PROFILE OF PEDIATRIC CROHN'S DISEASE IN BELGIUM.

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Short title:First report on Belgian pediatric Crohn's disease registry.

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Abbreviations

Belgian IBD Research and Development Group	BIRD
Belgian Registry for Pediatric Crohn’s Disease	BELCRO
Belgian Society for Pediatric Gastroenterology, Hepatology and Nutrition	BESPGHAN
Clinical report file	CRF
C reactive protein	CRP
Crohn’s disease	CD
Inflammatory bowel disease	IBD
Gastrointestinal	GI
months	m
Pediatric Crohn’s Disease Activity Index	PCDAI
Physician’s Global Assessment	PGA
weeks	w
year	y
5-aminosalicylic acid	5-ASA
6-mercaptopurin	6-MP

Abstract

AIM: A Belgian registry for pediatric Crohn's disease, BELCRO, was created in which year. This first report aims at estimating incidence, describing disease presentation and phenotype and determining associations between variables at diagnosis and registration in the database.

METHODS: Through a collaborative network, children with previously established Crohn's disease and newly diagnosed children and adolescents (under 18 y of age) were recruited over a 2 year period. Data were collected by 23 centers and entered in a database. Statistical association tests analyzed relationships between variables of interest at diagnosis.

RESULTS: Two hundred fifty-five previously and newly diagnosed patients under 18 y of age were included. Considering 100 newly diagnosed patients out of 255 included patients, the approximate estimated incidence was $2.2/10^5$ children <18y/year (CI 1.5-2.8). Median age at diagnosis was 12.5 y (range: 1.6-18y); median duration of symptoms prior to diagnosis was 3 m (range: 1-12m). Fifty three % of these patients presented with a BMI z-score <-1. Neonatal history and previous medical history did not influence disease onset nor disease behavior. CRP was an independent predictor of disease severity. Steroids were widely used as initial treatment in moderate to severe and extensive disease. Over time, immunomodulators and biological were prescribed more frequently, reflecting a lower prescription rate for steroids and 5-ASA. A positive family history was the sole significant determinant for earlier use of immunosuppression.

CONCLUSION: In Belgium, the median age of children presenting with Crohn‘s disease is 12.5 y. Faltering growth, extensive disease and upper GI involvement are frequent. CRP is an independent predictive factor of disease activity. A positive family history appears to be the main determinant for initial treatment choice.

Registered on clinical trials.gov (B00920083829).

Keywords: Pediatric, Crohn's disease, registry, diagnosis, profile, children, disease phenotype

Introduction

The incidence of Crohn's disease (CD) increases especially in Westernized countries [1]. Approximately 25% of patients are affected during childhood [2]. In children, a more severe and extensive disease phenotype is described compared to adults [3]. The impact on the child's growth and development is an important factor determining treatment strategies.

The natural course of CD remains unpredictable. Based on adult literature, risk factors for severe disease are younger age at diagnosis, the presence of perianal disease and smoking [4]. In pediatrics, these risk factors need confirmation and other factors, possibly related to growth and development need to be identified. High concordance of CD in monozygotic twins and a positive family history for inflammatory bowel disease (IBD) in 5-20% confirms an underlying genetic susceptibility [5]. Environmental influence is proven by the deleterious effect of smoking and the rise in CD in immigrant populations from regions with low prevalence to regions with high prevalence [1]. Regional information, captured in registries, aims at providing insights in disease presentation, disease course and influencing environmental factors [6]. We therefore initiated a registry of Belgian pediatric CD patients (BELCRO). In this manuscript we report on patient characteristics at diagnosis and at inclusion for previously diagnosed patients.

MATERIALS AND METHODS

Population

BELCRO was initiated in May 2008 through a collaboration of the IBD working group of the Belgian Society for Pediatric Gastroenterology, Hepatology and Nutrition (BESPGHAN) and the Belgian IBD Research and Development Group (BIRD). The aim of the registry is to describe a cohort of old and newly diagnosed pediatric CD patients recruited over a 2 y period

and to prospectively follow these patients for 5 y. All Belgian pediatric and adult gastroenterology centers were invited to participate in the registry. Twenty-three pediatric and adult units, representing all major Belgian centers and members of the scientific committees have recruited their patients. The diagnosis of CD had to be established according to the Porto criteria[7]. Informed consent was obtained from the parents or legal guardians. The registry was explained in a comprehensible way to the patients and they gave their assent. The study protocol was established following the declaration of Helsinki and Good Clinical Practice guidelines, approved by the ethics committee ZNA Middelheim, Antwerp Belgium (nr 3147) and registered on clinical trials.gov (B00920083829).

Data collection

A chart analysis was performed for previously diagnosed CD patients (diagnosed before May 1st 2008). Data at diagnosis and at inclusion in the registry were extracted from the medical files into a standardized clinical record file (CRF). Data from newly diagnosed patients (diagnosed after May 1st 2008) were collected in the CRF. All data were entered into an Excell® database (Microsoft Corporation, Washington, USA) by a dedicated data manager (DRC Data management, Gent, Belgium). The procedure for data collection and ownership was described in a Charter by a steering committee comprising the principal investigator and representatives of the participating scientific societies.

Description of variables

The following information was collected from all patients at diagnosis: demographics (race, age, gender), neonatal history (mode of delivery, birth weight, gestational age, mode of feeding), family history (CD, ulcerative colitis, auto-immune diseases), previous medical history (infections, surgery, stressful events, food allergies), concomitant conditions (hepatitis, celiac disease, psoriasis, lupus), symptoms and signs at presentation (abdominal

pain, diarrhea, perianal disease, extra-intestinal manifestations), diagnostic work-up (including laboratory, endoscopy, histology and imaging) and treatment. Upon inclusion in the database, data on symptoms, vaccinations, therapy, concomitant conditions and laboratory values were recorded from previously diagnosed patients. Age categories (<6 y, >=6 y-<=12 y, >12 y) were defined to further stratify the population.

Disease severity was scored using the Pediatric Crohn's Disease Activity Index (PCDAI), a validated scoring system based on symptoms, biochemical parameters, clinical exam and growth[8]. When PCDAI was not available, Physician's Global Assessment (PGA) was obtained, based on the clinical evaluation of the patient by his physician. Diagnostic procedures were recorded and the involved intestinal areas or disease location were derived from endoscopic data, histology and imaging. Disease location was classified following the Montreal classification (ileal (L1), colonic (L2) , ileocolonic (L3), upper gastrointestinal (GI) (L4)) [9] as well as by the more recently published Paris classification [6](L4A upper GI involvement until the angle of Treitz and L4B upper GI involvement beyond the angle of Treitz). Data on initial treatment were collected and stratified in the following categories: enteral nutrition, rectal therapy, 5 ASA, antibiotics, steroids (budesonide, prednisolone), immunomodulators (6 mercapotpurine, methotrexate, azathioprine), biologicals (infliximab, adalumimab), tacrolimus and cyclosporine.

Statistical analysis

All data were arranged and processed for handling using Microsoft™ Office Excel and analyzed with SPSS 17.0. Descriptive statistics were used to describe the population features. Non-parametric association tests were used to investigate relationships between variables of interest. In particular, Fisher's exact tests were used to assess relationships between categorical variables. For continuous variable outcomes and categorical explanatory variables, Mann-Whitney U tests (Kruskal-Wallis tests when > 2 categories) were performed. In addition, multiple regression analyses (linear and logistic analyses) were carried out

whenever appropriate. All tests were performed on available cases only. Tests were carried out at a significance level of 5%. To avoid bias, previously diagnosed patients (before May 1st 2008) and newly diagnosed patients (after May 1st 2008) were compared for their differences and a separate analysis was performed for the differing factors. Logistic regression models were fitted to investigate the association between the 2 groups of patients and the recorded variables.

RESULTS

Demographics and neonatal data

Two-hundred fifty-five patients under 18 y at diagnosis (born after May 1st 1990), with established diagnosis of CD according to the Porto criteria [10] and living in Belgium, were recruited over a 2 y period (May 1st 2008 - April 30th 2010). In this population 100/255 patients were newly diagnosed and 155/255 were previously diagnosed. The estimated incidence of pediatric CD in Belgium would be $2.2/10^5$ children <18 y/year (CI 1.5-2.8) based on the latest Belgian population count < 18 y of age [11, 12]. Male/female ratio was 1.2 and 98% of pediatric patients were Caucasian. The remaining 2% was of Asian or South American origin. Neonatal data reported a median birth weight of 3.3 kg (range 1.4 - 4.6 kg), a median gestational age of 40 w (range: 28-42w). Caesarian section occurred in 29 patients (11%) and 78% were exclusively or partially breast fed for a median duration of 7 w (range 0-140w). In comparing newly diagnosed and previously diagnosed patients no significant difference appeared for the demographic and neonatal data.

Previous medical history

Seventy percent of patients were diagnosed by a pediatric gastroenterologist and just more than half in a university center. In the 3 m before diagnosis, 23% took antibiotics, 23% suffered from an infectious episode of which 40% were labeled a GI infection. Twenty-three

% experienced a major stressful event (i.e. defined as being stressful for the patient by the patient himself, his parents and the physician) and 42% had past surgery, of which ear-nose-throat surgery in 45% and inguinal hernia correction and circumcision in 15%. Disease related surgery was reported in 17%, consisting of abscess drainages and surgical fistula treatment. Eight patients had previous appendectomy (7%). In previously and newly diagnosed patients 24% and 7% respectively had disease related surgery prior to diagnosis. With this exception, no significant differences were found in the medical history of the previously and newly diagnosed patients.

Immunization data were available from 248 patients. Polio was recorded in 222 patients (86%). Fifty three patients received vaccines in addition to the national recommendations[13], including hepatitis A, yellow fever, influenza and typhoid. Six patients were vaccinated for varicella.

Passive smoking was present in 16% of patients, active smoking in 1%.

Family history

A positive family history for IBD in first degree relatives occurred in 29 patients (11.4%). CD was mentioned in 25 patients, ulcerative colitis in 4. Both conditions were mutually exclusive. Auto-immune pathology, including psoriasis, lupus, diabetes type I and celiac disease affected the broader family (parents, siblings, grandparents, cousins, aunts and uncles) of 35.9% of patients. Family history was similar in previously and newly diagnosed patients.

Presentation

Belgian pediatric CD patients presented at a median age of 12.5 y (range 1.6 -18.0 y) after a median duration of symptoms of 3 m (range 1-12 m). Median symptom duration prior to diagnosis did not differ in patients with a positive family history. Symptoms at diagnosis are

presented in Figure 1. The main presenting symptoms were abdominal pain (84%), diarrhea (72%) and weight loss or lack of weight gain (72%).

Of the 208 patients from whom data on height velocity was available, 29% presented with faltering growth. Height z-scores and BMI z-scores were available from 240 patients. Median z-score for height was - 0.39 (range – 5.35 to 12.71). Severe growth retardation (z-score < -2SD) affected 8.7% of the population. Median z-score for BMI was -1.04 (range -6.74 to 2.07). Sixty patients (25%) had a BMI z-score <= -2SD. The previously diagnosed group belonged mostly to the age category >12 y whereas median and mean age were comparable for previous and recent diagnoses. The previously diagnosed patients had lower z-scores for height: median -0.52 (range -5.35 to 5.87) compared to a median z-score for height of -0.23 (range -3.40 to 12.71) in newly diagnosed patients. (p=0,016).

Disease location and severity at diagnosis

Disease location was determined by endoscopy, histology and imaging and classified according to the Montreal and Paris classification. Results are shown in Table 1. Even though the diagnosis had to fulfill the Porto criteria, 191/255 patients underwent an upper endoscopy and the ileum was not evaluated in 12 patients. The upper GI tract was evaluated by imaging and/or endoscopy in 205/255 patients and was involved in 70%. Isolated ileal disease (L1) was present in 32 (13%), isolated colonic involvement (L2) in 62 (24%) patients, ileocolonic disease (L3) in 157 (61 %) and isolated upper GI involvement in 4 patients (2%).

The Paris classification subdivides upper GI involvement in L4A (proximal to Treitz ligament) and L4B (distal to Treitz ligament). These regions were involved in 144 (56%) and 83 (32%) patients respectively. Fourty eight patients had both L4A and L4B involvement. Perianal disease, as described in the PCDAI, occurred in 28% of patients. Stricturing disease

was mentioned in 15 patients (5.8%) at diagnosis. Out of the 245 patients in whom extra intestinal manifestations as defined by the PCDAI were recorded (erythema nodosum, arthritis, uveitis, arthralgias, pyoderma gangrenosum), 72 scored positive (29%). Disease severity was measured by PCDAI or PGA. The results are presented in Table 2. Disease was mild in 24%, moderate in 43% and severe in 28% of the cohort. Disease severity and disease location were comparable in previously and newly diagnosed patients.

Therapy

Treatment at diagnosis was classified according to the following categories: enteral therapy, rectal therapy, 5-ASA, antibiotics, steroids (prednisolone, budesonide), immunomodulators (6MP, methotrexate, azathioprine), biologicals (infliximab, adalumimab), cyclosporine and tacrolimus. At diagnosis, monotherapy was initiated in 23.9% of patients: steroids in 10.9% or 5 ASA in 9%. In the majority of patients, combination therapy was initiated with steroids, immunomodulators and 5 ASA as main components in respectively 64%, 43% and 40%. In the previously diagnosed patients, the proportion of patients on 5-ASA as initial treatment was higher compared to the newly diagnosed patients.

Previously diagnosed patients at time of inclusion in the database

For the 155/255 previously diagnosed patients the median follow-up at registration in the database was 2.7 y (range 0.3 - 8.2y) with a median age at registration of 15.9 y (range: 5.3 - 19.8y). The majority of patients had inactive disease (70.4%) and was asymptomatic. Their median height z-score was -0.47 (range -2.69 to 4.82), their median BMI z-score -0.32 (range -2.98 to 1.91). Abdominal pain was mentioned in 28.2 %, diarrhoea in 12.4 %, weight loss in 12.5 %, perianal disease in 7.2 % and extra-intestinal manifestations in 10.5%. Twenty patients had undergone surgery of which 17 were disease related: 3 abscesses, 3

fistulectomies, 6 ileo-caecal resections and 1 small bowel resection, 3 colonic resections and 1 fissure treatment. The majority (84.2%) had received combination treatment including steroids (65.1%), immunomodulators (65.8%), 5-ASA (48.7%) and/or biologicals (28.9%). At the date of inclusion in the registry only 18/155 patients received steroids as part of their therapy (9 budesonide, 9 prednisone). The disease activity was inactive in 8/18 patients, mild in 7/18 patients and moderate in 3/18. In 14 other patients start and stop dates of steroid therapy were imprecise, so they possibly had ongoing treatment.

Associations at diagnosis* (Table 3*).

The analysis was carried out on the entire group for variables that did not differ in previously and newly diagnosed patients. A separate analysis was performed for the differing variables in order to avoid bias due to group heterogeneity. In the previously diagnosed group, follow-up data obtained at registration in the database were also analyzed.

Neonatal variables such as birth weight, gestational age and mode of delivery revealed no associations with age, disease location or disease severity at diagnosis. Breastfed children were diagnosed at a younger age (p=0.0003) and tended to have more colonic disease (L2) (p=0.013). No associations were found between medical history (antibiotic use, major stressful events, surgery and/or infections prior to diagnosis) and disease location or severity at diagnosis. Younger patients at diagnosis had more infectious episodes before diagnosis (p=0.015) and received more frequently antibiotics as initial treatment (p= 0.002), as well as steroids and 5 ASA (p=0.01; p=0.004). Their family history for IBD was more often positive (p=0.032). Age at diagnosis was not associated with disease location when analyzing the entire group but in the previously diagnosed, patients presenting with L3 tended to be older (p=0.057). Height z-scores (p=0.004) and ileocolonic disease location (L3) (p=0.011) were associated with more severe disease at diagnosis; patients with ileal (L1) (p= 0.013) disease

had less severe disease at diagnosis in univariate analysis. Nevertheless multiple regression analysis withheld only CRP as independent predictive factor for disease severity.

In the total cohort, several disease related factors influenced the initial treatment choice. Patients with moderate to severe disease and with L4 involvement were more likely to receive steroids in combination therapy (p= 0.045 and p=0.048) and enteral therapy in combination (p=0.005 and p=0.043) as initial management. Initial treatment with immunomodulator monotherapy was associated with height z-score, disease severity, L1 and L4 location, but the number of patients on this treatment was extremely limited (4 patients) as were patients on antibiotic monotherapy (4 patients). Patients with L1 involvement had more often antibiotic combination therapy (p=0.032).

In newly diagnosed patients, steroids were less likely to be used in patients with perianal disease (p=0.006) and patients with upper GI involvement (L4A) tended to be older (p=0.047). Patients with lower z-scores for height were more likely to start enteral nutrition at diagnosis (p=0.002).

Associations between variables at diagnosis and at inclusion for previously diagnosed patients (Table 4).

During the follow up of previously diagnosed patients, we noticed an important effect of the disease duration on several factors. Patients with a longer disease course at inclusion were diagnosed at a younger age (<0.001) and had better z-scores for height at diagnosis (p= 0.008). They were more likely to have had 5 ASA at diagnosis (p<0.001). An association was found between the z-scores for height at diagnosis and BMI z-scores at inclusion (p=0.025) with weight as interfering factor indicating a better weight gain over time compared to growth. Patients with concomitant conditions at diagnosis had a better height z-score at inclusion (p=0.001).

At the time of inclusion, patients with mild disease were more likely to have had steroids at diagnosis (p=0.004; OR=3.8 (95%CI 1.7-8.4). Patients with L3 had less severe disease at inclusion (p=0.02; OR 2.8- 95%CI 1.1-7.4), in contrast to patients with L1 who received less steroids (p=0.03; OR 0.3 -95%CI 0.1-0.9). Need for surgery was only influenced by disease behavior (S) (p=0.001; OR 6.8 -95% CI 1.8-25.3) not by disease severity, location or other treatment modalities. No further significant associations were found between disease related elements such as disease severity or disease location and initial treatment, but a positive family history for IBD was associated with the use of 5-ASA at diagnosis (OR 2.1 95% CI 1.07-4.49), and 5-ASA and immunomodulators during follow up (p=0.02; OR 2.5- 95%CI 1.1-4.3 and p=0.004; OR 2.7 - 95%CI 1.3-5.5).

There was a decrease in the use of steroids and 5-ASA (p= 0.001; OR 0.02 -95%CI 0.002-0.3; p=0.001; OR 0.03 -0.004-0.3) and an increase in prescriptions of immunomodulators (p=0.03; OR 1.8-95%CI 0.08-41.1) over time, paralleling a decrease in disease severity (p=0.01) (Table 5). The decrease in disease severity can be reflected by the decrease in perianal disease and extra-intestinal manifestations between diagnosis and inclusion in the database, respectively 28% vs 7.2% and 29% vs 10.5%. The association between immunomodulator monotherapy at diagnosis and a better height z-score at inclusion is based on too few patients (4 patients).

DISCUSSION

This is the first report on Belgian pediatric CD patients. Nationwide recruitment by pediatric and adult gastroenterologists, members of national scientific societies BESPGHAN and BIRD, intended to reach as many pediatric patients as possible. Even though virtually all pediatric GI centers caring for pediatric IBD patients participated in the study, it is impossible to evaluate the exact number of pediatric patients treated by adult gastroenterologists. It is

however improbable that adult gastroenterologist would treat patients below the age of 16 y. Therefore the incidence or prevalence rate presented here is but an approximation but the best one possible. A better alternative would be a centralized national registry based on health insurance data.

Based on BELCRO data, the estimated incidence of CD in Belgian children was 2.2/100 000 children <18y/y. This number compares with previous reports from France and Holland[11, 12], whereas incidence increases to 4.9/100000/y in Sweden [14] and 7/100 000/y in Finland[15]. There is a clear North-South gradient with a higher prevalence in Northern countries [1]. The median age of disease onset in BELCRO patients is comparable to what is found in surrounding countries [3, 11, 12, 14-19]. In contrast to the adult population, the majority of pediatric patients are male. Female preponderance started to show from age 15 y on. Median duration of symptoms prior to diagnosis was 3 m, which is shorter than in surrounding countries[18]. A possible explanation is that specialized medical care is easily accessible in Belgium, professional referral is not mandatory, travel distances are short and waiting lists are usually short or non-existent. Health insurance is offered to all citizens. There are no public campaigns, thus general awareness of CD is probably comparable to surrounding countries. The majority of patients were Caucasian, including immigrants from North Africa and Turkey for whom no subset was made.

Neonatal history and previous medical history did not neither influence disease severity nor disease location in this cohort. Younger age at diagnosis was associated with breastfeeding and an infectious episode prior to diagnosis. Seventy eight percent of BELCRO patients have been (partially/exclusively) breastfed in the neonatal period. These results compare to 71% of mothers starting breastfeeding in the general population [20]. The association between breastfeeding and young age at diagnosis, found in our cohort, differs from the protective effect suggested by other, limited data on the subject in pediatric IBD [21]. The relevance of the

correlation between breastfeeding and L2 remains to be confirmed. The breastfed group was heterogeneous and recall bias is often a problem in studies recording breastfeeding [22]. Therefore these data should be interpreted with extreme caution. In almost a quarter of children, an infectious episode was noted in the 3 m before diagnosis of which 40% was labeled a GI infection. Most of them belonged to the younger age category at diagnosis. This association is not surprising, as younger children are more prone to infections in general.

Vaccination data indicate good adherence to the vaccination scheme of the American Academy of Pediatrics also recommended by the Belgian authorities[13]. Only Polio vaccination is mandatory. General vaccination coverage is known to be over 80% because all recommended vaccinations are offered free of charge in special pediatric clinics [13, 23]. For CD patients additional vaccinations were recently recommended to prevent opportunistic infections [24-26]. Adherence to these recommendations is very low so far. We note that even though national vaccination coverage is excellent, the information is often not recorded in the medical files or not transferred when patients make a transition to adult care. Clearly, more attention is needed in documenting and updating vaccination status at diagnosis knowing the risk of opportunistic infections in this patient group due to the immunosuppressive medication as part of their usual treatment.

Abdominal pain, diarrhea and weight loss were the predominant clinical symptoms as was reported in literature [16, 18]. A BMI z-score below -1 was noticed in half of our pediatric patients. The importance of growth failure as a presenting feature of CD still needs to be emphasized. Early treatment and adequate nutrition are crucial for catch up growth and achieving full height and weight potential. The previously diagnosed group demonstrates symptom improvement following treatment and a decrease in growth failure. Height z-scores were inversely correlated to disease severity meaning less severe disease improved growth, reflected by better height z-scores. The relationship between BMI z-scores at inclusion and

406 height z-scores at diagnosis, imply in general an even better weight gain compared to growth
407 catch up. In the newly diagnosed population however, patients with lower z-scores were more
408 likely to receive enteral nutrition as part of the initial therapy indicating a recent, more
409 adequate therapeutic strategy for growth retardation at diagnosis. Certain data link growth
410 impairment to disease location [18], this could not be confirmed in our cohort. The size of the
411 study population or the limited group of patients with severe growth retardation may influence
412 this result.

413 BELCRO confirmed that children with CD present with extensive and severe disease and with
414 high upper GI tract involvement. Details on the upper GI tract findings were not available at
415 this stage and it is possible that they were mainly not specific as involvement was based on
416 endoscopic and/or radiologic data. While evaluation of disease location for different age
417 categories, confirmed the finding of predominant colonic disease in the children under 6y of
418 age [3, 11, 16, 17], it has to be stated that this was a very small group and the difference with ileal
419 and ileo-colonic disease is small.

420 The majority of patients had mild to moderate disease at diagnosis as evaluated by PCDAI
421 and PGA. Even though ileal and ileo-colonic disease seemed to be associated with disease
422 severity, multiple regression analysis only defined CRP as an independent risk factor for
423 disease severity. CRP is not part of the PCDAI as a reflection of disease severity but has
424 proven useful in several studies as a predictive factor for treatment response and to reflect
425 mucosal healing [27-29].

426 Family IBD was more often found in young patients, possibly due to an earlier expression of
427 the disease in the genetically predisposed. Only a positive family history for IBD influenced
428 initial treatment choice for 5-ASA and rapid introduction of immunomodulators. The high use
429 of 5 ASA reflects treatment schedules before 2008, when this drug was still frequently used
430 for Crohn's colitis. Recent meta-analysis does not confirm its efficacy in CD [30].

Our data demonstrates the importance of adequate therapy at diagnosis as more severe initial treatment results in less severe disease over time. Physicians in this cohort were definitely compelled to use steroids in combination therapy as initial treatment for more severe disease. After a mean follow up of 2.7 y for a subgroup, patients who presented with severe disease were more likely to receive steroids as initial treatment and were also more likely to have extensive disease (L3), while at inclusion, those patients appeared to be more controlled with inactive PCDAI scores. The opposite is true for patients with isolated ileal disease. While 65.1% of patients at inclusion had received steroids as part of their previous treatment, only 11.6% were still on this treatment. These findings are markedly better than the American data where, even though 61% of children showed a response to steroid treatment at 1 y, 31% developed steroid dependency [31]. Another study showed a 40% relapse within 18 months after discontinuation of this treatment [32]. Because of relapse rates, important side effects of steroid treatment and to improve long term outcome, alternative maintenance therapy and even induction therapy are investigated such as early immunomodulator use [32, 33], enteral therapy and in severe cases top down therapy with biologicals[34]. Enteral therapy, an effective treatment in the pediatric CD population, induces remission, improves growth and leads to mucosal healing[35-37]. Despite the safety of enteral therapy, our data demonstrate its very limited use as an initial mono therapeutic approach. The way this treatment is introduced by the medical team and the support to the patient and the parents determines its success. In the newly diagnosed patients we notice its increased use for patients with growth retardation. In this cohort disease location, disease behavior and age at diagnosis did not influence treatment choice at diagnosis and disease outcome, except for patients with stricturing disease whom had a greater need for surgery during follow up.

Immunomodulators were frequently prescribed, while biologicals only have a very limited place at diagnosis. Step down therapy was used as initial treatment in 2 patients because of the

extreme severe presentation of disease. A significant increase ($p<0.001$) in biological therapy and immuunmodulators is noticed over time, reflecting the step up therapy generally used in pediatrics. Today, except for the use of budesonide in mild to moderate ileal disease and the use of biologicals in fistulizing disease [38], therapeutic strategy is not influenced by disease location or behavior even though we notice in our cohort that patients with extensive disease tend to receive steroids more frequently at diagnosis and biologicals in combination therapy during follow up. Physicians are less inclined to use biologicals in ileal disease in order to avoid stricture formation. Recent American data compared the use of biologicals and immunomodulators within the first 30 days after diagnosis in a diverse group of newly diagnosed CD patients. No significant outcome differences were noted except that infliximab treated children tended to be sicker at diagnosis[39]. The RISK study group looked prospectively at the patients with deep ulcerations on colonoscopy at diagnosis. This was associated with worse clinical parameters at diagnosis and worse disease severity scores (PCDAI/PGA) at 1 y follow-up, more so for patients who lacked treatment with immunomodulators or biologicals within 3 months after diagnosis[40]. These findings indicate the possible important effect of adequate initial treatment on long term outcome data. Tailoring treatment becomes the subject of multiple studies; therefore the study of natural disease history is an important starting point. Further follow up of the BELCRO cohort will help to confirm or infirm whether step down therapy in severe and extensive cases is indicated.

BELCRO illustrates the management of pediatric CD in Belgium. Treatment trends change over time even though clear guidelines on pediatric CD treatment are lacking. Actual management is based on adult experience and expert opinion.

This first report of Belgian pediatric data confirms that pediatric CD patients present with extensive, severe disease and frequent upper GI involvement. Evaluation of factors

influencing onset of disease, disease location and disease severity remains difficult because of multiple interferences. At diagnosis neonatal parameters or previous medical history do not influence disease onset and development. The role of breastfeeding needs to be further defined. High dose corticosteroids at diagnosis seem to determine outcome and disease behavior over time. This confirms the importance of adequate and sufficient therapy from the start even though more recently, in pediatrics, we try to avoid long term steroid treatment because of the known side effects and possible alternatives are being used more often such as enteral therapy and early immunomodulators. Not disease location, not disease severity, not age at diagnosis influenced initial treatment choice, only family history played a role in this cohort. The initial follow up data illustrates an evolving therapeutic strategy. Follow-up of this cohort will provide a better insight in the impact of therapeutic strategy on disease course by comparing previously and newly diagnosed patients. Presenting features should help determine individualized therapeutic regimens in the future.

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