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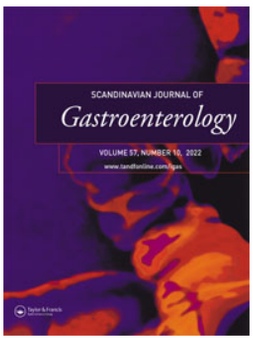

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ORIGINAL ARTICLE

Abdominal pain in Finnish young adults with juvenile idiopathic arthritis

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ABSTRACT

Objectives: Abdominal pain (AP) is a common feature in the general population. However, in patients with juvenile idiopathic arthritis (JIA) AP has scantily been studied. Among other reasons, gastrointestinal symptoms may present as side effects due to the medical treatment of JIA. The aim of the study was to explore the frequency of AP and its relationship to disease components and health-related quality of life (HRQoL) among young adults with JIA.

Methods: This study included a cohort of 97 Finnish patients belonging to the population-based Nordic JIA cohort at their 17-year follow-up study visit. Mean age of the patients was 23 years. AP, functional status, fatigue, HRQoL, disease characteristics of JIA, and comorbidities were evaluated. AP was classified into three categories according to frequency: (1) never, (2) seldom (one to three times a month) and (3) frequent (at least once a week).

Results: About 48 (50%) young adults with JIA reported AP. Seldom AP was reported by 37 (38%), and frequent AP by 11 (11%) patients. AP was significantly associated with fatigue, female gender, functional status and arthritis-related pain. Patients having frequent AP reported lower HRQoL. AP was associated with the use of methotrexate and sulfasalazine, but not with nonsteroidal anti-inflammatory drugs (NSAIDs).

Conclusion: AP is an important complaint in young adults with JIA and is associated with fatigue, female gender, methotrexate and sulfasalazine use. Patients with JIA reporting frequent AP with lower functional status and higher arthritis-related pain values have lower HRQoL.

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Introduction

Juvenile idiopathic arthritis (JIA) is the commonest chronic rheumatic disease diagnosed in children before the 16th birthday [1]. Patients with rheumatic diseases such as JIA might have concomitant abdominal pain (AP) associated with gastrointestinal inflammation [2] or induced by the treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) [3,4]. Previous review studies have shown that different gastrointestinal complaints are common in children and adolescents with JIA and in adults with RA receiving methotrexate [5,6], the most commonly used synthetic disease-modifying antirheumatic drug (sDMARD). Similarly, sulfasalazine use has been associated with AP in patients with rheumatic diseases [7,8].

A recent Finnish study [3] concerning AP among children with JIA and arthralgia revealed that 40% of those who had AP used nonsteroidal anti-inflammatory drugs (NSAIDs). One-third of them had elevated (>100 µg/g) faecal calprotectin (FC) values, which normalized after discontinuing NSAID use.

Children and adolescents have frequently AP, which can be related to psychosomatic symptoms or, among other reasons, unbalanced bowel function [9]. In different studies, functional AP has been associated with the decreased health-related quality of life (HRQoL), and increased health care use [10–12]. It has also been shown that patients with functional AP have a prolonged risk of anxiety in early adulthood and increased lifetime risk of depressive disorder [13]. Symptoms of irritable bowel syndrome (IBS) have been found to be prevalent in 16% of the general Danish population, with a female gender preponderance of 72% making it a significant problem for many individuals [14]. Previously, it has been shown that the prevalence of IBS in Finland varies from 5% to 16% when using different diagnostic criteria, and severe or very severe AP is present up to 44% of these patients [15]. Overall, AP is significant problem among individuals in general, and there is evidence that AP in adolescence may further lead to chronic pain in adulthood [9].

Furthermore, inflammatory bowel disease (IBD) is a known risk factor of other autoimmune disease and vice versa [16].

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A study from the BiKeR registry has shown that IBD incidence in patients with JIA was higher than in the general paediatric population [17]. In adults, IBD is mainly associated with spondylarthropathies [18].

There is lack of information regarding AP in young adults with JIA and the burden of AP in these patients is poorly known.

The aim of the study was to examine the frequency and features of AP in young adults with JIA, and to investigate the associations with HRQoL, fatigue, physical activity, disease activity and medications.

Materials and methods

The patient population of this study is a part of the original, population-based Nordic JIA cohort and has been previously described [19,20]. This study was conducted from the Helsinki University Hospital catchment area with disease onset between 1997 and 2000. In this study, all 143 Finnish patients with JIA were asked to answer questions about their abdominal pain at 17 years after disease onset when they participated in the follow-up study visit [20].

Respondents were asked about the frequency of AP not related to menstrual pain or IBD in the last two months. AP was classified into three categories according to the frequency: (1), never (2) seldom (one to three times a month) and (3) frequent (at least once a week).

If the patient reported to have AP at least once a week, additional questions about the duration of AP were asked. If the duration of AP was longer than one month, a more detailed questionnaire about the AP was filled in including visual analogue scale (VAS) for the intensity of AP (AP VAS pain; range 0–100), and questions about stools and defecation. Patients were asked to answer questions concerning how often did this pain or discomfort get better or stop after defecation, how often did this pain or discomfort was associated with loose or watery stools, how often did this pain or discomfort was associated with hard or lumpy stools and bowel movements.

The diagnostic Rome III criteria for IBS were used [21].

Disease activity was evaluated by the Disease Activity Score 28 (DAS28), which is a combined index comprising information from swollen joints, tender joints, acute-phase response and general health [22]. DAS28 scores range from 0 to 9.4 [23], and <2.6 is considered as remission [24]. Disability was measured by a Finnish version of the Health Assessment Questionnaire (HAQ) [25]. HAQ is scored on a scale of 0 ('no difficulty') to 3 ('unable to do'), where 0 indicates normal functional ability, and scores higher than one indicate a significant decrease in functional ability [26] The patients' medications and comorbidities were registered. FC, haemoglobin (Hb), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured.

HRQoL was evaluated by using the RAND 36-Item Health Survey [27] on eight scales of different health concepts: physical functioning, role functioning limitation due to physical health problems (role functioning/physical), bodily pain, general health perceptions, vitality, social functioning role functioning limitation due to emotional matters (role functioning/emotional), and emotional well-being. Each item scored on a 0–100 range, and higher scores indicating better HRQoL [28]. Remission off medication was defined according to the Wallace's preliminary criteria requiring inactive disease for at least 12 months [29]. Sleep quality was studied by the Pittsburgh Sleep Quality Index (PSQI) [30] comprising seven categories: sleep duration, sleep disturbance, sleep latency, daytime dysfunction due to sleepiness, sleep efficiency, sleep quality, and use of sleep medication. The total score ranges from 0 to 21, higher scores indicating poorer sleep quality [30]. Fatigue was evaluated by using the Fatigue Severity Scale (FSS) [31] consisting of nine items, each item ranges from 1 to 7, where 1 indicates strong disagreement and 7 strong agreement. In addition, FSS includes a 21-item VAS score to determine the severity of fatigue. Higher values indicate more severe fatigue [31,32]. Physical activity was evaluated by asking about the frequency of exercise: (1) less than once a week, (2) once a week, (3) two to three times a week and (4) almost daily.

Ethics

This study was approved by the local Ethics Committee (174/13/03/03/2014) and written informed consent was obtained from all the patients.

Statistics

The descriptive statistics were presented as means with standard deviation (SD), as medians with interquartile range (IQR) or as counts with percentages. Statistical significances for the hypothesis of linearity across categories of AP frequency were evaluated using the Cochran-Armitage (chi-squared) test for trend, ordered logistic regression models and an analysis of variance with an appropriate contrast. In the case of violation of the assumptions (e.g., non-normality) for continuous variables, a bootstrap-type method or Monte Carlo p-values (small number of observations) for categorical variables were used. The Finnish general population values for the eight Rand-36 domains were weighted to match the gender and age distribution of the study population [27]. The normality of variables was evaluated graphically and by using the Shapiro–Wilk W-test. The Stata 17.0, StataCorp LP (College Station, TX, USA) statistical package was used for the analysis.

Results

Ninety-seven of the 143 patients (68%) with diagnosed JIA answered the specific AP questions and were included in this study. Mean age of the patients was 23 (range 16–32) years. See Table 1 for additional demographics.

Fifty per cent ($n = 48$) of the patients reported AP. Frequent AP was experienced by 11% of the patients and it was more common in females (82%). The proportion of

Table 1. Characteristics of the patients with JIA at the study visit according to the frequency of abdominal pain (AP).

Characteristics	No AP $n = 49$	Seldom AP $n = 37$	Frequent AP $n = 11$	p Value*
Female, *n* (%)	23 (47)	30 (81)	9 (82)	.002
Age, mean (SD)	23 (4)	23 (5)	25 (5)	.36
BMI, mean (SD)	22.8 (3.6)	23.8 (4.9)	24.0 (4.5)	.24
JIA duration, mean (SD)	17.5 (1.3)	17.2 (1.3)	17.5 (1.3)	.61
JIA category, *n* (%)				.40
Persistent oligoarthritis	14 (29)	13 (35)	2 (18)	
Extended oligoarthritis	11 (22)	9 (24)	2 (18)	
Polyarthritis, RF-pos	1 (2)	0 (0)	0 (0)	
Polyarthritis, RF-neg	11 (22)	9 (24)	6 (55)	
Psoriatic	6 (12)	1 (3)	0 (0)	
Enthesitis-related	5 (10)	2 (5)	1 (9)	
Systemic onset	1 (2)	0 (0)	0 (0)	
Undifferentiated	0 (0)	3 (8)	0 (0)	
DAS-28, mean (SD)	1.81 (0.72)	2.03 (0.81)	1.90 (0.35)	.39
HAQ, mean (SD)	0.06 (0.22)	0.09 (0.22)	0.56 (0.91)	.002
Remission, *n* (%)**	26 (53)	15 (41)	2 (18)	.037
Pain VAS, mean (SD)***	8 (13)	21 (27)	31 (20)	<.001
ESR, mean (SD)	6.5 (6.9)	6.9 (7.0)	4.4 (3.6)	.65
CRP, mean (SD)	5.0 (19.2)	1.2 (2.5)	1.0 (1.4)	.29
PSQI total, mean (SD)	4.8 (3.0)	5.4 (2.6)	5.8 (2.8)	.21
Fatigue total, mean (SD)	2.6 (1.0)	3.1 (1.1)	4.2 (1.4)	<.001
Fatigue, VAS mean (SD)	32 (22)	42 (25)	57 (18)	<.001
Physical exercise frequency, *n* (%)				.79
Less than once a week	3 (7)	4 (12)	2 (20)	
Once a week	6 (14)	6 (18)	2 (20)	
Two to three times a week	20 (48)	14 (42)	1 (10)	
Almost daily	13 (31)	9 (27)	5 (50)	
Gastrointestinal comorbidities, *n* (%)	2 (4)	1 (3)	2 (18)	.32
Coeliac disease	1 (2)	0 (0)	0 (0)	
Ulcerative colitis	0 (0)	0 (0)	0 (0)	
Crohn's disease	1 (2)	1 (2)	0 (0)	
IBS	0 (0)	0 (0)	2 (4)	
Comorbidities (other), *n* (%)	0 (0)	0 (0)	7 (63)	<.001
Hypothyroidism	0 (0)	0 (0)	1 (10)	
Depression	0 (0)	0 (0)	2 (20)	
Panic disorder	0 (0)	0 (0)	2 (20)	
Uveitis	0 (0)	0 (0)	4 (36)	

AP: abdominal pain; BMI: body mass index; JIA: juvenile idiopathic arthritis; RF: rheumatoid factor; DAS-28: disease activity score; HAQ: health assessment questionnaire; VAS: visual analogue scale; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; PSQI: Pittsburgh Sleep Quality Index; IBS: irritable bowel syndrome according to the Rome III criteria [20].
*p Value for linearity.
**Remission off medication (28).
***Arthritis-related pain.

females ascended significantly when the frequency of AP increased (p for linearity .002).

Relationship between the frequency of AP- and JIA-related parameters and medication

Patients who had higher disability scores measured by the HAQ reported AP more frequently (p for linearity .002) (Table 1). Patients with no AP, patients with seldom AP, and patients with frequent AP had mean HAQ scores of 0.06 (0.22), 0.09 (0.22), and 0.56 (0.91), respectively.

When AP frequency increased, correspondingly the number of patients with JIA in remission off medication decreased from 53 to 18% (p for linearity 0.037).

Arthritis-related pain intensity was significantly associated with the frequency of AP (p for linearity <.001). Patients with no AP, patients with seldom AP, and patients with frequent AP had mean arthritis-related pain VAS scores 8 (13), 21(27), and 31(20), respectively. AP showed a significant association with fatigue measured by the FSS (p for linearity <.001) (Table 1). The relationship between the HRQoL scales (physical functioning, bodily pain, general health, vitality and

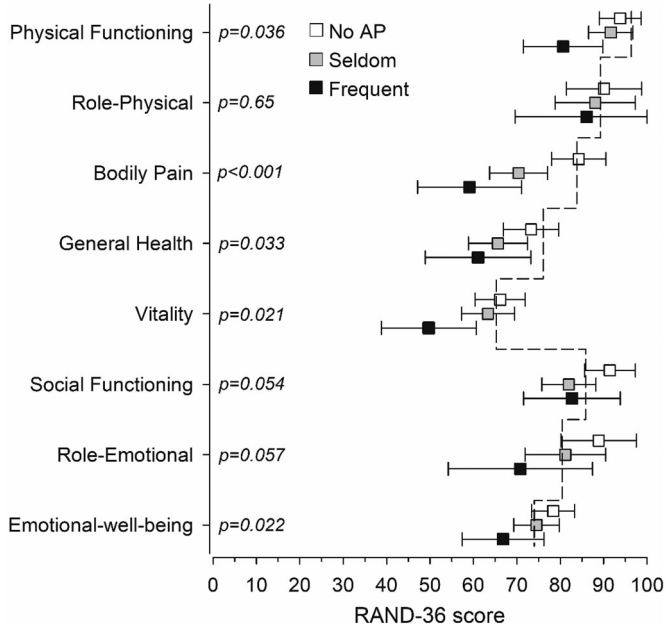

Figure 1. Health-related quality of life (HRQoL) components between the groups of AP measured by the RAND-36 survey. Age- and gender-matched healthy controls [26] are presented on the dotted line. AP: abdominal pain. p Value for linearity.

Table 2. Medication use of patients with JIA at the study visit according to the frequency of abdominal pain (AP).

Medication	No AP $n = 49$	Seldom AP $n = 37$	Frequent AP $n = 11$	p Value*
NSAIDs	12 (24)	10 (27)	6 (55)	.14
Prednisolone	0 (0)	2 (5)	1 (9)	.081
Methotrexate	5 (10)	9 (24)	4 (36)	.023
Azathioprine	1 (2)	0 (0)	0 (0)	.61
Hydroxychloroquine	3 (6)	4 (11)	2 (18)	.21
Leflunomide	1 (2)	1 (3)	1 (9)	.39
Sulfasalazine	2 (4)	3 (8)	3 (27)	.032
Cyclosporine	0 (0)	0 (0)	1 (9)	.11
bDMARDs	15 (31)	11 (30)	4 (36)	.87

Data are shown as n (%); AP: abdominal pain; NSAIDs: non-steroidal anti-inflammatory drugs; bDMARDs: biologic disease-modifying antirheumatic drugs.
*p Value for linearity.

emotional well-being) and AP frequency were significant (Figure 1). The HRQoL in healthy age- and gender-matched controls is shown in Figure 1.

Patients with frequent AP ($n = 11$) had higher mean VAS pain values [54 mm (SD 24)] due to AP. A duration of frequent AP of more than one year was reported by eight patients (73%) out of 11, five (45%) of whom described the pain as lasting for more than an hour at a time. Eight of the 11 patients (73%) reported that they had loose stools.

In total, five patients provided an FC sample. One of the values was marginally elevated (163 ug/g). After gastroesophageal reflux was diagnosed, NSAIDs were discontinued and FC returned to normal. None of the patients with frequent AP had IBD, lactose intolerance, or reported persistent constipation. All patients with frequent AP had normal Hb and ESR values. Altogether, 21 patients delivered FC samples in the study: with a median (IQR) of 17 μg/g (6, 113) if the two patients with IBD were included and 11 μg/g (6, 64) if excluded. There was no significant association between the FC level and AP frequency (data not shown).

In this cohort, no statistically significant associations between AP and the subgroups of JIA, disease activity scores, sleep quality or the frequency of physical activity were revealed.

Seven patients with frequent AP reported having hypothyroidism, depression, panic disorder, and uveitis (Table 1). In total, two patients (2%) concurrently had IBD, and one had coeliac disease (1%). Three patients (27%) having frequent AP, reported constipation occasionally.

A significant association between medication use and frequent AP was found regarding to methotrexate ($p = .023$) and sulfasalazine ($p = .032$) but not to NSAIDs (Table 2).

Discussion

The main finding of this study is that frequent AP was most common in JIA patients with higher disability scores, higher arthritis-related pain, and poorer quality of life. In addition, frequent AP was more evident in female patients.

AP and gastrointestinal symptoms are predominant features in functional gastrointestinal disorders (FGIDs) [33,34], which are highly prevalent worldwide [12] and affecting high proportion of females [14]. According to the comprehensive review study, the pooled prevalence of IBS in adults varies from 5.8% in Middle East and Africa to 17.5% in Latin America, and being 8.1% in North America, Europe, Australia and New Zealand [35]. Recently, the global prevalence of FGIDs has found to be more than 40% [12].

It has been shown that IBS-like symptoms (abdominal pain and discomfort) in patients with quiescent IBD were associated with lower quality of life (QoL), higher fatigue and depression scores [36].

Similarly, with previous studies [11,37], we found the association with AP and QoL in patients with no known IBD. In the general adult population AP has been associated with impaired QoL, depression and anxiety [37]. In the present study, we did not focus on depressive symptoms and anxiety. This requires to be observed in further studies.

We found that AP was associated with fatigue. This finding is consistent with previous studies [38,39]. Recently, a study from the Nordic JIA cohort has revealed that fatigue is common in young adults with diagnosed JIA, and it is associated with active disease, use of the antirheumatic medication, poor sleep, pain, disability, and lower HRQoL [40].

Patients with JIA may suffer frequently from AP, and NSAID use has been found to be a main cause for AP [3,4]. In our study, half of the patients reported AP and 11% had AP at least once a week. In the present study, however, no association between NSAIDs and AP was revealed. This finding could be explained by the analgesic properties of NSAIDs.

We found that the use of methotrexate and sulfasalazine was associated with the frequency of AP, though the number of patients in these categories was low. It is well known that AP and other gastrointestinal symptoms are common in patients receiving sDMARDs like methotrexate and sulfasalazine [5–8].

In this study, loose stools were the most common finding in the patients with frequent AP that can mimic the symptoms of IBD. Due to the small number of cases, we cannot make comprehensive causal interpretations. However, if a patient presents with these symptoms, it is advisable to test their calprotectin and if elevated a more detailed intestinal examination should be performed. In our cohort, all the patients with frequent AP had normal Hb and ESR values, had not been diagnosed with lactose intolerance and had not reported other GI – tract-related diseases, except the one patient with gastroesophageal reflux. Only one of the patients with frequent AP had a moderately increased value of FC, which normalized after discontinuing NSAIDs. It is also noteworthy that the patients with frequent AP were infrequently in remission off medication. This suggests that AP is a possible presentation of a medication induced gastrointestinal side effect. On the other hand, several congruences between the pathogenesis of the joint and gut inflammation have been identified, especially in spondylarthritis and psoriasis [41–44]. In addition, gut microbiota has been associated with the development of JIA and IBD [45,46].

In this study, we did not find statistical differences between AP groups and the frequency of physical activity. Previously it has been reported that youth with chronic

abdominal pain experience less time of moderate-to vigorous physical activity per day as recommended [47].

Strengths and limitations

There are several strengths of this study. To our knowledge, this study is one of the first to investigate AP in young adults with JIA. Another strength is its use of validated multidimensional measurements.

A limitation of the study is the small number of patients; however, 68% of the Finnish patients at the 17-year follow-up visit answered the AP questionnaire. Another limitation is the low number of analysed FC samples. Assaying FC is important for detecting inflammation in the bowel, but we experienced that patients with mild abdominal symptoms had limited motivation to provide samples.

Conclusions

In conclusion, this study shows that AP is a frequent complaint in young adults with diagnosed JIA. It is associated with female gender, disability, arthritis related pain, commonly used sDMARDs, and fatigue. AP in young adults with diagnosed JIA, even not related to IBD or other gastrointestinal disorders, should not be underestimated. This study provides valuable information about AP and functional outcomes in young adults with JIA. AP is potentially life interfering when the patient additionally suffers from poor quality of life, as we observed in this study.

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