Updated Incidence of Inflammatory Bowel Disease Among Girls Attended in the Spanish Public Health System

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Abstract

Objectives: As potential auto-immune process, Inflammatory Bowel Disease (IBD) was studied following papilloma vaccination. Preliminary, we assessed its incidence and description among girls at age to vaccinate.

Methods: Cohort study including girls aged 9-18 years between 2002-2016 using the Spanish Primary Care Database For Pharmacoepidemiological Research (BIFAP).

Results: Among 480,634 girls, 122 IBD 'confirmed' (51.6% CD, 44.3% UC and 4% undetermined) and 125 'possible' IBD (38.8% CD, 33.8% UC and 27.3% undetermined) occurred. 70% of cases had ≥1 symptoms suggestive of IBD before the diagnosis: abdominal pain (34.6%), diarrhoea (12.96%) and infectious gastroenteritis (10.53%). 16.4% Of confirmed and 10,4% of possible cases had Lower Gastrointestinal Bleeding (LGIB) 32-610 days before IBD diagnosis. Mesalazine (77.9%; 52.7%), azathioprine (59.0% ; 37.2%) and local corticosteroids (30.3% ; 27.1%) were prescribed anytime among confirmed and possible IBD cases, respectively. Incidence was 6.58 confirmed cases/10^5 person-years (2.68 [among aged 9-11y] to 14.40 [17-18y], and 13.31 (5.89 [9-11y] to 27.99 [17-18y]) when possible cases were added.

Conclusions: IBD incidence increased by age fluctuated over years and was higher than previously reported for paediatrics. LGIB before IBD could suggest delay in diagnosis. Non-specific conditions were highly consulted, their quantification as risk factors is guaranteed. Mesalazine was the drugs most prescribed.

Introduction

Inflammatory Bowel Disease (IBD) is a group of idiopathic chronic inflammatory intestinal conditions, mainly including Crohn's Disease (CD), Ulcerative Colitis (UC) and an undetermined form of colonic IBD. The pathogenesis of IBD remains poorly understood due to its multifactoriality, including genetic, environmental, and both parietal and luminal intestinal factors that induce a dysregulation of intestinal immunity, leading to gastrointestinal injury [1].

IBD primarily affects young adults, with 25% of patients diagnosed before the age of 20 [2,3]. Albeit the incidence of paediatric IBD greatly varies depending on the geographical setting, recent studies have consistently reported a steady increase in incidence trends over time worldwide [4,5]. In line with these findings, the incidence of paediatric IBD in Spain has almost tripled between 1996 and 2009 [6]. However, it still remains somewhat low (< 3 per 100,000 patients per year) when compared to recent data from Northern European countries [5]. Actually, in terms of prevalence, our previous estimation suggested that every 10^5 girls, between 53-94 live with IBD in Spain [7]. As IBD has been recognized with increasing frequency in children and adolescents, it is now considered one of the most relevant chronic diseases for paediatricians [8].

Childhood-onset IBD has differential characteristics compared with adulthood-onset. A higher proportion of Crohn´s disease and inflammatory behaviour, as well as a higher risk of treatment with immunomodulators and biologic agents has been lately reported for childhood-onset IBD [9]. Paediatric IBD may also impact on a critical period of physical and psychological development, potentially leading to growth failure, delayed puberty, depression, school absenteeism and social isolation [8,9-11].

Unravelling potential environmental factors that may trigger IBD is essential, especially in the paediatric age, since early intervention may help prevent the disease [2]. In fact, Crohn's & Colitis Foundation of America (CCFA) regularly develops and updates a consensus document called Challenges in IBD Research, which sets the direction for basic science research on IBD and suggests several areas for research including investigation for environmental triggers [11]. Among triggers, we are currently addressing the potential relationship between the Human Papilloma Virus Vaccination (HPVv) and the development of certain potentially immune mediated disorders, including IBD. Within this framework, and as preliminary step to study the link with the HPVv, we aimed to estimate the incidence trend of IBD from 2002 to 2016 among girls at age to vaccinate across the Spanish National Health System and describe clinical factors consulted by the girls before IBD diagnosis.

Methods

Source of data

Electronic Health Records (EHR) generated during primary care consultations In the Spanish Public National Health System (S.N.S.), namely the Spanish Primary Care Database For Pharmacoepidemiological Research (BIFAP), was used for the current IBD research [12,13]. During the study period, around 98.9% of the population was covered by the S.N.S. [14], and therefore registered with a local primary care paediatrician or physician (PCPs), who act as gatekeepers to secondary care.

Patients are referred to gastroenterologists by the PCPs in order to confirm the IBD diagnosis [14], the result of the referral is subsequently recorded in the primary care clinical profiles. The IBD recording in BIFAP has been previously validated for research [7], as well as several other diseases [13].

Data available in BIFAP include patient age, sex, life-style factors, clinical events (recorded by using the International Classification of Primary Care (ICPC) and the International Classification of Diseases 9th Revision (ICD-9) medical terms [15,16], anonymised PCPs free-text notes, specialist referrals and discharge letters, prescriptions issued in primary care and their dispensations in pharmacies, vaccinations and laboratory test results. During the current study period,such data correspond to 7 of the 9 regions in Spain and 57% of the overall Spanish population (66% of the girls aged 10-19 years according to the Spanish Statistical Office [14].

BIFAP is fully funded by the Spanish Agency on Medicines and Medical Devices (AEMPS), belonging to the Department of Health, and is maintained with the collaboration of the local governments of participating regions.

The study protocol was approved by the Scientific Committee of the BIFAP database (Reference BIFAP_01_2016).

Study design and follow-up to IBD ascertainment

In this observational cohort study, girls aged 9-18 years registered in BIFAP between 2002 and 2016 and with Primary Care (PC) medical records for at least 1 year, were included. Information was collected retrospectively. The start date was defined as the last date of fulfilling all the inclusion criteria. Individuals were followed up from the start date until there was a recording of an IBD diagnosis, they reached 19 years of age, left the database, died, or the study ended. Incident IBD cases were those with a first ever code during each patient's follow-up.

The precision and sensitivity of the IBD recording and date in BIFAP was assessed and described elsewhere [7]. In summary, two patterns of IBD diagnosis evidence were identified, i.e. 1) IBD recording with a positive colonoscopy or biopsy, a referral/hospital letter or free-text comments mentioning it (so-called confirmed IBD cases) or 2) IBD recording without that written information in the clinical histories (so-called possible IBD cases)

In order to assess IBD incidence trend by calendar year, the follow-up was replicated yearly from 2002 to 2016.

Description of IBD incident cases

Among IBD incident cases, the type of IBD, whether Crohn's Disease (CD), Ulcerative Colitis (UC) or undetermined (mentioned as no clear type or without information) is described, as well as the age at diagnosis, the proportion of gastrointestinal and systemic signs and symptoms (retrieved both, automatically through ICPC or ICD-9 or manually through physicians' free-text comments) related with IBD during the year prior to or any time before the incident IBD date for acute and chronic conditions respectively, and the intestinal anti-inflammatory agents prescribed anytime in the girls' primary care records.

Intestinal anti-inflammatory agents included corticosteroids acting locally (ATC A07EA) and aminosalicylic acid (i.e. sulfasalazine [A07EC01] and mesalazine [A07EC02]), the immunosuppressant azathioprine (L04AX01), mercaptopurine (A07EC02), corticosteroids for local oral treatment (A01AC), methotrexate (L04AX03), combinations of corticosteroids for systemic use (H02BX) and hydroxycobalamin (B03BA03). Glucocorticoids for

systemic use were also collected (H02AB),

Statistical analysis

The Incidence Rate (IR) of IBD cases per 10^5 person-years (py) was estimated by dividing the number of confirmed incident IBD cases by the total number of years contributed by each girl included in the study cohort. A second IR was calculated by adding possible IBD cases in the numerator. IR was also estimated by age and calendar year from 2002 to 2016.

Results

Baseline characteristics of incident cases

Among a total population of 480,634 girls forming the study cohort and 1,855,075 py to follow-up (mean of 3.8 years per girl), 247 new IBD cases (incident cases) were found during the study period (122 confirmed and 125 possible). The study flow chart, with details on incidence calculations, is displayed in Figure 1. The mean age at IBD onset was 15.1 years (p25%–75% 13–17), with the highest peak of incident cases at the age of 17-18 (Figure 2). As for IBD type in confirmed cases, CD was slightly more common (51.6%) than UC (44.3%), while undetermined colitis was a minor diagnosis (4%). Regarding possible IBD cases, CD and UC were almost similar (38.8% vs. 33.8%), with a relevant proportion of undetermined colitis cases (27.3%).

Around 70% of both confirmed and possible cases had at least one gastrointestinal symptom suggestive of IBD, recorded before the IBD code. Lower gastrointestinal bleeding (16.4%), infectious gastroenteritis (13.1%) and diarrhoea (10.7%) were the most prevalent conditions among so-called confirmed IBD cases, while abdominal pain (25.6%), diarrhoea (15.2%) and lower gastrointestinal bleeding (10.4%) among possible IBD cases. Lower gastrointestinal bleeding was recorded between 32-610 days prior to the IBD. Almost half of the cases had symptoms/signs described only in free-text comments, mainly on the same day of the IBD code or shortly after. Manual review revealed similar data to that obtained from automatic search, with abdominal pain, diarrhoea and blood in stools (i.e. lower gastrointestinal bleeding) being the most common symptoms. Table 1.

Specific anti-inflammatory intestinal drugs were prescribed in a majority of confirmed (94.3%) and possible (63.6%) IBD cases. In order of frequency, the most prescribed drugs were mesalazine (77.9% and 52.7% respectively), followed by azathioprine (59.0% and 37.2%) and local corticosteroids (30.3% and 27.1%). Systemic glucocorticoids were prescribed in 56.6% of confirmed and 44.2% of possible incident IBD cases. Table 1.
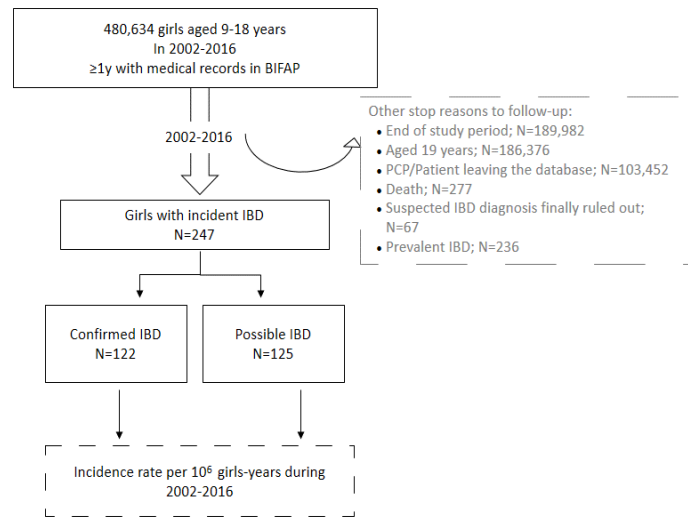
Incidence

The incidence was 6.58 new confirmed IBD per 100,000 py (3.39 CD, 2.91 UC and 0.26 undetermined cases/10^5 py), increasing up to 13.31/10^5 py when confirmed and possible IBD cases were included (6.01 CD, 5.19 UC and 2.06 undetermined cases/10^5 py respectively).
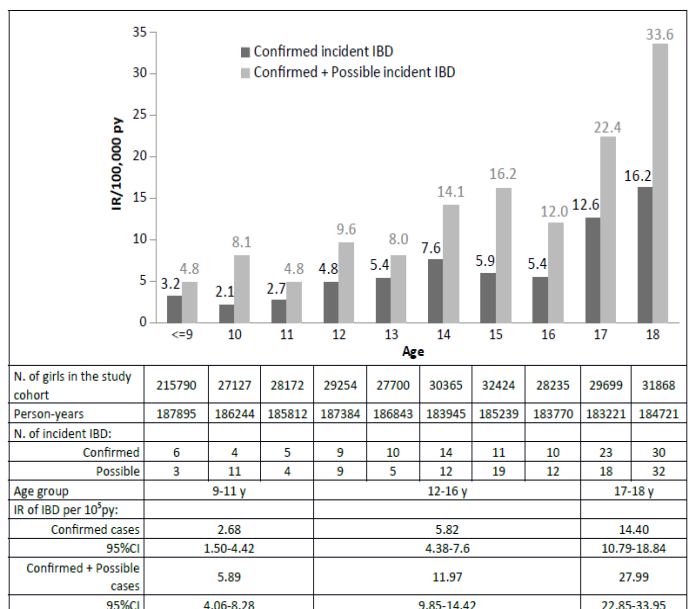
The IR of confirmed IBD increased with age from 2.68/10^5 py among girls aged 9-11 years to 5.82/10^5 py among those aged 12-16 years and 14.40/10^5 py for girls 17-18 years. Those figures were 5.89, 11.97 and 27.99 /10^5 py respectively, when confirmed plus possible cases were included. Figure 2.

During the study period (2002-2016), the IR ranged from 3.3 to 9.6 confirmed IBD per 10^5 py, and from 9.0 to 17.1 per 10^5 py
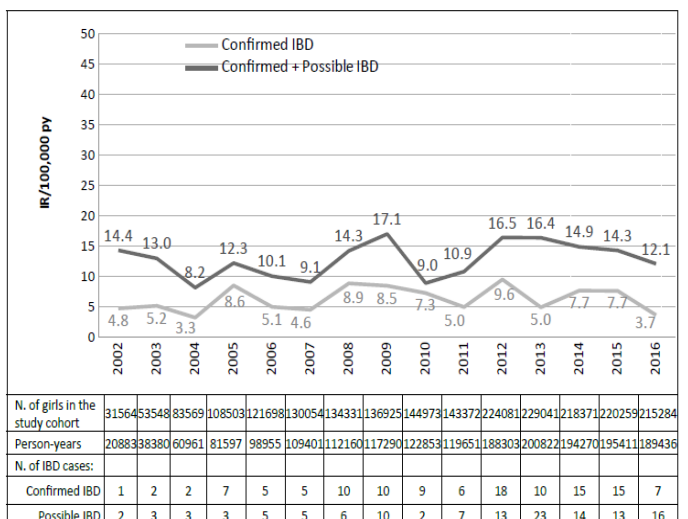
when possible IBD cases were added. No clear time trend was suggested. Figure 3.

Figure 1: Study flow chart - with IBD case ascertainment

N. of girls in the study cohort	215790	27127	28172	29254	27700	30365	32424	28235	29699	31868
Person-years	187895	186244	185812	187384	186843	183945	185239	183770	183221	184721
N. of incident IBD:										
Confirmed	6	4	5	9	10	14	11	10	23	30
Possible	3	11	4	9	5	12	19	12	18	32
Age group	9-11 y			12-16 y				17-18 y		
IR of IBD per 10^5 py:										
Confirmed cases	2.68			5.82				14.40		
95%CI	1.50-4.42			4.38-7.6				10.79-18.84		
Confirmed + Possible cases	5.89			11.97				27.99		
95%CI	4.06-8.28			9.85-14.42				22.85-33.95		

Figure 2: Number of IBD cases and Incidence Rate (IR) per 100,000 person-years among girls by age during 2002-2016.

N. of girls in the study cohort	31564	53548	83569	108503	121698	130054	134331	136925	144973	143372	224081	229041	218371	220259	215284
Person-years	20883	38380	60961	81597	98955	109401	112160	117290	122853	119651	188303	200822	194270	195411	189436
N. of IBD cases:															
Confirmed IBD	1	2	2	7	5	5	10	10	9	6	18	10	15	15	7
Possible IBD	2	3	3	3	5	5	6	10	2	7	13	23	14	13	16

Figure 3: Number of IBD cases and Incidence Rate (IR) per 100,000 person-years among girls by calendar year.

Table 1: Symptoms and signs consulted to primary care paediatrician or physician previous to IBD diagnosis among girls and IBD related prescriptions in BIFAP electronic health records.

	'Confirmed' IBD cases (N=122)		'Possible' IBD cases (N=125)	
	N.	%	N.	%
IBD compatible symptoms/signs codes	85	69.7	85	68.0
Gastrointestinal symptoms/sings				
Abdominal pain	11	9.0	32	25.6
Diarrhoea	13	10.7	19	15.2
Lower gastrointestinal bleeding (incl. blood in stools)	20	16.4	13	10.4
Infectious gastroenteritis	16	13.1	10	8.0
Perianal fistula disease	5	4.1	7	5.6
Gastritis	4	3.3	4	3.2
Appendicectomy	2	1.6	5	4.0
Chronic diarrhoea	4	3.3	2	1.6
Constipation	3	2.5	2	1.6
Altered bowel habit	0	0.0	2	1.6
Aerophagia	1	0.8	1	0.8
Irritable Bowel Syndrome	1	0.8	1	0.8
Dyspepsia	1	0.8	0	0.0
Bloody diarrhoea	0	0.0	1	0.8
Other IBD compatible symptoms/signs				
Anaemia	8	6.6	9	7.2
Fever	12	9.8	4	3.2
Growth impairment/failure	6	4.9	3	2.4
Underweight	4	3.3	3	2.4
Iron deficiency	5	4.1	2	1.6
Tiredness/Asthenia	2	1.6	3	2.4
Anorexia (loss of appetite)	0	0.0	2	1.6
Vitamin B12 or Folic Acid deficiency	0	0.0	1	0.8
IBD compatible symptoms/signs in free-text comments	33	27.05	26	20.8
No recording of symptoms/signs	4	3.29	14	11.2
Specific anti-inflammatory intestinal drugs:	115	94.3	79	63.2
Aminosalicylic acid:	95	77.9	68	54.4
- Sulfasalazine	0	-	3	2.4
- Mesalazine	95	77.9	65	52.0
Corticosteroids acting locally:	37	30.3	34	27.2
- Budesonide	29	23.8	24	19.2
- Beclometasone	10	8.2	11	8.8
- Triamcinolone	1	0.8	2	1.6
Azathioprine	72	59.0	46	36.8
Mercaptopurine	3	2.5	5	4.0
Other treatment:				
Glucocorticoids for systemic use	69	56.6	55	44.0

*No patient received a prescription of methotrexate, combinations of corticosteroids for systemic use and hydroxyco-balamin.

Discussion

The present study provides updated epidemiological data for paediatric IBD in a specific subset of girls aged 9-18 years in Spain. The incidence rate obtained in this selected group of girls (6.5/100,000 py) means a 2- to 6-fold increase compared to previous data for paediatric Spanish population, including boys and girls up to 18 years-old [6,17]. Both previous studies, which results were in line with other studies from Southern European countries [4,5], alerted on a potential underestimation of paediatric IBD in Spain [6]. Higher incidence rates reported in Northern European countries and the United States (>15-30/100,000 population) [4,5], have contributed to the well established concept of a north/south gradient in incidence across Europe for paediatric IBP. Our findings, along with recent data from Slovenia (7.6/100,00 children and adolescents per year [18], and France (13/100,000 children and adolescents) [19], hint at a potential underestimation of IBD incidence in previous studies. Most past European studies on IBD epidemiology were carried out more than a decade ago, in selected areas, included a small number of patients, and were mostly based on multicenter surveys, so their results may not accurately reflect the current incidence of IBD. In Europe, the IR reported in the literature for younger than 19 years ranges from 0.2 to 23 per 100,000 py between 1951-2017 [4,20]. Further reasons explaining this disparity may include methodological differences and either selection or detection bias, aside from actual differences in populations [6].

Specifically regarding females aged 10-19 years, our IR for confirmed IBD (6.58 per 10^5 py) overlapped with those based on an IBD registry in the Netherland (5 cases of UC and 10 CD per 100,000 py) [20], while our broad IR including confirmed and possible cases (13.31 per 100,000 py) was close to the one reported for girls aged 13-16 years in France between 2008 and 2012 (15.3 IBD per 100,000 py) [21]. Also, for the period 2005-2007, both incidences, confirmed only or broad, overlapped with those reported of CD among females aged 9-25 years in the UK primary care database CPRD for that period (7.71/100,000py; 95%CI: 2.50-18.00) [22]. Our incidence rate reached its peak at the age of 17-18 years. It is interesting to note that a recent multicenter international cohort study exhibited that female patients had a lower risk of CD during childhood until the age range of 10-14 years, but then the risk was significantly higher as compared with male patients. Unfortunately, and due the purpose of the current project, we did not explore a comparative cohort of male patients, but these findings merit further research in order to elucidate what factors may contribute to a higher risk in females over 14 years-old.

As for adults in Spain, the EpidemIBD study is an ongoing first large-scale nationwide population-based cohort study to investigate the incidence of IBD in Spain [23]. Preliminary results, published in 2019, have shown an incidence rate of 14.3/100,000 py, which is closer to that reported in Northern European countries for adults [24]. Well-conducted nation-scale prospective studies in children are also warranted in order to decipher whether the European north-south gradient in paediatric IBD is true or partially a reflection of methodological issues in previous studies.

Our incidence rate remained stable over time from 2002 to 2016, which is in line with data for adults in western countries [25], but conflicts with Spanish and worldwide studies for children [5,6,17], which have shown up to a 3- to 16-fold incidence increase in one to two decades. However, some other paediatric studies did not observe that secular trend [20,26] A low number of annual cases in the present study could also preclude a precise interpretation of the potential trend.

In a previous validation of the date of incident IBD recording in BIFAP [7], we observed that 16% of cases had a past prescription of specific anti-inflammatory intestinal drugs or signs or symptoms linked to the IBD by the PCP, from 1 day to 4.7 years before that IBD date. In our current analysis, IBD as observed in our study compatible symptoms/signs were highly consulted to PCP previous to IBD diagnosis but most of them are not specific of the disease. LGIB (most specific of the disease) could suggest an underlying IBD process up to 610 days prior to the IBD as observed in our study. In order to see to what extent they are red flags of an underlying IBD or be determinants of a subsequent IBD among girls, their link with IBD in multivariate statistical models in comparison with girls without the disease is guaranteed.

The strengths of the current study include the large number of girls forming the study population and their potential diversity in terms of baseline clinical and social characteristics, representing the paediatric population attended under primary care routine. However, our sample does not include the whole Spanish population so potential variation in registries or incidence among regions could make our sample not be fully representative of Spain. Other limitations to the study should be acknowledged. Cases defined as "confirmed" IBD were not checked directly with their IBD specialists by the authors but only the recordings in the clinical history were reviewed as mentioned above [7]. Incidence rates of confirmed IBD shown in the present study may have been underrated due to exclusion of the so-called possible IBD cases. In fact, two third of them were prescribed with specific anti-inflammatory intestinal drugs mostly linked to the recording of IBD or its symptoms by the PCP (supporting the IBD indication). So we also provide the incidence including both, confirmed only and confirmed plus possible IBD cases. Although false positive could be higher among those last, the real incidence should be somewhere in between. Also, a comparison with the incidences found in previous studies aforementioned may provide information about the most valid and accurate algorithm (confirmed only or confirmed plus possible cases) for each research. A higher incidence is not expected, since none false IBD negative were estimated in the study cohort after checking other gastrointestinal records compatible with IBD diagnosis as reported elsewhere [7].

Due to the primary care nature of the source of data, pharmacological treatments prescribed or provided in the secondary setting were not available, such as the biological drugs (i.e. TNF-α inhibitors, mercaptopurine, or other immunosuppressants). To what extent such treatments are frequently used in this population is unknown.

Conclusions

In conclusion, this study suggests that current incidence in paediatric IBP underestimate the actual magnitude of the disease. The present study, conducted in girls aged 9-18 from 2002 to 2016, exhibits an incidence rate with a 2-to-6-fold increase compared to previous estimations in the Spanish paediatric population. Further nationwide studies should clarify this discrepancy. The extent to which clinical factors consulted to physicians constitute risk factors of the subsequent IBD onset, needs to be studied among girls and paediatric population. Quantification of those links can be informative for the early identification of IBD.

Acknowledgements

Ethical Approval

The investigators had access to secondary use of only fully anonymized data, and under this condition, no specific ethics review was required according to Spanish law.

Key points

1. A new estimation of the incidence of IBD among girls aged 9-18 years is provided (6.58-13.31 cases/100,000 person-years) that was higher than previously reported for paediatric Spanish population.

2. Incidence increased with age and fluctuated by years.

3. Clinical conditions were frequently consulted by the girls to primary care practitioners before IBD diagnosis, suggesting delay in IBD diagnosis in some cases.

4. The evaluation of those conditions as risk factors of IBD in comparison with girls without the disease is guaranteed to improve timely diagnosis.

5. Mesalazine was the most prescribed drug followed by azathioprine.

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