Rheumatology International (2019) 39:317–322
https://doi.org/10.1007/s00296-018-4129-7

Rheumatology
INTERNATIONAL

COMORBIDITIES

Is Henoch–Schönlein purpura a susceptibility factor for functional gastrointestinal disorders in children?

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Received: 26 July 2018 / Accepted: 9 August 2018 / Published online: 12 August 2018

Abstract

Henoch–Schönlein purpura (HSP), the most common childhood vasculitis is characterized by non-thrombocytopenic palpable purpura, arthritis/arthralgia, abdominal pain and renal involvement. Functional gastrointestinal disorders (FGIDs) are heterogeneous disease spectrum with unclear etiology and include the most common subtypes: functional dyspepsia, irritable bowel syndrome (IBS), functional abdominal pain and functional constipation. Formerly, FGIDs were known as non-organic disorders; however, recent advances revealed that low-grade inflammation may also play a role. We aimed to clarify whether HSP predisposes to FGIDs in pediatric population. Seventy-four children with HSP, diagnosed at least 6 months before the study and 78 healthy controls were enrolled to the study. Patients with red flag signs for organic GI disorders were excluded. Rome IV criteria were utilized for FGIDs diagnosis. We compared the frequencies of FGIDs between HSP patients and healthy subjects. We also examined the parameters including age, abdominal pain, arthralgia, bloody stool, renal involvement and treatment with corticosteroids and laboratory results at HSP diagnosis such as erythrocyte sedimentation rate, C-reactive protein, hemoglobin, leukocytes and platelet counts among patients with and without FGIDs. Overall FGIDs and IBS frequency were 35.1% ($n=26$) and 10.8% ($n=8$) in HSP patients, 19.2% ($n=15$) and 2.6% ($n=2$) in healthy controls, respectively. Disease characteristics and laboratory parameters at disease onset were similar between HSP patients with and without FGIDs. Overall FGIDs rate, particularly IBS were statistically higher in HSP patients. We speculate that children with preceding HSP may be predisposed to FGIDs. Since the FGIDs pathogenesis is still remains unclear, further studies are needed to confirm this hypothesis and clarify the etiology. Physicians also should pay attention to FGIDs in HSP patients with ongoing abdominal pain and thus prevent this comorbidity with dietary and psychologic measures.

Keywords Henoch–Schönlein purpura · Child · Functional gastrointestinal disorder · Abdominal pain · Constipation · Irritable bowel syndrome

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Introduction

The most common vasculitis in childhood is Henoch–Schönlein purpura (HSP), which is also named as IgA vasculitis in the subcategory of immune complex small vessel vasculitis in 2012 Chapel Hill Consensus Conference [1]. The pathogenesis is still unclear although several hypotheses had been suggested that vascular inflammation is due to galactose-deficient IgA1-dominant immune deposits, complement activation and neutrophil infiltration leading leukocytoclastic vasculitis. Since the disease predominantly occurs in fall season and often preceded by an upper respiratory tract infection, researchers also hypothesized that infections may trigger HSP with cross-reactive IgA and IgG to surface *N*-acetylgalactosamine of pathogens [2, 3].

Characteristic symptoms of HSP are non-thrombocytopenic palpable purpura, arthritis/arthralgia, abdominal pain and renal involvement. Purpura is usually symmetrical and present in pressure-dependent sites of body, including lower limbs and buttocks. Gastrointestinal manifestations are reported in 40–75% of HSP patients [4, 5]. HSP, as a self-limiting disease occasionally lead to severe gastrointestinal involvement, especially intussusception and nephritis/renal impairment [2, 6].

Functional gastrointestinal disorders (FGIDs), a heterogeneous disease spectrum with unclear etiology, are common causes of admissions to pediatric gastroenterology departments. Diagnosis and treatment are usually difficult due to absence of obvious structural or biochemical alterations in gastrointestinal system [7, 8]. Besides FGIDs were known as non-organic or functional disorders previously; recent advances revealed that immune dysregulation and low-grade inflammation take part in FGIDs [9].

Several autoimmune and autoinflammatory diseases have been linked with an increased risk of FGIDs and one of those is HSP [10–12]. It is noteworthy to clarify whether HSP that often affects gastrointestinal system predisposes to FGIDs afterwards. Thus, we aimed to define FGIDs rate and susceptibility factors in pediatric patients with preceding HSP.

Materials and methods

Patients

This retrospective study was performed with 74 HSP patients between 4 and 18 years of age and 78 healthy controls. Patients were diagnosed according to EULAR/PRINTO/PRES 2010 criteria between February 2017 and February 2018 in our department and followed up for at least 6 months after disease onset [13]. Patients with red flag signs for organic GI disorders such as involuntary weight loss, significant vomiting, chronic diarrhea, bloody stool, fever and family history of inflammatory bowel disease were excluded from the study [14]. Control group consisted of children without any parent-reported health problems and aforementioned red flag signs.

On the other hand; data including age at diagnosis, gender, duration of follow-up, preceding infections, medication, arthritis/arthralgia, abdominal pain, severe GI involvement, invagination and renal involvement were retrospectively recorded from medical files of the patients. Ethics committee of our medical faculty approved the study (number 76/53; date, 13/04/2018). Informed consent was obtained from the parents from the patients prior to the present study.

Assessment of functional gastrointestinal disorders

We utilized Rome IV criteria for diagnosis of FGIDs at the study enrollment, at least 6 months after HSP onset which are simply categorized in three sections: functional nausea and vomiting disorders, functional abdominal pain disorders (FAPD) and functional defecation disorders [15]. Functional nausea and vomiting, abdominal migraine and non-retentive fecal incontinence were absent among both patients and control group according to criteria. Diagnostic criteria for subcategories including functional dyspepsia, irritable bowel syndrome, functional abdominal pain and functional constipation revealed these conditions in both the study and control groups.

Functional dyspepsia diagnosis requires the occurrence of at least one of the following at least 4 times/month for the last 2 months: postprandial fullness, early satiation, epigastric pain or burning not associated with defecation. Patients are diagnosed with IBS if they suffer from abdominal pain at least 4 days/month associated with one of the following: related with defecation, changes in frequency and form of the stool plus permanent symptoms even after resolution of the constipation. According to Rome IV criteria, one must have episodic or continuous abdominal pain more than 4 times/month for last 2 months and insufficient criteria for another FAPD. Furthermore, functional constipation is considered when a patient had two or more of the following criteria at least once per week for minimum 1 month and insufficient criteria for IBS: two or fewer defecations per week, fecal incontinence more than one time per week, retentive posturing, painful or hard bowel movements, large fecal mass in rectum and large diameters of stool. Absence of explanation of symptoms by other medical conditions after appropriate evaluation is also necessary for all types of FGIDs [15].

Statistical analysis

All analyses were performed using SPSS 20.0 statistical software package (IBM SPSS Statistics). Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation and as median and minimum–maximum where appropriate. Chi-square test was used to compare categorical variables between groups. Continuous variables were analyzed between two groups with Mann–Whitney *U* test. The statistical level of significance for all tests was considered to be 0.05.

Results

A total 74 patients (40 male, 34 female) with HSP and 78 healthy subjects (52 male, 26 female) between 4 and 18 years of age were included in the present study. The median age is 9.04 (range 4.27–17.56) years in HSP group and 9.15 (range 4.47–17.69) years in control group.

All patients had purpura at the diagnosis of HSP; whereas, 46 patients (62.2%) had abdominal pain, 20 (27%) had bloody stool, 5 patients (6.8%) were diagnosed with invagination, 45 (60.8%) had arthralgia, 17 (23%) had urinary finding (proteinuria or hematuria) during the disease course. NSAIDs were prescribed in 48.6% of patients ($n=36$) with a median of 5 (range 1–10) days and corticosteroids were administered in 51.4% of patients with a median of 20 (7–30) days. None of the patients had renal insufficiency or/and persistent urinary abnormality and required renal biopsy.

The prevalence of FGIDs and subtypes among the patient and control groups are shown in Table 1. Overall FGIDs rate was 35.1% ($n=26$) in patients with preceding HSP and 19.2% ($n=15$) in control group. Furthermore, IBS frequency was 10.8% ($n=8$) in patients with preceding HSP and 2.6% ($n=2$) in healthy controls. In detail, functional dyspepsia, FAP and functional constipation prevalence were similar between these two groups. Additionally, we investigated if symptoms or laboratory parameters differ between HSP patients with or without FGIDs. However, there was no significant difference in disease characteristics between these two groups (Table 2).

Table 1 Demographic features and functional gastrointestinal disorders among patients with Henoch–Schönlein purpura and healthy controls

Parameters	Patients with preceding HSP		Control group		*p*
	n	%	*n*	%	
Gender (M/F)	40/34	54.1/45.9	52/26	66.7/33.3	0.077
FGIDs	26	35.1	15	19.2	**0.021**
Functional dyspepsia	11	14.9	8	10.3	0.270
Irritable bowel syndrome	8	10.8	2	2.6	**0.041**
Diarrhea predominant	1	1.4	1	1.3	0.738
Constipation predominant	7	9.5	1	1.3	0.058
Functional abdominal pain	6	8.1	4	5.1	0.340
Functional constipation	6	8.1	3	3.8	0.318

Significant *p* values (< 0.05) are in bold

HSP Henoch–Schönlein purpura, *FGIDs* functional gastrointestinal disorders

Discussion

The prevalence of FGIDs varies between 2.4 and 23% of children with different race and ethnicities [16, 17]. Socioeconomic status, stress, trauma and personality may be the other possible precipitating factors of FGIDs. The most commonly reported FGIDs are functional dyspepsia, irritable bowel syndrome and functional abdominal pain among children.

Today, it is widely suggested that bi-directional axis between gut and brain including microbiota, neurons, neuroendocrine and immune system play role in FGIDs. Since researchers showed that IBS symptoms may arise from low-grade inflammation, systemic and local inflammatory markers became a new area of interest in FGID pathogenesis [9, 18]. Furthermore, tissue biopsies revealed decreased IL-10, elevated IL-1β and IFN-γ levels in intestinal mucosa of patients with post-infectious IBS [19, 20]. There is also rising evidence that IBS may be a mild, subclinical form of inflammatory bowel disease which is a group of chronic organic inflammation including Crohn's disease and ulcerative colitis [21].

Additionally, several studies previously showed that FGIDs were more prevalent in adult patients with autoimmune and inflammatory diseases; systemic lupus erythematosus and rheumatoid arthritis in which anti-inflammatory drugs were often prescribed [12, 22]. In another study, adults with FMF had higher rate of FGIDs, however this was not statistically significant [11].

Thus, we wondered if HSP patients subsequently develop FGID symptoms due to maintenance of a low-grade inflammation. To the best of our knowledge, only one preliminary study examined FAPD among patients with HSP along with phone contact questioning, at least 6 months after the disease onset. Twenty-one percent of 38 HSP patients had a diagnosis of FAPD (IBS 10.5%, FAPS 7.9%, and FAP 2.6%), whereas only 2.6% of control group met Rome III criteria for FAPD in that study. Presence of abdominal pain

Table 2 Demographic and disease characteristics of patients with Henoch–Schönlein purpura according to the presence of functional gastrointestinal disorders

Parameters	Patients with preceding HSP and FGIDs (+) ($n=26$)	Patients with preceding HSP, FGIDs (−) ($n=48$)	p
Age (years), median (min–max)	7.88 (4.60–15.11)	9.16 (4.27–17.56)	0.387
Age at diagnosis (years), median (min–max)	6.94 (3.05–13.45)	8.30 (4.01–17.06)	0.336
Time elapsed between HSP onset to FGIDs assessment (months), median (min–max)	5.66 (6–105.8)	8.82 (6–85.5)	0.162
Manifestations at HSP onset			
Preceding infections	17 (65.4%)	32 (66.7%)	0.912
Abdominal pain	17 (65.4%)	29 (60.4%)	0.803
Bloody stool	7 (26.9%)	13 (27.1%)	0.607
Invagination	3 (11.5%)	2 (4.2%)	0.231
Arthralgia	16 (61.5%)	29 (60.4%)	0.928
Renal involvement	6 (23.1%)	11 (22.9%)	0.988
Subcutaneous edema	3 (11.5%)	6 (12.5%)	0.906
NSAID administration	12 (46.2%)	24 (50%)	0.883
Steroid administration	12 (46.2%)	26 (54.2%)	0.622
Recurrence	3 (11.5%)	13 (27.1%)	0.155
Laboratory results at HSP diagnosis, median (min–max)			
Hemoglobin (g/dl)	12.3 (9.2–14.2)	12.7 (10.3–14.3)	0.437
Leukocytes (/mm^3)	11,600 (5990–18,070)	11,200 (5100–23,560)	0.714
Thrombocytes (/mm^3)	371,000 (245,000–597,000)	392,000 (183,000–802,000)	0.671
ESR (mm/h)	20 (2–47)	17 (2–88)	0.155
CRP (mg/dl)	0.6 (0.11–5.85)	0.54 (0.1–6)	0.525

HSP Henoch–Schönlein purpura, *FGIDs* functional gastrointestinal disorders, *NSAID* non-steroidal anti-inflammatory drugs, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein

and steroid administration at HSP onset was associated with higher FGID rate. IBS was the most common FGID in the same study [10].

Distinctively, we investigated all subtypes of FGIDs with Rome IV criteria and medical assessment by the physician. We showed that overall FGIDs frequency and IBS prevalence were more frequent in HSP patients than control subjects. Occurrence of FGIDs did not differ with clinical manifestation, recurrence and laboratory parameters at disease onset. With these results, our study only supported the hypothesis that FGIDs are more common in patients with previous HSP than healthy controls. Otherwise, treatment with steroids and abdominal pain frequency at HSP onset were similar between HSP patients with and without FGIDs in our study. We also tried to compare our results with other epidemiological study from our country; however, they all investigated IBS with previous Rome criteria and lack of information about other FGIDs categories. In one of the recent studies on 2217 adolescents, IBS prevalence was found 10.8%, which is higher from our control group [23]. We think that this difference is due to the wide range of age in our study. Until more comprehensive prevalence studies with large number of participants are done, we interpret our results as FGIDs in preceding HSP are more frequent than control subjects.

HSP clinically refers to leukocytoclastic vasculitis and small vessel involvement with IgA-mediated immune complexes and complement activation. Besides, several studies demonstrated pro-inflammatory cytokine elevation at the disease onset, with increased serum levels of IL-2, IL-2sRα and particularly TNF-α which diminishes at the end of follow-up [24]. Levels of TNF-α was correlated with von Willebrand factor, a marker of endothelial injury in another study [25]. Two comprehensive studies recently indicated that significant compositional and structural microbiota changes were present in the gut of HSP and IgA nephritis. *Bifidobacterium* subtypes were decreased whereas *Parabacteroides* and *Enterococcus* were increased in these children [26, 27].

It is not clear whether HSP affects microbiota or microbiota alterations lead to HSP. However, it is conceivable that alterations in microbiota may predispose to FGIDs in children with preceding HSP. As the pathogenesis of FGIDs is very complex, we think that patients with HSP may also be predisposed to FGIDs owing to subclinical inflammation, altered microbiota and disease stress.

Another mechanism of action in FGIDs is neural and neuro-immune interactions leading to afferent nervous activation and thus, visceral hypersensitivity. This mechanism is more prominent in FAPD, particularly IBS [28]. The pathogenesis of pain in HSP lacks evidence-based information currently. We may assume that the inflammation causes the stimulation of the afferents of the enteric nervous system, however there are not any in vivo or in vitro studies performing neuroimaging or electrophysiological recording techniques in systemic vasculitis and suggesting this hypothesis so far. Nevertheless, it can be speculated that continuous low-grade inflammation in HSP may lead to visceral insensitivity in individuals with other predisposing factors to FGIDs.

The major limitation of the present study is small number of patients, since HSP is the most common vasculitis in childhood. The other limitations are lack of prospective design and elimination of confounding factors for FGIDs, such as stress, nutrition and microbiota.

There are growing evidence about the presence of low-grade inflammation in FGIDs pathogenesis. Thus, it is still important to clarify if HSP is a risk factor for FGIDs or not, even in the absence of qualified evidence for low-grade inflammation in these patients. Thus, this preliminary study led us to think the idea that microbiota, intestinal inflammatory markers and neuroimaging techniques might be studied with a prospective design in a large number of pediatric HSP patients in the future.

In conclusion, due to the limitations of our preliminary study, we can only speculate that HSP patients have higher frequency of FGID symptoms compared to healthy controls; thus, HSP may predispose to FGIDs in children. Since the FGIDs pathogenesis is still remains unclear, further studies are needed to confirm this hypothesis and clarify the etiology. Physicians also should pay attention to FGIDs in HSP patients with remittent abdominal pain and thus prevent this comorbidity with dietary and psychologic measures.

Author contributions Dr. RMKE and Dr. MY conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Dr. SB, Dr. GT, Dr. SY and Dr. DD collected data, carried out the initial analyses, and reviewed and revised the manuscript. Dr. DUA, Dr. OOM and Dr. HC designed the data collection instruments, and coordinated and supervised data collection, and critically reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding No funding was received.

Compliance with ethical standards

Conflict of interest Authors Rabia Miray Kisla Ekinci, Sibel Balci, Okkes Ozgur Mart, Gokhan Tumgor, Sibel Yavuz, Halil Celik, Dilek Dogruel, Derya Ufuk Altintas, Mustafa Yilmaz declare that they have no conflicts of interest.

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