Early-onset Crohn's disease is a risk factor for smaller final height

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Objectives Growth retardation is a frequent complication of paediatric inflammatory bowel disease (IBD). Only a few studies report the final height of these patients, with controversial results. We compared adult height of patients with paediatric IBD with that of patients with adult-onset disease.

Methods Height data of 675 women 19–44 years of age and 454 men 23–44 years of age obtained at inclusion in the Swiss IBD cohort study registry were grouped according to the age at diagnosis: (a) prepubertal (men ≤ 13, women ≤ 11 years), (b) pubertal (men 13–22, women 11–18 years) and (c) adult (men > 22, women > 18 years of age), and compared with each other and with healthy controls.

Results Male patients with prepubertal onset of Crohn's disease (CD) had significantly lower final height (mean 172 ± 6 cm, range 161–182) compared with men with pubertal (179 ± 6 cm, 161–192) or adult (178 ± 7 cm, 162–200) age at onset and the general population (178 ± 7 cm, 142–204). Height z-scores standardized against heights of the normal population were significantly lower in all patients with a prepubertal diagnosis of CD (-0.8 ± 0.9) compared with the other patient groups (-0.1 ± 0.8, $P < 0.001$). Prepubertal onset of CD emerged as a risk factor for reduced final height in patients with prepubertal CD. No difference for final height was found between patients with ulcerative or unclassified IBD diagnosed at prepubertal, pubertal or adult age.

Conclusion Prepubertal onset of CD is a risk for lower final height, independent of the initial disease location and the necessity for surgical interventions. *Eur J Gastroenterol Hepatol* 26:1234–1239 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Growth retardation is a frequent extra-intestinal manifestation of paediatric onset inflammatory bowel disease (IBD) [1]. Its prevalence ranges from 13 and 58%, although much higher values have also been reported. Growth retardation is more commonly encountered in Crohn's disease (CD) than in ulcerative colitis (UC) [2], and most importantly, in patients with disease onset before or during early stages of puberty [3–5]. In contrast, most patients with a later diagnosis achieve normal adult height [6]. However, it remains unclear whether the growth deceleration at disease onset is temporary and compensated by a catch-up growth or whether it results in a reduced final height. Only a few reports have documented final adult height [4–9]. Most of these studies have been carried out in paediatric populations and define adult height as having completed 18 years of age and no further, or less than a 1 cm increase in

linear growth over a minimum of 6 months [5,6]. However, a recent Spanish study on growth including 32 064 normal individuals measured increasing height up to the age of 24 years, and the median growth between 18 and 24 years was 1.33 cm in men and 0.01 cm in women [10], a finding that challenges former definitions of final height. Thus, we hypothesized that, if final height is measured during early adulthood, patients with prepubertal disease onset would be found to have a smaller adult height than patients with later disease onset. Thus, the aim of the study was to compare the final height of IBD patients diagnosed during childhood with that of patients diagnosed during adulthood and to healthy controls. For this purpose, we analysed data collected in a nationwide multicentre cohort study on patients with IBD, the Swiss IBD cohort study, that was initiated in 2006 by the University of Lausanne [11].

Patients and methods

As of November, 2012, 2069 patients diagnosed with CD, ulcerative colitis (UC) or IBD-unclassified (IU) according to standard criteria [12], included at least 4 months after diagnosis, were registered in the Swiss IBD cohort study database. The study protocol for this registry had been approved by the central and the local ethics committees in 2006. As described by Pittet *et al.* [11], patient inclusion was performed by the following six university centres from western through eastern Switzerland: Geneva, Lausanne, Bern, Basel, Zurich and St Gallen, with the University of Lausanne as the coordinating centre and database location. We retrieved the two types of data from the registry: (a) information obtained from the patient chart at the time of enrolment, such as date of birth, sex, age at inclusion, age at IBD diagnosis, type of IBD (CD, UC, IU), disease location recorded according to Montreal classification [13], after verification of a work up according to inclusion criteria, and the necessity for surgery, defined as the sum of resectional and minor perianal surgery, excluding non-IBD-related surgeries, the cumulative use of corticosteroids and biologic agents, and (b) measured information, such as height and weight measured by the study nurse at the visit of enrolment using the wall stadiometers and weight scales available at the various study centres. Data of controls were obtained from the Federal Office of Public Health survey of 2007 [14]. For patients' inclusion, see the flow diagram shown in Fig. 1.

Statistics

Continuous data distribution was assessed using Normal-QQ-plots. Gaussian distributed data were presented as mean ± SD and range, and non-Gaussian distributed data were presented as median, interquartile range and range. Differences in continuous data distribution between two groups were assessed using Student's *t*-test in case of Gaussian data or using the Wilcoxon–Mann–Whitney rank sum test in case of non-Gaussian data. Differences in continuous data distribution between more than two groups were assessed using Fisher's *F*-test in case of Gaussian data or using the Kruskall–Wallis test in case of non-Gaussian data. Categorical data were presented as raw count and relative percentages. Differences in categorical data distribution between groups were assessed using the χ^2-test or Fisher's exact test in case of insufficient sample size. Simple linear regression was used to assess the effects of several factors on adult standardized height. Age category for disease onset, disease location at diagnosis and history of surgery were used as predictors for each sex and each disease separately. For the purpose of this study, a *P*-value less than 0.05 was considered statistically significant. Bonferroni's correction was applied in case of multiple testing.

Results

Male CD patients with prepubertal disease onset had a significantly lower final height than patients diagnosed at pubertal or adult age and the male Swiss population. The diagnosis was made before 1980 in two (final height 170 cm, both), between 1980 and 1989 in six (168, 2 × 170, 171, 179, 182 cm) and between 1990 and 1997 in eight patients (161, 163, 164, 171, 173, 175, 181, 184 cm). Seven female patients had prepubertal onset of CD (diagnosis between 1980 and 1989 in four, final height 160 × 2, 164, 173 cm, and between 1990 and 1994 in three, final height 143, 160, 165 cm) and their final height was not significantly smaller than that of the patients of any other group. The number of UC/IU patients with prepubertal disease onset was too small for analysis. There was no difference for final height in UC/IU patients with pubertal disease compared with that of patients with adult-onset disease or the Swiss population (Table 1). After standardization of the final

Fig. 1
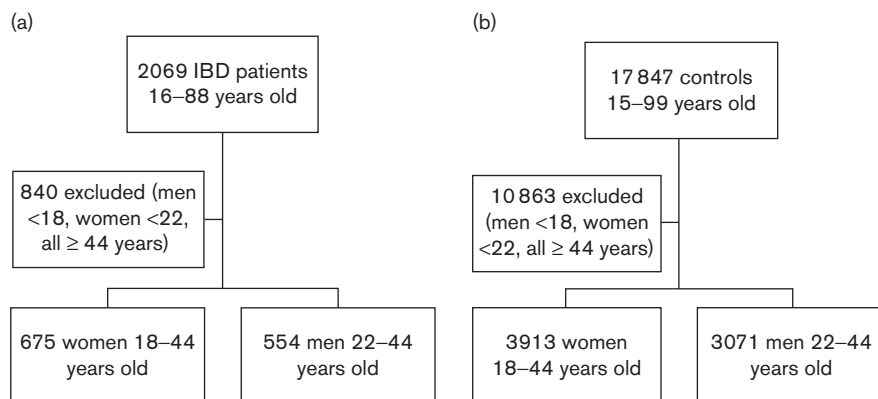
Flow diagram of patients included in our study: (a) patients enrolled into the registry of the Swiss IBD Cohort Study, (b) healthy individuals recruited by the Federal Office of Public Health in 2007 at the time of the public health survey. IBD, inflammatory bowel disease.

Table 1   Final height of patients with IBD grouped according to the age at disease onset

Disease onset	Prepubertal (pre)	Pubertal (pub)	Adult (adu)	Healthy controls (HC)	P-value overall[a]	Pre vs. pub[b]	Pre vs. adu[b]	Pub vs. adu[b]	Pre vs. HC[b]	Pub vs. HC[b]	Adu vs. HC[b]
Male patients with CD					0.001	<0.001	0.001	0.134	0.001	0.331	0.235
Number of patients	16	90	186	3071							
Height (cm)	172±6	179±6	178±7	178±7							
Mean±SD, range	161–182	161–192	162–200	142–204							
Female patients with CD					0.072	0.065	0.035	0.569	0.172	0.229	0.301
Number of patients	7	87	320	3913							
Height (cm)	161±9	165±6	166±6	166±6							
Mean±SD, range	143–173	151–178	152–183	130–186							
Male patients with UC/IU					0.406	0.741	0.587	0.163	0.778	0.466	0.151
Number of patients	2	68	192	3071							
Height (cm)	175±13	179±6	178±7	178±7							
Mean±SD, range	166–184	164–194	160–197	142–204							
Female patients with UC/IU					0.900	0.740	0.927	0.449	0.466	0.457	0.756
Number of patients	2	27	232	3913							
Height (cm)	166±1	167±6	166±6	166±6							
Mean±SD, range	165–166	157–181	150–185	130–186							

CD, Crohn's disease; IBD, inflammatory bowel disease; UC/IU, ulcerative colitis or IBD-unclassified.
[a]Fisher's F-test.
[b]Student's t-test.

heights of patients against the heights of the coeval Swiss population, age classes could be compared independent of sexes, and all patients with prepubertal disease onset of CD, but not UC/IU had significantly smaller final heights (Table 2 and Fig. 2) than the other groups.

At disease onset and for both sexes together, ileal disease location was present in five prepubertal (21.7%), in 31 pubertal (17.5%) and in 116 adult (22.9%), ileocolonic location was present in 12 prepubertal (52.2%), in 96 pubertal (54.2%) and in 237 adult (46.8%), colonic

Table 2   Standardized final heights of patients with IBD, normalized against coeval healthy individuals, grouped according to the age group at disease onset, sex and disease type
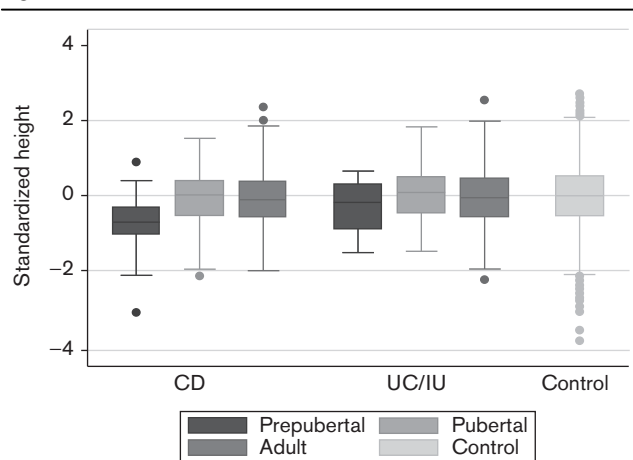
Disease onset	Prepubertal (pre)	Pubertal (pub)	Adult (adu)	Healthy controls (HC)	P-value overall[a]	Pre vs. pub[b]	Pre vs. adu[b]	Pub vs. adu[b]	Pre vs. HC[b]	Pub vs. HC[b]	Adu vs. HC[b]
Male patients with CD					0.001	<0.001	0.002	0.111	0.001	0.332	0.189
Number of patients	16	90	186	3071							
Standard height	−0.8±0.7	0.1±0.7	−0.1±0.7	0.0±0.8							
Mean±SD, range	−2.1–0.4	−2.1–1.5	−2.0–2.3	−3.8–2.7							
Female patients with CD					0.023	0.276	0.199	0.249	0.170	0.061	0.259
Number of patients	7	87	320	3913							
Standard height	−0.8±1.2	−0.2±0.8	−0.1±0.8	0.0±0.8							
Mean±SD, range	−3.1–0.9	−2.0–1.4	−2.0–2.0	−4.4–2.5							
Male patients with UC/IU					0.375	0.734	0.804	0.190	0.763	0.542	0.136
Number of patients	2	68	192	3071							
Standard height	−0.4±1.5	0.0±0.7	−0.1±0.7	0.0±0.8							
Mean±SD, range	−1.5–0.7	−1.5–1.8	−2.3–2.0	−3.8–2.7							
Female patients with UC/IU					0.977	0.334	0.406	0.734	0.428	0.795	0.793
Number of patients	2	27	232	3913							
Standard height	−0.2±0.2	0.0±0.8	0.0±0.8	0.0±0.8							
Mean±SD, range	−0.3–0.1	−1.3–1.7	−2.2–2.5	−4.4–2.5							
All patients with CD					<0.001	0.001	0.001	0.760	0.001	0.480	0.086
Number of patients	23	177	506	6983							
Standard height	−0.8±0.9	−0.1±0.8	−0.1±0.8	0.0±0.8							
Mean±SD, range	−3.1–0.9	−2.1–1.5	−2.0–2.3	−4.4–2.7							
All patients with UC/IU					0.515	0.504	0.626	0.245	0.568	0.478	0.258
Number of patients	4	95	424	6983							
Standard height	−0.3±0.9	0.0±0.7	−0.1±0.8	0.0±0.8							
Mean±SD, range	−1.5–0.7	−1.5–1.8	−2.3–2.5	−4.4–2.7							

CD, Crohn's disease; IBD, inflammatory bowel disease; UC/IU, ulcerative colitis or IBD-unclassified.
[a]Fisher's F-test.
[b]Student's t-test.

Fig. 2

Comparison of standardized final heights of patients with CD or UC/IU and disease onset at prepubertal, pubertal or adult ages. CD, Crohn's disease; UC/IU, ulcerative colitis or inflammatory bowel disease-unclassified.

location was present in one prepubertal (4.4%), in 30 pubertal (17.0%), and in 117 adult (23.1%), and unknown location in 5 (21.7%) prepubertal, in 19 (10.7%) pubertal and in 31 (6.1%) adult patients. The difference of unknown locations makes up for the significant difference between age groups.

Perineal and resectional surgical interventions in patients with CD of both sexes were required in 18 with prepubertal (78.3%), in 93 with pubertal (52.5%) and in with 193 adult-onset (38.1%) disease ($P < 0.05$ for each comparison), and in 0% with prepubertal, in nine with pubertal (9.5%) and in 21 with adult-onset (5%) disease of UC/IU ($P = $ NS for each comparison).

Univariate regression analysis enabled exclusion of factors such as the necessity for surgery or the initial disease location such as predictors of final height, and age at diagnosis emerged as the only predictive factor for final height (Table 3).

Corticosteroid therapy administered before study entry was recorded in 68% male and 86% female patients with prepubertal, in 50% male and 47% female patients with pubertal and in 45.7% male and 44% female patients with adult onset of CD ($P = $ NS between all groups), in 48% male and 59% female patients with pubertal and in 33.3% male and 42% female patients with adult onset of UC or unclassified colitis. Corticosteroid consumption during growth was not available as cumulative dose per kilo body weight. Infliximab, authorized for in 1999 for adult and in 2007 for patients 6–17 years of age, was administered in 12.5% male and 0% female patients with prepubertal, in 4.4% male and 16.1% female patients with pubertal and in 9.6% male 10.6% female patients with adult onset of CD, in

9.4% male and 3.7% female with pubertal, in 4.2% male and 2.6% female patients with adult-onset UC/IU.

Discussion

With this study, we could clearly show that final height in patients diagnosed with CD before the beginning of the pubertal growth spurt, that is before 13 years in males and 11 years in females, is significantly smaller than that of patients with later disease onset. Only a few reports have assessed the final adult height in IBD patients with paediatric onset disease [4–9]. Prospective studies mostly included paediatric patients up to the age of 18 years [4,5], and retrospective studies carried out in adult patients either analyse patients with CD diagnosed before the age of 16 or 17 years [7,8] as a single group, patients with UC and CD as a mixed group [1,9] or report height measures collected by telephone or from passports [4]. In this study, we have separately analysed patients with either UC/IU or CD and with either prepubertal, pubertal or adult-onset disease, and we have compared measured and dated final height of patients with prepubertal disease onset with that of patients with pubertal or adult disease onset and with that of healthy controls. Our age groups were constituted according to the tables of Tanner and Whitehouse [15], where the median age at onset of pubertal growth spurt is 13 years in boys and 11 years in girls, according to data of the Spanish cohort [10] for the age of achievement of final height and data of multiple reports [16,17] for the beginning of significant height loss during adult life. It is noteworthy that the cutoff of less than 17 years for paediatric age used by the Montreal classification is based on the need for a pediatric age group and the cutoff of less than 10 years of age proposed by the Paris classification on the different clinical and serologic phenotypes of CD at age before 10 years [18]. None of these classifications are evidence based for the dynamics of linear growth.

The smaller number of female patients with prepubertal disease onset in our study most likely reflects the well-known later onset of CD in females in this age group [19], and was the reason why a comparison of height was not possible. However, on comparing pooled standardized final heights, we could show that all patients with prepubertal onset of CD attained a significantly smaller final height compared with that of patients with later disease onset. Furthermore, univariate regression analysis identified age at diagnosis as the only predictive factor for adult height of CD patients. No difference in final height was found in patients with UC, in agreement with the results of other studies [2].

Corticosteroids were administered in all age groups, with no statistical difference. Yet, the relevant doses, that is the cumulative dose administered per kilo body weight before the beginning of, or during the growth spurt, was not available for analysis. However, there has always been a controversy on the impact of corticosteroids on

Table 3 Predictive factors for final height in patients with IBD according to the age class at disease onset

Outcome: standardized height	Male CD patients			Female CD patients			All CD patients		
	Estimated effect size	95% CI	P-value	Estimated effect size	95% CI	P-value	Estimated effect size	95% CI	P-value
Age at diagnosis									
Prepubertal	0 (ref)	–	–	0 (ref)	–	–	0 (ref)	–	–
Pubertal	0.8	0.4–1.2	<0.001	0.6	−0.1–1.2	0.075	0.7	0.4–1.0	<0.001
Adult	0.7	0.3–1.0	<0.001	0.7	0.1–1.3	0.028	0.7	0.4–1.0	<0.001
Surgery occurrence	0.1	−0.1–0.3	0.269	−0.1	−0.3–0.1	0.083	0.0	−0.2–0.1	0.548
Initial disease location									
Ileal	0 (ref)	–	–	0 (ref)	–	–	0 (ref)	–	–
Colonic	0.0	−0.3–0.3	0.967	0.0	−0.2–0.3	0.825	0.0	−0.2–0.2	0.839
Ileocolonic	0.0	−0.2–0.3	0.804	0.0	−0.2–0.1	0.626	0.0	−0.2–0.1	0.845
Upper GI only	0.9	0.1–1.6	0.026	−0.9	−2.0–0.3	0.132	0.3	−0.3–0.9	0.373
	Male UC/IU patients			Female UC/IU patients			All UC/IU patients		
Outcome: standardized height	Estimated effect size	95% CI	P-value	Estimated effect size	95% CI	P-value	Estimated effect size	95% CI	P-value
Age at diagnosis									
Prepubertal	0 (ref)	–	–	0 (ref)	–	–	0 (ref)	–	–
Pubertal	0.5	−0.6–1.5	0.360	0.2	−1.0–1.4	0.748	0.3	−0.4–1.1	0.386
Adult	0.3	−0.7–1.4	0.507	0.1	−1.0–1.3	0.810	0.2	−0.5–1.0	0.530
Surgery occurrence	−0.1	−0.5–0.3	0.620	0.1	−0.3–0.6	0.519	0.0	−0.3–0.3	0.903
Initial disease location									
Proctitis	0 (ref)	–	–	0 (ref)	–	–	0 (ref)	–	–
Left-sided colitis	0.0	−0.2–0.4	0.976	0.0	−0.3–0.2	0.750	0.0	−0.2–0.2	0.796
Pancolitis	0.1	−0.3–0.3	0.560	−0.1	−0.3–0.2	0.656	0.0	−0.2–0.2	0.969

CD, Crohn's disease; CI, confidence interval; IBD, inflammatory bowel disease; UC/IU, ulcerative colitis or IBD-unclassified; upper GI, upper gastrointestinal tract.

growth dynamics [19,20]. Treatment with biological agents played no role in the patient groups with pre-pubertal disease onset of our study as infliximab was authorized for paediatric patients only in 2007. Initial disease locations were not found to be different between age groups of patients with CD and had no impact on final height. Even though the cumulative lifetime requirements of perineal and resectional surgery, representing the severity and behaviour of the disease, were significantly higher in patients with prepubertal disease onset, mostly minor perineal surgery, the difference was not important enough to emerge a predictive factor.

This study has several limitations worth mentioning: first, our study is not population based. In Switzerland, many adult IBD patients are followed by gastroenterologists in private practice, especially patients with uncomplicated disease living in regions without easy access to university hospitals. Second, pubertal stages and bone ages of patients with prepubertal and pubertal diagnosis of IBD were not available, and some patients categorized as pubertal may still have been prepubertal, despite their age. Third, parental heights were not available, but instead and as useful, we compared patients' final heights with population-based height data of coeval healthy individuals.

In conclusion, by grouping patients according to ages relevant for growth dynamics, we could show that patients with CD diagnosed before the onset of growth spurt achieve a significantly lower final height than patients with later disease onset, independent of the initial disease location, need for surgery or corticosteroid use. Future studies should explore factors delaying or reducing the pubertal growth spurt in patients with a prepubertal diagnosis of CD, such as the severity and the duration of the disease before the beginning of the growth spurt.

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