Diagnosing and treating pediatric Crohn's disease patients : is there a difference between adult and pediatric gastroenterologist's practices ? Results of the BELCRO cohort

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Introduction

In many countries the cut off age for pediatric care lies between 15-18 y of age (1). Above that age, patients are transferred to gastroenterologists for adult patients. Adequate transition for these patients has been the subject of many publications (1-3). Even though pediatric Crohn's disease (CD) patients differ from adults (4), there is often a grey zone for teenagers, whom gastroenterologists accept under their care.

Pediatric CD patients present more often with severe and extensive disease, growth retardation and pubertal delay (4,5). Growth is specific to childhood and adolescence and it is a crucial factor at diagnosis. Disease management needs to incorporate the achievement of full growth potential (6). Even though general treatment practices for pediatric care are derived from adult practice, specific approaches such as nutritional therapy, have proven to be particularly efficient in the pediatric age group (7). Specific criteria for the diagnosis of pediatric inflammatory bowel disease (IBD), the Porto Criteria, have been published evoking the importance of clinical, biochemical and endoscopic evaluation of upper and lower gastrointestinal (GI) tract as well as small bowel imaging (8). The diagnostic yield of an upper endoscopy in pediatric CD is around 10% in recent studies (9,10), while upper endoscopy in adult care is not considered mandatory. In this article we review the difference in presentation, diagnostic procedures and initial treatment between pediatric CD patients registered in the Belgium registry for pediatric Crohn's disease (BELCRO) by pediatric gastroenterologists and gastroenterologists for adult patients. The BELCRO database 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 registry recruited previously and newly diagnosed pediatric CD patients over a 2 y period and is following them prospectively for 5 years. All Belgian pediatric and adult gastroenterology centers were invited to participate in the registry. More details about the recruitment and the initial findings of this cohort were published elsewhere (11).

Materials and methods

In the BELCRO database 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) and 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. Data on initial treatment were stratified in the following categories : enteral nutrition, 5 ASA, antibiotics, steroids (budesonide, prednisolone), immunomodulators (6 mercapotpurine, methotrexate, azathioprine), biologicals (infliximab, adalimumab). Disease severity was scored using the Pediatric Crohn's Disease Activity Index (PCDAI) (12). Physicians treating adults do not have the habit of measuring PCDAI, so when the PCDAI was not available, Physician's Global Assessment (PGA) was obtained. Disease location was derived from endoscopic data and imaging and classified according to the Montreal classification (ileal (L1), colonic (L2), ileocolonic (L3), upper gastrointestinal (GI) (L4))(13) as well as by the more recently published Paris classification (L4A upper GI involvement until the angle of Treitz and L4B upper GI involvement beyond the angle of Treitz) (14). Whether the diagnosing physician was a practitioner in pediatric or adult care was indicated in the database (11).

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Submission date : 30/08/2013
Acceptance date : 26/10/2013

Statistical analysis

All data were arranged for handling using Microsoft™ Office Excel and analyzed with SPSS 20.0. Non-parametric association tests were used to study relationships between variables of interest. In particular, chi-square tests were applied to evaluate associations between categorical variables. If necessary due to low expected cell count, Fisher's exact tests were considered. For continuous outcome variables and categorical explanatory variables, Mann-Whitney U tests were performed. In addition, the effect of age on the aforementioned associations involving non-treatment variables was studied using logistic regression. The effect of a tertiary care center was also analysed by logistic regression analysis. Furthermore, a backward stepwise regression to find a final model, was performed.

Tests were carried out at a significance level of 5% and only on complete cases for the given test.

Results

Population

The BELCRO database includes 255 patients. Hundred eighty-two (71%) patients were diagnosed by a pediatric specialist and 73 (29%) by an adult specialist (11). These two groups will further be called 'peds' and 'adult'. Median age at diagnosis for the whole group was 12.5 y (range 1.6-18 y). Median age at diagnosis for the peds group was 12.2 y (range 1.6 to 17.3 y), which was significantly younger than the median age of the adult group : 14.3 y (range 4.8 y to 18y) ($p < 0.001$). However, of the 16 patients under 12 y of age who were diagnosed by gastroenterologists for adults, the youngest was 4.8 y old. Further results were corrected for this significant age difference between both groups. Diagnosis was less frequently made in a tertiary care center for the adult group 26/73 (37%) compared to the peds group 106/182 (58%) ($p = 0.002$; OR = 0.42 ; 95% CI 0.24-0.74). No further differences were found between the peds and adult group regarding gender, race, or the proportion of patients included prospectively and retrospectively in the cohort.

Medical history and presentation

No differences were found between both groups in the neonatal factors recorded at diagnosis (gestational age, delivery mode, breastfeeding) or passive and active smoking. In the peds and adult group, the number of first degree relatives with IBD was similar, but while correcting for age we noticed that more pediatric patients, diagnosed by adult gastroenterologists had a family member affected with CD ($p = 0.039$, OR = 2.07 ; 95% CI 1.04-4.12). There were no differences in specific CD related surgery. Further medical history was comparable between both groups.

Disease presentation at diagnosis was similar in both groups. The complaints of abdominal pain, diarrhea, general functioning as well as the clinical findings for extra-intestinal and perianal disease were comparable. The presence of concomitant conditions did not differ significantly. Height and weight were significantly different because of the median age difference in both groups. Growth retardation (z-score < = -2 SD), standardised by Body Mass Index (BMI) z-scores, was present in 25% of patients and in 8.7% of patients when standardised in height z-scores. There was no significant difference between the adult and peds group regarding growth retardation. Disease severity, evaluated by PCDAI or PGA was also comparable at diagnosis. Disease was inactive in 5%, mild in 24%, moderate in 43% and severe in 28% of the cohort (15). Disease location was similar in both groups using Montreal or Paris classification when corrected for age.

Diagnostic Procedures

Ileo-colonoscopy, upper GI endoscopy, abdominal computed tomography (CT-scan), magnetic resonance Imaging (MRI), contrast studies (upper GI series and small bowel follow through), abdominal ultrasound, white blood cell scan, PET-scan and capsule endoscopy were mentioned as diagnostic procedures (Table 1).

Endoscopic full bowel evaluation and small bowel imaging is recommended at diagnosis as stated by the Porto Criteria (8). Colonoscopy was performed in 252 patients (99%). The terminal ileum was not visualised in 12 (5%) patients (11 peds, 1 adult). There was no significant difference in the performance of colonoscopy between peds and adults.

In 3 patients, colonoscopy was not mentioned, 1 patient had only a small bowel follow through, another patient an abdominal ultrasound and one received a small bowel follow through and abdominal ultrasound as sole diagnostic procedures.

Upper endoscopy was performed in 191 (75%) patients. Pediatric gastroenterologists performed significantly more upper endoscopies at diagnosis compared to their adult colleagues (83% vs 55%) ($p < 0.001$, OR = 3.51 ; 95% CI 1.85-6.69). This difference was specifically relevant in patients with severe disease even though presenting symptoms between both groups did not differ.

Small bowel involvement was evaluated by different techniques : 38 by CT abdomen, 33 by MRI, 65 by contrast studies, 10 by white blood cell scan and 1 by capsule endoscopy. All were used in similar ways by pediatric and adult physicians.

Abdominal ultrasound was used in 144 (56%) patients during diagnostic workup with a significant higher frequency in the peds group ($p < 0.001$, OR = 4.10 95% CI 2.21 – 7.60), but it was not the procedure that made the diagnosis.

Of the 191 patients having had upper and lower endoscopy, only 97 (51%) completed the workup with small bowel imaging (19 abdominal CT, 6 abdominal CT and MRI, 21 MRI, 48 contrast studies, 2 white blood cell

Table 1. — **Diagnostic procedures at diagnosis adult vs peds**

Diagnostic Procedure	Total n = 255	Adult n = 73	Peds N = 182	P	OR (95% CI)
Colonoscopy	252	72	180	NS	
Upper endoscopy	191	40	151	< 0.001	3.51 (1.85-6.69)
CT abdomen	38	11	27	NS	
MRI abdomen	33	7	26	NS	
Small bowel Follow through	65	23	42	NS	
Abdominal Ultrasound	144	23	121	< 0.001	4.10 (2.21-7.60)

NS = non significant.

scans and 1 capsule endoscopy). It means that only 97/255 patients (38%) met the Porto Criteria. In the remaining 94 patients no small bowel imaging was mentioned.

The Porto criteria were published in 2005. Seventy three of 255 (29%) patients were diagnosed before or during 2005 (56 peds - 17 adult) and could not be aware of those criteria. In patients diagnosed after 2005, colonoscopy was performed in 180/182 (99%) cases. Of those 180 patients, 135 (74%) had also upper endoscopy. Results for small bowel imaging were available in 64 (35%) of these 135 patients meaning that 35% of patients diagnosed after 2005 met the Porto Criteria. Forty five (70%) were diagnosed by a pediatric physician and 19 (30%) by a physician for adults.

Initial treatment

Because more peds patients were diagnosed in a tertiary care hospital, we corrected the treatment for the institution in which they were diagnosed. It seemed that the effect of institution was not significant. All treatment is presented in table 2.

Monotherapy, mostly steroids or 5-ASA, was initiated in the minority of patients (24%). Twenty-eight/255 (11%) received corticosteroid monotherapy (13 peds/15 adult). Immunomodulator monotherapy was prescribed in 3 patients from the adult group. 5-ASA as monotherapy was prescribed more by adult physicians ($p = 0.048$, OR = 2.5 95% CI 1.01-6.4).

In 65% of patients steroids were part of their combination therapy, immunomodulators in 44% (80% peds vs 20% adults) and 5-ASA in 41%. Of the 155 patients diagnosed before 2008, 90 (58%) received 5-ASA in comparison to 38/100 (38%) diagnosed after 2008.Three patients received biologic therapy at diagnosis (2 peds, 1 adult), all as part of a combination therapy (15).

Adult gastroenterologists were less inclined to use combination therapy comprising steroids ($p < 0.001$, OR = 0.34 ; 95% CI 0.19-0.62), immunomodulators ($p = 0.004$, OR = 0.41 ; 95% CI 0.22-0.75), antibiotics ($p = 0.001$, OR = 0.19 ; 95% CI 0.07-0.49) or enteral supplements ($p = 0.037$, OR = 0.11 ; 95% CI 0.01-0.88). The use of 5-ASA as part of a combination therapy was similar in both groups. Adult gastroenterolgists used enteral supplements twice, whereas it was prescribed in 21 (11.5%) peds patients. Only one single patient was treated with exclusive enteral nutrition.

Discussion

The majority of pediatric IBD patients in Belgium were diagnosed by a pediatric physician in a tertiary care centre. In Belgium, these centres tend to concentrate specialized care through pediatric subspecialties. Still, around a quarter of the BELCRO patients was diagnosed by adult specialists ; more so in pediatric patients having a family member affected. Possibly, those patients were referred to the adult physician taking care of the other family member. Whereas pediatric gastroenterologist follow IBD patients and their parents in the first years of the disease, focussing on growth and development, adult gastroenterologists often expect their patients to be more responsible and independent towards their disease and treatment (1-3). IBD care for adults is more common in peripheral hospitals compared to IBD care for children.

Nationwide recruitment by pediatric and adult gastroenterologists, members of national scientific societies BESPGHAN (Belgian Society for pediatric gastroenterology, hepatology and nutrition) and BIRD (Belgian IBD Research and Development), intended to reach as many pediatric patients as possible and represents the actual care takers. Even though participation was large (almost all tertiary care centers of pediatric GI participated), it was not complete. Even though almost all pediatric GI centers participated, covering most pediatric IBD patients followed by a pediatric GI, not all patients gave their consent. Evaluating how many pediatric IBD patients are followed by adult GI specialists is impossible as there is no national registration of (pediatric) patients with IBD. Therefore this registry is the most complete data available in the country.

This is the first report on differences in diagnostic and therapeutic strategies between pediatric and adult gastroenterologists at the time of diagnosing pediatric CD.

Previous medical history and disease presentation was similar in both groups. Disease presentation did not influence the choice of referral.

Recently, the Paris classification was established to evaluate disease location and disease behaviour more

Table 2. — **Treatment at diagnosis in the group diagnosed by gastroenterologists for adults (adult) vs pediatric gastroenterologists (peds) corrected for age**

Therapy	Total n = 255	Adults n = 73	Peds N = 182	P	OR (95% CI)
Monotherapy :					
– 5 ASA	28	14	14	0.016	2.5 (1.01-6.4)
– Corticosteroids	28	15	13	NS	
– Immunomodulators	3	3	0	NS	
– Enteral therapy	1	0	1	NS	
Combination therapy :					
– 5 ASA	100	23	77	NS	
– Corticosteroids	165	33	132	< 0.001	0.34 (0.19-0.62)
– Immunomodulators	111	22	89	0.006	0.41 (0.22-0.75)
– Antibiotics	64	5	59	< 0.001	0.19 (0.07-0.49)
– Enteral supplements	23	2	21	0.011	0.11 (0.01-0.88)
– Biologicals	3	1	2	NS	

NS = non significant. Corticosteroids = prednisolone and/or budesonide ; Immunomodulators = azathioprine and/or 6 mercaptopurine and/or methotrexate ; Biologicals = infliximab and/or adalimumab. Enteral therapy = Modulen®.

adequately for children (14). Comparing ileo-colonoscopies and gastroscopies, no differences in disease location according to the Montreal classification and Paris classification were noticed once data was corrected for age.

Pediatric and adult gastroenterologists differed in their diagnostic approach. The Porto criteria were published in 2005 as consensus-based diagnostic criteria for pediatric IBD. These recommend upper endoscopy and ileo-colonoscopy as part of the diagnostic workup (8), however not all pediatric guidelines agree on this (16,17). Upper endoscopy was performed in only 75% of patients, with a preponderance of adult gastroenterologists not performing the examination (45% vs 17%), a significant difference especially in the most severely sick children even though there was no difference in presenting symptoms between adult and peds. BELCRO scores better than the European standards published from the Eurokids database where only 64% had both examinations at diagnosis (18). Whether diagnosing upper GI disease affects disease course, treatment and outcome is yet to be determined.

Only 38% of the work-ups met the full Porto Criteria. However, 73 patients (29%) were diagnosed before these criteria were published. In the 35% who adhered to the Porto Criteria after 2005, a similar proportion was diagnosed by adult gastroenterologists compared to the entire BELCRO cohort (30% vs 29%).

Differences in treatment strategy between pediatric and adult gastroenterologists for pediatric IBD patients have not been reported but a clear difference in practice appears from the BELCRO data. First of all, the possible influence of tertiary care centres on the therapeutic approach was ruled out.

The main difference in treatment between both groups was the fact that adult physicians prescribe more monotherapy while pediatric physicians feel safer using treatment combinations.

Despite the popularity of exclusive enteral nutrition described for pediatric CD patients (19), this treatment modality was not used. Often, its success is mainly dependent on the motivation of the patient and the support of the family. Not many hospitals have adequate support programs to increase the chances of success with enteral nutrition. Despite this, enteral supplements were more often prescribed by pediatric physicians reflecting their concern for nutritional status and growth.

5-ASA for Crohn's colitis was not withheld as efficient therapy in a meta-analysis in 2008. A decrease in its use since 2008 is reflected in this cohort (20).

In conclusion, pediatric and adult expert physicians differ in their approach for diagnostic workup and therapeutic strategy of pediatric CD. The relevance on disease outcome is yet to be determined.

Aknowledgement

The BELCRO cohort was funded by a Research Grant from MSD Medical Belgium.

We thank Drs. Hoffman I., Scaillon M., Hauser B., Paquot I., Alliet P., Arts W., Dewit O., Peeters H., Baert F., D'Haens G., Rahier J.F., Etienne I., Bauraind O., Van Gossum A., Vermeire S., Fontaine F., Muls V., Louis E., Van de Mierop F., and Coche J.C. as members of the Belgian Society of Pediatric Gastroenterology and Nutrition and of the Belgian IBD Research and Development

for gathering the BELCRO data en reviewing the manuscript critically.

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