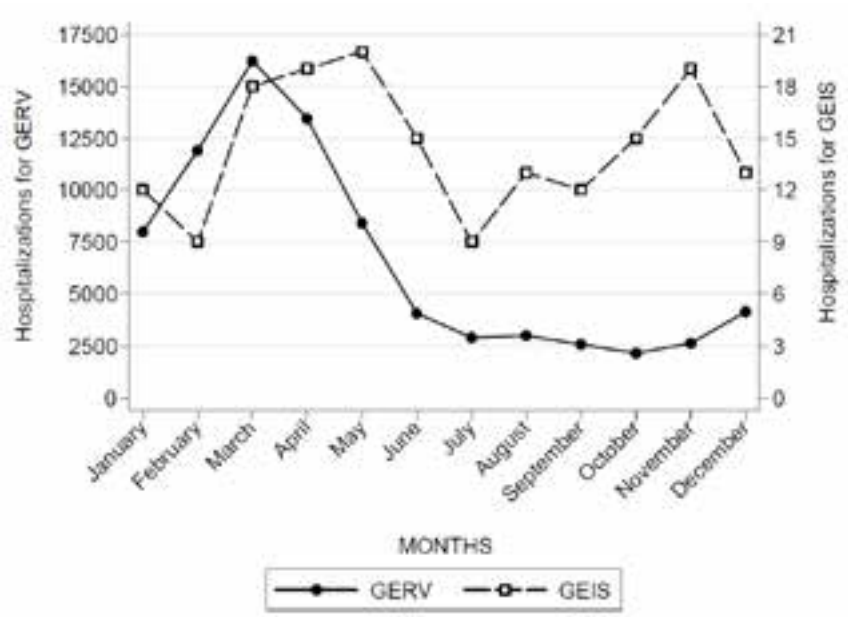

TABLE 2. Hospitalization rates x 100000 children for intussusception with concurrent gastroenteritis (GEIS) by age group.

	2005	2006	2007	2008	2009	2010	2011	2012	AHR	β (p-value)
0-11 months	1.80	1.46	0.90	0.54	1.23	1.78	1.62	0.94	1.28	-0.02 (0.774)
12-23 months	0.55	0.72	0.54	0.53	0.71	0.87	1.06	1.84	0.85	0.14 **(0.019)**
24-35 months	1.10	0.73	1.60	0.54	1.06	0.53	0.87	1.44	0.98	<0.01 (0.950)
36-47 months	0.55	0.00	0.36	0.53	0.18	0.88	0.52	0.53	0.44	0.04 (0.323)
48-59 months	0.00	0.00	0.18	0.18	0.18	0.00	0.17	0.36	0.13	0.03 (0.079)
60-71 months	0.00	0.18	0.18	0.00	0.00	0.52	0.53	0.18	0.20	0.05 (0.171)
0-71 months	0.67	0.52	0.63	0.39	0.56	0.76	0.79	0.88	0.65	0.04 (0.107)

AHR: average hospitalization rate (2005-2012); β: coefficient of the trend test.
Statistically significant trends are shown in bold (p-value<0.05).

The GEIS HRs, during the eight years under consideration, showed an increase of about 0.04 x 100000 children per year, going from values of 0.67 x 100000 children in 2005 to 0.88 x 100000 children in 2012 (Table 2). Stratifying the data by sex, the AHR for the reporting period is greater in males, equal to 0.81 x 100000 children, than in females (AHR =0.48 x 100000 children), and this trend increased, although not statistically significantly for both of them (data not shown).

Stratifying the HRs for GEIS by age group (Table 2), it was observed that the 0-11 months class was the most affected by the admission to these contributing causes (AHR for 0-11 months =1.28 x 100000 children). However, in this age group the trend decreased, although this decrease was not significant. In contrast, for the other age groups the trend increased; in children between their first and second year of life, in particular, a statistically significant increase of HR, equal to 0.14 x 100000 children on average per year (trend test: β coefficient =0.14; p =0.019), was estimated.

With regard to the macro-areas of the country, there was a greater tendency towards admission for GEIS in Central Italy (AHR =0.74 x 100000 children), with a statistically significant increase in AHR (trend test: β coefficient =0.11; p =0.029) and in the North (AHR =0.74 x 100000 children), than in the South and the Islands (AHR =0.49 x 100000 children), for which the trend showed no statistically significant changes (data not shown in the table).

Through an analysis of the HRs of each region, throughout the period considered in this study, the AHRs for GEIS only exceeded the unit in four regions (Emilia Romagna, Liguria, Sardinia, Molise), although AHRs higher than 3 admissions x 100000 children were only recorded in Valle d'Aosta (data not shown in the table).

TABLE 3. Multivariate logistical regression for the associations between the development of intussusception in the presence of gastroenteritis and the explanatory variables (sex, age, secondary diagnosis of GE and geographical location).

EXPLANATORY VARIABLES	OR°	95% CI
SEX		
Female[a]	1.00	
Male	1.39	1.02 – 1.90
AGE		
0-11 months[a]	1.00	
12-23 months	0.61	0.40 – 0.91
24-35 months	1.24	0.83 – 1.84
36-47 months	0.87	0.52 – 1.45
48-59 months	0.39	0.17 – 0.92
60-71 months	0.83	0.41 – 1.68
SECONDARY DIAGNOSIS of GASTROENTERITIS (GE)		
Unspecified GE of presumed non-infectious aetiology[a]	1.00	
Unspecified GE of presumed infectious aetiology	1.82	1.04 – 3.17
Viral GE (no RV)	2.91	1.60 – 5.29
GERV	0.99	0.53 – 1.88
Bacterial GE	5.15	2.29 – 11.57
GEOGRAPHICAL LOCATION		
South and Islands[a]	1.00	
Centre	2.49	1.62 – 3.83
North	2.97	2.07 – 4.27

[a]: reference category; °: adjusted ORs for the other factors in the model.

The estimate of the adjusted ORs for the other factors in the model (Table 3), through a multivariate regression, showed the significant contribution that sex (OR 1.39, 95% CI 1.02 to 1.90), the different associated SD of GE (unspecified GE of a presumed infectious aetiology: OR 1.82, 95% CI 1.04 to 3.17; viral GE without RV; OR 2.91, 95% CI 1.60 to 5.29; bacterial GE: OR 5.15, 95% CI 2.29 to 11.57) and geographical location (Center: OR 2.49, 95% CI 1.62 to 3.83; North: OR 2.97, 95% CI 2.07 to 4.27) made in the hospitalizations for GEIS. No association between GERV and development of IS was observed. The probability of intussusception became statistically significant lower from 12 months of age to ≤23 months (OR 0.61, 95% CI 0.40 to 0.91) and for age 48-59 months (OR 0.39, 95% CI 0.17 to 0.92).

DISCUSSION

IS is a fairly rare condition, usually considered idiopathic [13], in whose pathogenesis enteric pathogens appear to be involved, especially viruses, although a causal relationship has not yet been proven: the data from our study were consistent with the literature, highlighting the involvement of viral GE, including RV, in 40.80% (71/174) of cases of GEIS, rising to 87.65% (71/81), considering only GE with a specified aetiology [11, 14, 15]. However, the analysis we conducted showed a greater involvement of bacterial GE in cases of IS, compared to all the other infectious causes of GE. The highest HRs were found in males with an AHR of 0.81 x 100000 children, who also had a higher risk of developing IS in the presence of GE compared to females, confirming an already known fact [16-19]. An explanation of this male predominance in the incidence of IS observed worldwide, has not yet been identified [20, 21]. Future studies should look further into the possible effects caused by sexual hormones [21]. Unlike the seasonality of GERV hospitalizations, with a typical peak in March, GEIS hospitalizations showed two annual peaks in the months of May and November, suggesting the absence of a temporal association between these pathological events [22]. The temporal trend of HRs for GEIS and GERV had a countertendency, confirming the independence of the two phenomena, as shown by the logistical regression: the HRs between 2005 and 2012, in fact, decreased for GERV and increased for GEIS [23]. This increase amounted to 31.34%, and it was observed most clearly in the 12-23 months age group, for which the annual increase in HRs was significant

and amounted on average to 0.14 hospitalizations x 100000 children per year. This figure was in agreement with the one shown by a study carried out in France, although on a different population (patients <18 years old), which demonstrated an increase in the incidence of IS, especially in the age group between the first and second year of life, but it was not considered to be related to the rotavirus vaccination [24]. The HRs for GEIS in children in the first year of life were in contrast to the HRs for other age groups, with a decrease between 2005 and 2012 of 0.02 hospitalizations x 100000 children on average per year. The logistical regression model highlighted that in Central and Northern Italy there was a greater association with GEIS hospitalizations than in the South: this could suggest in part the influence of environmental factors on the development of IS, and in part it might indicate a different attitude to the deepening diagnostic of this condition in different areas of the country, as evidenced by the AHRs, which were higher in central and northern regions, compared to the South and the Islands.

One of the limitations of our study was the use of the database of HDRs as an information flow, without diagnostic confirmation of the aetiological agents of GE through specific laboratory tests, or the possibility of applying the specific case definition for acute intussusception in the paediatric population developed by the Brighton Collaboration. Nevertheless, the national scope of this study makes the analysis of HDRs a good indicator of the phenomenon of paediatric hospitalizations for IS with concurrent GE in Italy. Another limitation was considering only cases of GEIS that required hospitalization, excluding cases treated in emergency departments, which accounted for approximately 40% of the total cases of IS [25,26]. However, as postulated in a recent study, if the proportion of cases treated in emergency departments was stable over time, it would be plausible to consider the data on hospitalizations as reliable indicators of temporal trends of rates of GEIS [21].

CONCLUSIONS

Our observational study highlighted males, affected by enteric infections other than rotavirus and parasitic, living in North and Centre of Italy, have an increased risk of developing intussusceptions. In the second and fifth year of life the probability of intussusceptions becomes lower than in the first year. Additional research is needed to confirm these findings and evaluate the pathogenesis which may link such infections with intussusception.

Statement of conflict of interests

The authors did not declare any conflict of interests.

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