Prevalence of Allergic Diseases in Juvenile Idiopathic Arthritis Patients

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Background : Prevalence of allergic and autoimmune diseases are simultaneously rising. The data on potential association between the two disorders is conflicting.

Objectived : To evaluate the prevalence of allergic diseases in patients with juvenile idiopathic arthritis (JIA) and the association between severity of allergic diseases and disease activity of JIA.

Method : This study included JIA patients aged < 18 years who visited the pediatric rheumatology clinic at Khon Kaen University Hospital, Thailand between November 2019-October 2020. Allergic diseases were screened using International Study of Asthma and Allergies in Childhood (ISAAC) questionnaires and then confirmed by clinical criteria and tests. Severity of allergic diseases were assessed using standardized clinical scores. The correlations between severity of allergic diseases and disease activity of JIA were analyzed.

Results : A total of 40 patients were included in this study. Nine patients (22.5%) were confirmed to have allergic rhinitis. None of them were confirmed to have either asthma or atopic dermatitis. The most common clinical presentation of allergic rhinitis was sneezing/itching. The most common allergen causing allergic rhinitis is Dermatophagoides farinae. There were no significant correlations between severity of allergic rhinitis and disease activity. There were no statistically significant differences between the patients who had and did not have allergic rhinitis.

Conclusions : Prevalence of allergic rhinitis in JIA patients in our study was 22.5%, higher relative to the general population. JIA patients should be screened and evaluated for concomitant allergic diseases.

Keywords : Juvenile idiopathic arthritis, allergic dieases, prevalence of allergic rhinitis

Introduction

Prevalence of allergic and autoimmune diseases are simultaneously rising[1,2]and cause a significant burden[3,4]. This parallel increasing prevalence of these two disorders indicates a possibility of their association.

The pathogenesis of allergic and autoimmune diseases occurs through complex immune responses. Allergic diseases are prototypic T helper cell type 2 (Th2) –mediated[5]. In contrast, one of the major pathogeneses of autoimmune diseases is a failure of tolerance that subsequently activates self-reactive T helper cell type 1 (Th1) and characterized by a Th1 cytokine profile[6] .

According to aforementioned Th1 /Th2 paradigm mechanistic theory the two disorders should be mutually exclusive or even confer some protection from one another as previously demonstrated in patients with rheumatoid arthritis who had lower prevalence of clinical and serological atopic features[7] and house dust mite sensitivity compared, to healthy controls[8].

However, there is evidence that the two disorders could co-exist. A classic example of this is found in immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome. Patients with IPEX syndrome typically present with triad of enteropathy, autoimmune endocrinopathy and dermatitis in which atopic dermatitis is a frequent finding[9]. Other examples are co-occurrence of asthma and the inflammatory bowel diseases[10] celiac disease[11], type I diabetes and even rheumatoid arthritis in a different study[12] Furthermore, it has been demonstrated that allergic diseases could pose a long-term risk of autoimmune diseases[13] and vice versa[14]

Due to this conflicting data, further research is essential. Therefore, we conducted a cross sectional study to evaluate prevalence of allergic diseases in patients with juvenile idiopathic arthritis (JIA), the most common rheumatologic disease in children[15] in which one of the main pathogenesis is autoimmunity[16] The accuracy of the diagnoses were certified by a pediatric allergist and rheumatologist using standardized criteria. In addition, the association between severity of allergic diseases and disease activity of JIA activity was evaluated. If an association was discovered, controlling allergic diseases could lead to improved disease activity of JIA. Our study aimed to evaluate the prevalence and clinical manifestations of allergic diseases in patients with JIA and their association with disease activity of JIA.

Method

Subjects

JIA patients aged $\leq$18 years who visited a pediatric rheumatology clinic at Khon Kaen University Hospital, Thailand from November 2019-October 2020 were included in the study. Patients with an overlapping syndrome were excluded. JIA and its subtype were diagnosed according to the International League Against Rheumatism (ILAR) criteria[17] by a pediatrician who subspecialized in both allergy/immunology and rheumatology.

Disease activity of JIA was assessed as the following: the 27-joint Juvenile Arthritis Disease Activity Score (JADAS27)[18], the Thai version of Childhood Health Assessment Questionnaire-disablitiy index (CHAQ-DI)[19], the number of active joint count, the physician's global assessment of overall disease activity (PGA), and the parent's or patient's global assessment of overall disease activity (PtGA)[20]. The PGA and PtGA were recorded on a range of 0–10 using a visual analogue scale, with 0 representing no disease activity and 10 representing very severe disease activity or the worst pain. Laboratory parameters were erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

Diagnosis and severity assessment of allergic diseases

The International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire [21,22] was used to screen for allergic rhinitis, asthma

and atopic dermatitis. Allergic diseases were then confirmed and assessed for severity by a pediatric allergist and rheumatologist.

The diagnosis of allergic rhinitis was based on the international consensus report on the diagnosis and management of rhinitis[23], in which the patients must have history of 2 or more of these following symptoms; nasal discharge, blockage, sneeze/itch, which last more than 1 hour on most days. Skin prick tests of common aeroallergens for Thai children were done[24]. Severity of allergic rhinitis was assessed using a visual analog scale (VAS)[25] and was classified into intermittent/persistent and mild/moderate-severe as the allergic rhinitis and its impact on asthma (ARIA) recommendations[26].

The diagnosis of asthma was based on the history of characteristic symptom patterns such as wheezing, shortness of breath, dyspnea, chest tightness or cough, and variable expiratory airflow limitation as documented by pulmonary function test. Asthma symptom control was classified as well controlled, party controlled and uncontrolled according to the Global Initiative for Asthma (GINA)[27] classification of symptom control. The Thai-Translated version of the Childhood Asthma Control Questionnaire (C-ACT)[28] was used as numerical asthma control score.

Atopic dermatitis was diagnosed based on Hanifin and Rajka's diagnostic features of atopic dermatitis[29]. Severity of atopic dermatitis was assessed by SCORing Atopic Dermatitis (SCORAD)[30].

Statistical analysis

Data was analyzed using non-parametric descriptive statistics (percentage, median and interquartile range; IQR), as the data were mainly non-normally distributed. Proportional data were compared using Chi-squared or the Fisher exact test, as appropriate. Continuous variables between groups were analyzed using Mann–Whitney U test. Correlation between severity of allergic diseases and disease activity of JIA was assessed by Spearman rank-order correlation coefficient. All data analyses were performed by SPSS version 19. P-value < 0.05 was considered significant.

Results

A total of 40 patients met the inclusion and were included in this study. 26 (65%) of them were female. The median age and duration of disease were 11.16 (IQR 7.69-13.84) and 2.79 (IQR 0.60-6.05), respectively. Three patients had a self-reported history of food or drug allergy. The most common subtype of JIA was systemic JIA (32.5%), and the second most common was enthesitis-related arthritis (20%). Disease activity of JIA and inflammatory markers as shown in table 1.

Twelve (30%) of patients had a positive screening questions for allergic diseases

(9 for allergic rhinitis, 2 for asthma and 1 for atopic dermatitis). Among them, 9 patients (22.5%) were confirmed to have allergic rhinitis. None of them were confirmed to have asthma or atopic dermatitis.

The most common clinical presentation of allergic rhinitis was sneezing/itching (100%). One patients (11.11%) had severe persistent symptoms and had not been had been diagnosed with or was previously known to have allergic rhinitis. The rest of the patients (88.89%) had mild intermittent allergic rhinitis, in which only one patient had been previously diagnosed and prescribed regular medication. The most common allergen, as defined by positive skin test was Dermatophagoides farinae (66.67%).

We found no significant correlations between severity of allergic rhinitis, as defined by VAS and ARIA classification, and disease activity of JIA as assessed, by JADAS27 and other parameters (Table 2).

No significant differences in characteristics were found when comparing between patients with allergic rhinitis and those without. Subtypes of JIA did not show any associations with having allergic rhinitis (Table 1).

Table 1 Patient characteristics

Characteristic	All patients	Patients with confirmed allergic disease	Patients without confirmed allergic disease	*P-Value
Number (n, %)	40 (100)	9 (22.50)	31 (77.50)	-
Female (n, %)	26 (65.00)	8 (88.89)	17 (54.84)	0.12
Age (Year, IQR)	11.16 (7.69-13.84)	10.20 (7.59-16.18)	12.21 (7.96-13.57)	0.60
Duration of disease (years, IQR)	2.79 (0.60-6.05)	2.14 (0.54-5.93)	2.93 (0.46-6.18)	0.70
Food or drug allergy (n, %)	3 (7.50%)	2 (22.22%)	1 (3.23%)	0.12
JADAS27 (score, IQR)	4.10 (2.15-8.15)	4.30 (3.75-20.50)	4.00 (1.10-7.00)	0.13
CHAQ-DI (score, IQR)	0 (0.00-0.00)	0 (0.00-0.125)	0 (0.00-0.00)	0.50
Active joint count (n, IQR)	0.00 (0.00-1.75)	1.00 (0.00-9.00)	0.00 (0.00-1.00)	0.11
PGA (score, IQR)	3 (2.50-4.50)	3 (2.50-4.50)	2.00 (1.00-3.00)	0.11
PtGA (score, IQR)	0.00 (0.00-2.36)	0.00 (0.00-6.00)	0.00 (0.00-1.00)	0.79
ESR (mm/hr, IQR)	21.00 (11.00-35.00)	19.50 (15.50-31.75)	22.00 (11.00-40.00)	0.84
CRP (mg/L, IQR)	2.81 (0.76-14.69)	3.92 (0.91-14.14)	2.78 (0.59-14.10)	0.96
Subtype of JIA (n, %)				
- Systemic	13 (32.50)	2 (22.22)	11 (35.48)	0.69
- Oligoarthritis (persistent)	6 (15.00%)	1 (11.11)	5 (16.13%)	1.00
- Oligoarthritis (extended)		-	-	-
- Polyarthritis (RF-)	6 (15.00)	2 (22.22)	4(12.90)	0.60
- Polyarthritis (RF+)	5 (12.50)	1 (11.11)	4 (12.90)	1.00
- Psoriatic arthritis		-	-	-
- Enthesitis-related arthritis	8 (20.00)	2 (22.22)	6 (19.35)	1.00
- Undifferentiated arthritis	2 (5.00)	1 (11.11)	1 (3.23)	0.40

*Compared between patients with and without confirmed allergic disease
CHAQ-DI, childhood health assessment questionnaire disability index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; JADAS27, 27-Joint Juvenile Arthritis Disease Activity Score; JIA, juvenile idiopathic arthritis; PGA, physician's global assessment; PtGA, patient's global assessment; RF, rheumatoid factor.

Table 2 correlation between severity of allergic rhinitis (VAS) and disease activity of JIA

	JADAS27	CHAQ-DI	Active joint count	PGA	PtGA	ESR	CRP
Correlation	0.43	0.16	0.43	0.24	0.53	0.39	-0.23
P-value	0.24	0.68	0.25	0.54	0.14	0.34	0.59

CHAQ-DI, childhood health assessment questionnaire disability index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; JADAS27, 27-Joint Juvenile Arthritis Disease Activity Score; JIA, juvenile idiopathic arthritis; PGA, physician's global assessment; PtGA, patient's global assessment

Discussion

Previous research has demonstrated the coexistence of autoimmune diseases, which are primarily driven by Th1, and allergic diseases which are associated with Th2 activation[9-12].

Our study supports these findings. We found that prevalence of allergic rhinitis in JIA patients was 22.5%, higher than a recent study in Thai children[31] and the global population[32]. The study on school-age children in Bangkok, Thailand, revealed prevalence of current allergic rhinitis in children aged 6–7 and 13–14 years at 15.0% and 17.5%, respectively[31]. This study used GAN 2016 standardized written core questionnaire for allergic rhinitis modifying from the ISAAC questionnaire, which is identical to our questionnaire but a question about doctor-diagnosed asthma, rhinitis and eczema was added. Globally, prevalence for allergic rhinitis as surveyed by the ISAAC questionnaire was 8.5% in the 6-7-year age and 14.6% in the 13-14-year age group [32].

Prevalence of allergic rhinitis in JIA patients in our study was smilar to a study in China in which 52 JIA patients were diagnosed with allergic rhinitis from a pool of 189 patients (27.5%)[33]. A population-based case-control study using data from the Taiwan National Health Insurance Research Database found prevalence of pre-existing allergic rhinitis at 31.9% and also found it to be a risk factor for developing JIA[34]. Conversely, a case-control study in Turkey found a decreased frequency of allergic rhinitis in juvenile idiopathic arthritis patients (1%) compared to the control group (7.8%)[35].

The plausible immunological explanation for co-occurrence of JIA and allergic rhinitis is dysfunction of regulatory T-cells causing immunodysregulation. Regulatory T-cells play a fundamental role in the maintenance of immune tolerance, helping to prevent autoimmune and allergic diseases[36]. Regulatory T-cells number are reduced and their function impaired in JIA[37,38]. Similarly, alterations in the regulatory numbers and function have been identified in allergic rhinitis[39].

We did not find any patients with concomitant asthma or atopic dermatitis. This contrasts with previous studies, in which JIA patients have been demonstrated to have atopic dermatitis and asthma as comorbidities or pre-existing diseases. A possible explanation is our small sample size. More patients' enrollment is required for more accurate estimations of prevalence of these allergic diseases.

Severity of allergic disease did not correlate with disease activity of JIA in our study. This contradicted previous findings, in which JIA patients with concurrent allergic rhinitis who had received treatment for their allergic rhinitis had better control of JIA[35]. This discrepancy could be attributed to the limitations of conducting a cross-sectional study in which severity of JIA was assessed at one time point per patient, and the phase of treatment at the time of assessment varied among the patients. A longitudinal follow-up of the patients may demonstrate a clearer association.

Interestingly, of all patients, including patients with severe persistent allergic rhinitis, only one had been previously diagnosed with and treated for allergic rhinitis. The majority of the patients were under the universal health coverage scheme and had had multiple visits with primary physicians before referred to our hospital, a tertiary referral center. This indicates underrecognized and underdiagnosed of allergic rhinitis. Therefore, raising awareness of the disease in both patients and physicians is essential. Treatment of concurrent allergic rhinitis should be initiated promptly to improve the patients' quality of life[40].

Potential limitations of this study include the following. Firstly, as this is a pilot study, the number of patients was limited as we enrolled the patients from a single center during a limited period of time. Secondly, our study was a cross-sectional study. Hence, the precision of correlation between severity of allergic diseases and disease activity of JIA is limited. Thirdly, the prevalence of allergic rhinitis was compared to the population using existing data from studies with similar but

not identical method. Due to the initial promising results and conflicting data with previous studies, a further prospective study with more patient enrollment and normal control will be conducted.

In conclusion, prevalence of allergic rhinitis in JIA patients was higher relative to the general population. JIA patients should be screened for allergic disease and if found to be positive, should be thoroughly evaluated for concomitant allergic diseases. Severity of allergic disease did not correlate with disease activity of JIA.

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ความชุกของโรคภูมิแพ้ ในผู้ป่วยโรคข้ออักเสบชนิดไม่ทราบสาเหตุในเด็ก

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ความเป็นมา : ปัจจุบันความชุกของโรคภูมิแพ้ (Allergic disease) และโรคภูมิต้านทานเนื้อเยื่อตัวเอง (Autoimmune disease) มีแนวโน้วเพิ่มขึ้น แต่ข้อมูลเกี่ยวกับความสัมพันธ์ระหว่างทั้งสองภาวะนั้น ยังไม่มีข้อสรุปที่ชัดเจน

วัตถุประสงค์ : เพื่อหาความชุกของโรคภูมิแพ้ ในผู้ป่วยโรคข้ออักเสบไม่ทราบสาเหตุในเด็ก (Juvenile Idiopathic Arthritis) และหาความสัมพันธ์ระหว่างระดับความรุนแรงของโรคภูมิแพ้ และระดับภาวะการอักเสบของโรคข้ออักเสบไม่ทราบสาเหตุในเด็ก

วิธีการศึกษา: การศึกษาวิจัยนี้ ศึกษาในผู้ป่วยโรคข้ออักเสบไม่ทราบสาเหตุในเด็ก ที่มีอายุน้อยกว่า 18 ปี และเข้ารับการตรวจและติดตามการรักษาที่ห้องตรวจโรคข้อและรูมาติซั่มในเด็ก โรงพยาบาลศรีนครินทร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น ในช่วงเดือนพฤศจิกายน 2562 - ตุลาคม 2563
โดยโรคภูมิแพ้จะถูกคัดกรอง โดยการใช้แบบสอบถามของ International Study of Asthma and Allergies in Childhood (ISAAC) และจะได้รับการยืนยันการวินิจฉัย โดยการทดสอบทางห้องปฏิบัติการ และเกณฑ์การวินิจฉัยทางคลินิก ส่วนความรุนแรงของภาวะโรคภูมิแพ้จะได้รับการประเมิณโดยใช้ เกณฑ์การให้คะแนนมาตรฐานทางคลินิก สุดท้ายจึงนำมาวิเคราะห์ถึงความสัมพันธ์ระหว่างความรุนแรงของโรคภูมิแพ้ และระดับภาวะการอักเสบของโรคข้ออักเสบไม่ทราบสาเหตุในเด็ก

ผลการศึกษา : จำนวนของผู้ป่วยทั้งหมดที่เข้าร่วมการศึกษาวิจัย มีทั้งหมด 40 คน ผู้ป่วยทั้งหมด 9 คน (คิดเป็น 22.5%) ได้รับการยืนยันการวินิจฉัยว่ามีภาวะโรคจมูกอักเสบจากภูมิแพ้ (Allergic Rhinitis), จากจำนวนผู้ป่วยทั้งหมด พบว่าไม่มีผู้ป่วยรายใดได้รับการยืนยันการวินิจฉัยว่าเป็นโรคหอบหืด (Asthma) หรือโรคภูมิแพ้ผิวหนัง (Atopic dermatitis) จากการศึกษาครั้งนี้ พบว่าอาการแสดงที่พบมากที่สุดของภาวะจมูกอักเสบจากภูมิแพ้ คือ อาการจาม และอาการคันจมูก ในเรื่องของสารก่อภูมิแพ้ (Allergen) ที่พบว่าเป็นสาเหตุของโรคภูมิแพ้ส่วนใหญ่เกิดจากไรฝุ่นชนิด Dermatophagoides farinae จากการศึกษาวิจัยนี้พบว่า ไม่มีความสัมพันธ์อย่างมีนัยสำคัญระหว่างความรุนแรงของ Allergic rhinitis และระดับการอักเสบของโรคปวดข้อไม่ทราบสาเหตุในเด็ก และพบว่าไม่มีความแตกต่างทางสถิติ ระหว่างผู้ป่วยโรคข้ออักเสบไม่ทราบสาเหตุในเด็กที่มีและไม่มีภาวะ Allergic rhinitis

สรุป : ความชุกของโรคจมูกอักเสบจากภูมิแพ้ ในผู้ป่วย JIA ในการศึกษานี้คิดเป็น 22.5 % โดยพบว่าเป็นความชุกที่สูงกว่า ความชุกของโรคจมูกอักเสบจากภูมิแพ้ ในประชากรทั่วไป ดังนั้นผู้ป่วย JIA จึงควรได้รับการคัดกรอง และประเมิณภาวะภูมิแพ้ที่เป็นภาวะที่อาจเกิดขึ้นร่วมด้วย

คำสำคัญ : โรคปวดข้ออักเสบไม่ทราบสาเหตุในเด็ก , โรคภูมิแพ้ , ความชุกของโรคจมูกอักเสบจากภูมิแพ้

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