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Retrospective Study

Prevalence, phenotype and medication for the Paediatric Inflammatory Bowel Disease population of a State in Southeastern Brazil

Adalberto Lima Martins, Renata de Sá Brito Fróes, Maria da Penha Zago Gomes

Abstract

BACKGROUND

Inflammatory bowel disease (IBD) can lead to social and economic impacts worldwide. In Brazil, where its adult prevalence is increasing, the epidemiology of the pediatric population is not well-known, although there is a documented increase in pediatric IBD incidence in the world. Brazil has continental dimensions, and Espírito Santo is a State of Southeastern Brazil, region of the highest demographic densities and economically most important in the country.

AIM

Assess the prevalence, incidence, phenotype and medications in Southeastern Brazil pediatric population.

METHODS

Data were retrieved from the Public Medication-Dispensing System of the Department of Health in Espírito Santo state by carried out through from documentation required in order to have access to highly expensive medication from 1st of August, 2012 to the 31st of July, 2014. There were registered 1048 patients with IBD of all ages and of these patients the cases ≤ 17 years were selected. The data was obtained through the analysis

of administrative requests of these medications, and included medical reports, endoscopy exams, histopathology and imaging tests, which followed the Clinical Protocols and Therapeutic Guidelines of the Brazilian Government. Only confirmed cases of IBD are included in the study.

RESULTS

There were 55 pediatric patients/1048 registered patients (5.34%), Crohn's disease (CD) representing 30/55(55%), Ulcerative Colitis (UC) 24/55 (43.6%) and 01 unclassified IBD (U-IBD), with statistical difference from adult patients ($P = 0.004$). The prevalence of IBD in pediatric patients was 5.02 cases/100.000 inhabitants; the incidence in 2014 was 1.36 cases/100,000 inhabitants. The mean age at diagnosis was 12.2 years (± 4.2). There were 7 children diagnosed up to 06 years old, 7 from 07 to 10 years old and 41 between 11 and ≤ 17 years old. There was no difference in the distribution of UC and CD between these age categories ($P = 0.743$). There was no difference in gender distribution in relation to adults. Children and adolescents with UC had a predominance of pancolitis, unlike adults ($P = 0.001$) and used amino salicylates and immunomodulators for their treatment. Pediatric patients with CD did not present difference in diseases location but had a higher frequency of fistulizing behavior ($P = 0.03$) and perianal disease phenotype ($P = 0.007$) than adult patients. Patients with CD used more immunomodulators and biological therapy. Treatment with biological therapy was more frequently used in pediatric patients than in adults ($p < 0.001$).

CONCLUSION

Although the data from this study demonstrate incidence and prevalence have low rates in Southeastern Brazil these data demonstrate the severity of IBD in pediatric patients, with the need for early diagnosis and therapy, avoiding serious damage.

INTRODUCTION

Inflammatory bowel disease (IBD) can lead to social and economic impacts worldwide. In Brazil, where its prevalence is increasing, the epidemiology of the pediatric population is not well-known, although there is a documented increase in pediatric IBD incidence in the world^{1,2}. Represented by ³Ulcerative Colitis (UC), Crohn's Disease (CD) and Unclassified inflammatory bowel disease (U-IBD), these diseases have a chronic evolution, with more severe clinical manifestations and complex treatment when started in the pediatric age group^{3,4}. The frequency of IBD initiated in childhood and adolescence is described in up to 25% of patients^{3,5}.

The main signs and symptoms of IBD in the pediatric age range are diarrhea, abdominal pain and stunting, which can be confused with other diseases, causing a delay in diagnosis and inappropriate therapies. Considering more aggressive phenotypes and worse therapeutic response in this age group, early recognition of the disease becomes extremely important^{4,5,6}.

We can say that we still have few epidemiological studies in the pediatric age group, however this information is of relevance, as it can define characteristics specific to each region and provide improvements to the health system with programming of costs related to propaedeutics and treatment. In addition, early diagnosis and adequate therapy could provide better results, that is, deep remission, with better quality of physical, social and school health⁴.

Some epidemiological studies of IBD have been carried out in Brazil^{7,8}, however the majority was in reference centers for adult care, and others recent studies used the database of records of the "Sistema Único de Saúde (SUS)" or Brazilian Health Unic System^{9,10}. Brazil has continental dimensions but there is no obligation to notify a case of IBD in the country and also there is no unified registry, although the Brazilian government provides medication for the treatment of IBD through the sector of the supply of high-cost drugs for chronic diseases, which all citizens are entitled access to.⁴ The aim of this study is to evaluate the epidemiology, phenotype and treatment of IBD in pediatric patients in the state of Espírito Santo, a state of Southeastern Brazil, region of the highest demographic densities and economically most important in the country,

to contribute to possible improvements, both in the assistance and administrative areas of the health service.

MATERIALS AND METHODS

Study location and data collection

The study was conducted between the 1st of August, 2012 and the 31st of July, 2014 in Public Medication Dispensing System of the Department of Health of Espírito Santo, sector for Pharmaceutical Assistance, which is responsible for dispensing medications for patients with IBD in the whole State.

This study evaluated patients with a confirmed diagnosis of IBD aged ≤ 17 years old, from a total sample containing 1048 patients of all ages, with phenotype and treatment available, who received medications through the Federal Government and for whom the incidence and prevalence of IBD was determined in previous study⁹.

In medication-dispensing services the evaluation is conducted by a gastroenterologist doctor, in this case, the author of the research, who was responsible for dispensing the medication for IBD, and data analyzed was obtained through the analysis of administrative requests of these medications, and included personal identification documents, medical reports, endoscopy exams, histopathology and imaging tests, which followed the Clinical Protocols and Therapeutic Guidelines of the Brazilian Government^{11,12}.

As the study includes patients aged 17 years, we chose to use Montreal classification to established the phenotype of IBD for Crohn's disease (CD) and ulcerative colitis (UC)¹³. For the patients whose endoscopic examination, image, and histopathological, laboratorial examination associated to medical reports showed a difficulty to define CD and UC the terminology "unclassified inflammatory bowel disease" (U-IBD) was applied.

Dependent variables included the diagnosis, IBD classification, medications, new cases (diagnosis made less than 12 mo before the time of the process of evaluation at the

Pharmaceutical Assistance) and old cases (diagnosis older than 12 mo), distributed in the assessment year 1 (1st of August, 2012 to 31st of July, 2013) and year 2 (1st of August, 2013 to 31st of July, 2014). Independent variables included age and gender.

Study limitations

The study was conducted with secondary data and some information may not be complete. Not all patients with CD included in the study had an upper gastrointestinal endoscopy/biopsy, and magnetic resonance, medical reports and few older documents have been damaged due to time, making it impossible to define the localization of the disease in some cases.

In Brazil, medications for IBD are expensive and provided by the Public Healthcare System for patients treated in the public and private systems. However, it is possible that some patients in the private system obtained their oral medications directly from drugstores, without utilizing the public system.

Ethical considerations

This study was approved by the Ethics and Research Committee of the Nossa Senhora da Gloria Children's Hospital (CAAE 19602813.8.0000.5069) after obtaining authorization from the State Office for Pharmaceutical Assistance. The term of clarification and consent was waived because the data used is secondary data.

Statistical analysis

An Excel spreadsheet was used to collect all the data, then all patients aged ≤ 17 years of age when diagnosed were selected, building a new Excel table that was analyzed using SPSS Statistics 20.0 software. Data was tabulated and analyzed through descriptive analysis of frequencies, percentages, averages, and standard deviations (SD). To determine associations between categorical variables, a chi-square test was used, and Fisher's exact test was also used when appropriate. A p value of <0.05 was considered statistically significant.

Data from the Brazilian Institute of Geography and Statistics (IBGE) was used to calculate prevalence and incidence based on the estimated census of 2014, in which the total estimated population of Espírito Santo was 3.885.049 inhabitants¹⁴ and the

population of ≤ 17 years old was 1.095.669 inhabitants¹⁵. To calculate incidence, new cases arising in the second year of the study were used (1st of August, 2013 to 31st of July, 2014) and prevalence was calculated as the number of children (≤ 17 years) during the study period that end on the 31st of July, 2014 that received dispensed IBD-related drug prescriptions.

RESULTS

Incidence and Prevalence

Out of a total sample of 1048 patients analyzed in medication-dispensing services, at the Pharmaceutical Assistance in Espírito Santo, who were diagnosed with IBD, 55 (5.24%) were diagnosed at ≤ 17 years old, with a predominance of CD 30/55 (54.5%) and UC 24/55 (43.6 %) and 01 with a diagnosis of U-IBD, different from the sample of adult patients ($P = 0.004$).

In 2013, 33 patients were registered, and in 2014, 22 patients were registered, coming to a total 55 of cases. Out of the 22 cases registered in 2014, 14 were new cases, 07 of those were CD and 07 cases were UC. The calculate prevalence and incidence is based the estimated census of 2014^{14,15}. ² The prevalence of IBD in pediatric patients in the state of Espírito Santo, Brazil, was 5.02 cases/100.000 inhabitants/year, while the incidence in 2014 (year) was 1.27 cases/100.000 inhabitants/year. The prevalence of CD was 2.73/100,000 inhabitants and the incidence was 0.63 cases/100.000 inhabitants/year. The prevalence of UC was 2.19/100.000 inhabitants and the incidence was the same as that of CD (0.63 cases/100.000 inhabitants).

Demographic characteristics

Seven children were diagnosed up to 06 years old, 07 diagnosed from 07 to 10 years old and 41 between 11 and 17 years old and there was no difference in the distribution of UC and CD between these age categories ($P = 0.743$) are summarized in Table 1. The distribution regarding gender was shown in Figure 1, but without statistical difference ($P = 0.357$).

Phenotype disease and Medication

The distribution of UC and CD phenotype comparing with adult group and we can observe in group ≤ 17 years the highest frequency of pancolitis in UC and perianal disease in CD, show in Table 2. The behavior phenotype in CD and we can see perianal disease more associate with fistulizing disease in CD, show in Figure 2. The distribution of biologics used in this group was compared with adult group and no statistical difference were observed and can be seen in Table 3.

Oral aminosalicylates (mesalazine/sulfasalazine) were the drugs most used in UC and in CD we observed a greater use of the immunomodulators when compared to aminosalicylates and can be seen in Figure 3.

DISCUSSION

That is the first epidemiological study of the incidence and regional prevalence of inflammatory bowel disease in a pediatric / adolescent population in a state of our country, based in search in National Center in Biotechnology Information (NCBI). There is a documented increase in the incidence and prevalence of pediatric IBD in the world and although this information is of great value for the planning of the health system, the few existing studies present different methodologies, which makes a more reliable analysis difficult^{3,16,17,18,19,20}.

In this study, we observed that ⁵ the prevalence of IBD ≤ 17 years in the state of Espírito Santo, southeastern Brazil, in 2014 was of 5.02 cases/100.000 inhabitants/year (CD: 2.73/100.000 and UC: 2.19/100.000), higher than the prevalence of IBD in Mexico¹⁸, Central America in patients <18 years old with 0.18 cases/100.000 inhabitants, but much lower than other regions, as in the study by Ludvigson, 2017³ in Sweden, in the period of 1993 to 2010, where there were 75 cases/100.000 inhabitants (CD 29/100.000 and UC: 25/100.000) and the study of 2019 by Jones²¹ in Scotland, in the period of 2009 to 2018, which found prevalence in children under 17 of 106 cases/100.000 inhabitants. Roberts, 2020²² in a systematic review of pediatric IBD in Europe found few prevalence studies using national and regional data. The highest prevalence rates of CD was in Hungary ~ 60 /100.000, in the period from 2011 to 2013. Regarding UC, the highest prevalence was

~30/100.000 in 3 regions: Hungary, Sweden and Denmark²². In North America, in Canada (Manitoba), a 1978-2007 study showed an increase in prevalence from 3.1 to 18.9/100.000 in CD and UC from 0.7 to 12.7/100.000 inhabitants in UC²³.

The incidence of pediatric IBD in this study was 1.36 cases/100.000 inhabitants/year, with CD and UC with equivalent values of 0.63/100.000. Our incidence was higher than that observed in Argentina (0.4/100.000)¹⁷ and Mexico (0.04/100.000)¹⁸, but lower than in other areas of the world as noted in the systematic review of the incidence of IBD in children / adolescents from Sýkora, 2018¹⁶, from 1985 to 2018 which found the highest annual pediatric incidences of IBD were 23/100.000 person/years in Europe (Finland), 15.2/100.000 in North America (Canada) and 11.4/100.000 in Asia/Middle East and Oceania. However, the highest pediatric CD incidence was 13.9/100.000 in North America (Canada), followed by 12.3/100.000 in Europe (France). Regarding UC, the highest annual incidences of ulcerative colitis (UC) was 15.0/100.000 in Europe (Finland) and 10.6/100.000 in North America (Canada)¹⁶. In the analysis of incidence and prevalence we can conclude that we still have low rates.

The frequency of IBD in the pediatric range in our region was 5.34%, below the global values (10 to 25%)^{2,6}. Despite different methodologies, this study had a higher frequency than the West-Eastern European study in 2014, in children under 15 years old, which presented a frequency of 3% (45/1560 patients)¹⁹ and less than a study in Mexico in 2015 which showed that frequency in pediatric patients under 18 years old was 7.1% (32/479)¹⁸.

In the distribution of IBDs, there was a slight predominance of CD (54.5%) compared to UC. Worldwide data is quite variable. A study by Burisch, 2014 of West-Eastern Europe¹⁹ found Western have an equivalent distribution between CD / UC and in Eastern Europe, predominance of UC¹⁹. In Argentina¹⁷, equivalence between CD and UC was observed. The study by Van Limbergem in the United Kingdom, 2008⁶ observed in 416 pediatric patients <17 years old, a predominance of CD (66%) vs UC (23.7%), Buderus, 2015²⁰ in Germany, found a predominance of CD (64%) in relation to UC (29%) and Chaparro, 2018²⁸ in Spain (period of 2007-2017) also found a

predominance of CD (61.5%). In Mexico, the Yamamoto-Furusho study¹⁸ observed a predominance of UC in 2015 (85%). We still have a lot of diversity in the distribution of the disease.

In the study of the UC phenotype, pancolitis prevailed, similar to other pediatric studies worldwide^{16-18,21,24}. In addition, our study showed a statistical difference in relation to the adult group with a higher frequency of extensive disease (pancolitis) in younger people.

In pediatric DC, the ileocolonic form predominated, as in other studies: Germany²⁰, Italy²⁵, Spain²⁴, Argentina¹⁸ and Mexico.¹⁸ Four patients had involvement of the upper intestinal tract (16%), similar to the study in Spain (15.4%)²⁴ and different from the result in Germany (53.6%)²⁰. These differences may have occurred due to the limitations of the current study, as they were based on secondary data and possibly a smaller study of the upper gastrointestinal tract using imaging methods was performed.

Our study showed no statistical difference of the location's phenotype CD in relation to adult patients.

We observed a high frequency of perianal disease ("p") with 46.6% of pediatric/adolescent CD, which demonstrates the most serious behavior in this age group. Our data was higher than Germany study²⁰ with 11.5% of perianal disease, Canada²⁶ with 16% in 2019 and Spain²⁴ with 16.4% in 2018. When compared to the adult group, we observed the highest frequency of fistulizing behavior (B3) and perianal disease (p) in the pediatric age group, that is, more severe behavior in the youngest.

In the treatment of UC, oral aminosalicylates (mesalazine/sulfasalazine) were the drugs most used, compatible with current therapeutic recommendations²⁹. The use of corticoid was not evaluated in this study, as it is not dispensed by this state health care sector.

On the other hand, in CD we observed a greater use of the immunomodulators when compared to aminosalicylates, according to guidelines³⁰. Biological therapy was used in 56.7% (17/30) of pediatric patients with CD, while adult patients used it in 42.2% of individuals, but no statistical difference was found ($P = 0.126$). We were able to observe

that the use of medication is consistent with the data of the literature in line with the findings of international studies and recommendations^{29,30}, in our region.

CONCLUSION

In Brazil, where incidence and prevalence of IBD is increasing in adults, was observed that the prevalence and incidence in pediatric age is higher than other regions in Latin America, lower than in Europe and North America and in relation to the data worldwide, our pediatric IBD prevalence and incidence still low. Children and adolescents with UC had more extensive form (pancolitis), compared to adults, as in CD, fistulizing forms (B3) and perianal diseases ("p") were more prevalent, which led to the high frequency of biological therapy in these patients with IBD before the age ≤ 17 . These data, added to other epidemiological studies, demonstrate the severity of IBD in pediatric age group, with the need for early diagnosis and early intervention, with the correct use of specific therapy, avoiding serious secondary damages of the disease's evolution.

Although we recognize the limitations of this study as not all patients included have complete image study (magnetic resonance image, an upper gastrointestinal endoscopy/biopsy) and the use of secondary data based on documentation of Public Health System, it is the first epidemiological pediatric IBD data published of the country and even though more studies are need, this one shows data about our reality that can contribute to the planning of public health actions.

ARTICLE HIGHLIGHTS

Research background

Pediatric Inflammatory Bowel disease in a region of Brazil

Research motivation

The pediatric inflammatory bowel disease data are practically unknown in Brazil and South America.

Research objectives

To know the epidemiology of pediatric inflammatory bowel disease and its characteristics in Brazil, South America

Research methods

The data were retrieved from ² the Public Medication-Dispensing System of the Department of Health in Espírito Santo state of Brazil.

Research results

The prevalence and incidence in pediatric age is higher than other regions in Latin America. More severe behavior in the youngest.

The pancolitis is more frequent in ulcerative colitis and fistulizing and perianal disease is more frequent in Crohn's disease.

The biological therapy was used in the same way comparing pediatric and adult groups.

Research conclusions

We have little data on inflammatory bowel disease in Latin America. We need to know better the epidemiology, phenotype and medication used on the treatment of the inflammatory bowel disease in each region.

Research perspectives

Obtain better therapeutic approaches and contribute to the planning of the public health actions.

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