Factors related to Juvenile Idiopathic Arthritis Complicated with Hyperuricemia

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Abstract

Background

Clinical findings reported that some cases of Juvenile Idiopathic Arthritis (JIA) gradually suffer from hyperuricemia (HUA) during the course of follow-up, followed by the detection of high urate crystal, gout, renal impairment, and other manifestations. And those patients would influence the prognosis.

Methods

This was a retrospective study of 60 patients diagnosed with JIA between October 2016 and March 2019 and followed up for > 1 year. Single-factor analyses of the clinical data, laboratory data, and the special drug used for JIA complicated with hyperuricemia (Group A, n = 18) and JIA without hyperuricemia (Group B, n = 42) were conducted.

Results

Comparison between Groups A and B revealed differences in sex; disease course; high disease activity; diastolic pressure; the levels of serum albumin (ALB), alanine aminotransferase (ALT), aspartate transaminase (AST), triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), glucose (GLU), and urea nitrogen (BUN); NSAIDS application, systemic glucocorticoid application, MTX application, and tumor necrosis factor-alpha (TNF-α) inhibitors application were not statistically significant (P > 0.05). However, the differences in age, active sacroiliitis, body mass index (BMI), systolic pressure, serum creatinine (Scr) level, and salicylazosulfapyridine (SASP) application showed a statistical significance (P < 0.05).

Conclusions

JIA patients were obese, with high systolic pressure, and after SASP treatment will be more likely to be complicated with hyperuricemia.

Background

Juvenile idiopathic arthritis (JIA) is a common pediatric rheumatic disease that manifests mainly as joint impairment complicated with systemic multiple organ dysfunctions. Hyperuricemia is the immediate cause of gout, which shows clinical manifestations such as acute arthritis, chalkstone, and renal impairment. Joint symptoms also aggravate, and the impairment of different organs becomes exceptionally severe in the event of these two diseases occurring in combination. Clinical findings reported that some cases of JIA gradually suffer from hyperuricemia during the course of follow-up, followed by the detection of high urate crystal, gout, renal impairment, and other manifestations. However,
no case of JIA complicated with hyperuricemia has yet been reported in this context. This study attempted to identify the risk factors associated with JIA complicated with hyperuricemia and to explore the potential connections between them. It is expected that the knowledge about these associations will greatly add to the data on the prevention and treatment of JIA complicated with hyperuricemia, including gout.

Participants And Methods

Participants

A total of 60 patients diagnosed with JIA between October 2014 and March 2017 and who had completed >1 year follow-up visits with a complete set of related data were selected for the present analysis. High uric acid (UA) levels were defined as level > 416 µmol/L. As per the International League of Associations for Rheumatology (ILAR), JIA is defined as arthritis of unknown etiology that begins before the 16th year of age and persists for at least 6 weeks with other known conditions excluded. For the JIA treatment and disease activity, the relevant recommendations by the 2011 American College of Rheumatology were considered [1].

Methods

During the disease diagnosis and regular follow-up until 1-year, the sex, age, disease course, JIA group type, disease activity, height, weight, body mass index (BMI) (as an indicator of body fat level and health), systolic pressure, diastolic pressure, biochemical indices including glucose (GLU), serum albumin (ALB), alanine aminotransferase (ALT), aspartate transaminase (AST), triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), UA, serum creatinine (Scr), blood urea nitrogen (BUN), and the application of various special drugs including non-steroidal anti-inflammatory drugs (NSAIDs), methotrexate (MTX), salicylatesulfapyridine (SASP), tumor necrosis factor-alpha (TNF-α) inhibitors, and systemic glucocorticoid (GC) of pediatric patients were recorded in details. The UA level was monitored once every 1–2 months; the patients whose UA level gradually rose with ≥2 incidences of hyperuricemia were classified as cases of JIA complicated with hyperuricemia (Group A), while others were classified as cases of JIA without hyperuricemia (Group B). Single-factor analyses was performed between Groups A and B for 24 indices, including JIA general clinical data, laboratory biochemical indices, and use of special medications. The sex, age, disease course, JIA group type, disease activity, BMI, and blood pressure were measured at the baseline (as the time of diagnosis), the remaining factors were measured at the baseline and at 1-year follow-up. The dual-energy computed tomography (CT) of the joints was examined at 6 and 12 months after Group A pediatric patients developed hyperuricemia.

Statistical analysis
Normality test was conducted on all measurement data using the SPSS19.0 statistical package. The measurement data in the normal distribution was denoted by $x \pm s$, independent sample $t$ test was performed, the measurement data in skewed distribution was denoted by $M (Q1, Q3)$, the independent sample rank sum test was performed, and the measurement data was analyzed by Chi-square test. $P < 0.05$ was considered to be statistically significant.

**Results**

**General data**

A total of 60 cases of JIA pediatric children were selected (40 boys, 20 girls; age range: 3–16 years) of average age 10.9 ± 3.4 years at the time of diagnosis. The course of disease ranged from 1.5 months to 7 years, with the median course of 0.5 years. A total of 22 and 12 cases belonged to $\leq 4$ and $\geq 5$ arthritis group, respectively. A total of 16, 2, and 8 cases showed active sacroiliitis, systemic arthritis with systemic symptoms, and systemic arthritis with arthritis symptoms, respectively. A total of 6, 18, and 36 cases showed low, medium, and high disease activities, respectively. At the time of diagnosis, other than 25 patients who irregularly applied NSAIDs, the remaining had no history of special medication. At the time of diagnosis, 2 JIA cases were complicated with hyperuricemia, both the patients were obese, and 16 JIA patients gradually suffered from hyperuricemia during the 1-year follow-up.

**Comparison of the general clinical conditions between Groups A and B at the time of diagnosis is given in Table 1.**

The differences in the age, active sacroiliitis status, BMI, and systolic pressure between Groups A and B revealed a statistical significance ($P < 0.05$), albeit there was no statistical significance in the sex, disease course, cases of high disease activity, and diastolic pressure ($P > 0.05$). The JIA pediatric patients were older, had high BMI and systolic pressure, had active sacroiliitis, and were more vulnerable to hyperuricemia.
Table 1
Comparison of the general clinical conditions between Groups A and B

|               | Gender (n) | Age (y) ± | Disease course (y) | Active sacroiliitis (n) | High disease activity (n) | BMI (kg/m²) ± | Systolic pressure (mmHg) ± | Diastolic pressure (mmHg) ± |
|---------------|------------|-----------|--------------------|------------------------|--------------------------|---------------|-----------------------------|----------------------------|
| Group A       | 18         | 15        | 13.4 ± 1.5         | 0.5 (0.4, 1.3)         | 11                       | 20.3 ± 3.4    | 114.8 ± 9.8                 | 69.1 ± 11.4                |
| Group B       | 42         | 25        | 9.8 ± 3.4          | 0.5 (0.25, 1.0)        | 5                        | 18.0 ± 3.3    | 104.6 ± 8.3                 | 64.0 ± 7.2                 |

X²/Z/t:

|               | P          |
|---------------|------------|
| Group A       | 0.135      |
| Group B       | 0.000      |
| X²/Z/t        | 0.346      |
| P             | 0.000      |
| X²/Z/t        | 0.49       |
| P             | 0.017      |
| X²/Z/t        | 0.000      |
| P             | 0.094      |

Comparison of the special medication between Groups A and B in the 1-year follow-up is given in Table 2.

The therapeutic program was based on the 2011 American College of Rheumatology recommendations for the treatment of JIA. Both the groups of patients were applied with NSAIDs, except for 3 cases who could not tolerate gastrointestinal reactions. SASP was widely applied to the active sacroiliitis group. TNF-α inhibitors were applied to the cases with the features of poor prognosis, high disease activity, and poor therapeutic effect of NSAIDs and/or MTX or SASP application. After SASP treatment, the patients were more likely to be complicated with hyperuricemia, and the difference was statistically significant (P < 0.05).

Table 2
Comparison of the special medications between Groups A and B

|               | NSAIDs (n) | MTX (n) | SASP (n) | Glucocorticoids (n) | TNF-α inhibitor (n) |
|---------------|------------|---------|----------|---------------------|---------------------|
| Group A       | 18         | 17      | 3        | 12                  | 2                   | 13                  |
| Group B       | 42         | 40      | 17       | 4                   | 9                   | 25                  |

X²:

|               | P          |
|---------------|------------|
| Group A       | 0.735      |
| Group B       | 0.135      |
| X²            | 0.000      |
| P             | 0.000      |
| Group A       | 0.56       |
| Group B       | 0.35       |

Comparison of the biochemical indices between Groups A and B in the 1-year follow-up (Table 3).
Of the biochemical indices, blood glucose, blood lipids, liver function, and renal function were closely related to occurrence of hyperuricemia. The comparison of the related indices indicated that the Scr level was slightly higher in Group A than in Group B, although the levels did not rise beyond the normal upper limit in both the groups, and the difference was statistically significant ($P < 0.05$). The risk of renal impairment was higher when the UA levels increased.

The dual-energy CT of the joints in Group A identified 8 cases of urate crystal, in which 5 cases occurred after 6 months of hyperuricemia and 3 cases occurred after 12 months of hyperuricemia; none of the groups experienced gout attack.

| Table 3 |
|---------|

**Comparison of the biochemical indices between Groups A and B**

|                  | Group A       | Group B       | Z/t     | P      |
|------------------|---------------|---------------|---------|--------|
| n                | 18            | 42            |         |        |
| UA (µmol/L)      | 452.3 ± 49.1  | 276.1 ± 59.4  | 11.067  | 0.000  |
| GLU (mmol/L)     | 4.8 ± 0.7     | 5.2 ± 0.9     | -1.685  | 0.097  |
| TC (mmol/L)      | 4.0 ± 0.9     | 3.9 ± 1.0     | 0.174   | 0.862  |
| TG (mmol/L)      | 1.1 ± 0.6     | 1.4 ± 1.1     | -0.9    | 0.372  |
| LDL (mmol/L)     | 2.1 ± 0.6     | 2.0 ± 0.6     | 0.52    | 0.605  |
| HDL (mmol/L)     | 1.2 ± 0.3     | 1.3 ± 0.4     | -0.714  | 0.478  |
| ALB (g/L)        | 45.2 ± 3.8    | 43.8 ± 3.6    | 1.434   | 0.157  |
| ALT (U/L)        | 13.5 (10.0, 22.0) | 13.0 (9.8, 18.3) | -0.154 | 0.878  |
| AST (U/L)        | 25.0 (19.8, 31.8) | 25.0 (22.0, 28.3) | -0.057 | 0.955  |
| Scr (µmol/L)     | 68.2 ± 8.8    | 58.1 ± 9.8    | 3.371   | 0.000  |
| BUN (µmmol/L)    | 4.3 ± 0.7     | 4.2 ± 1.2     | 0.376   | 0.708  |

**Discussion**

In this study, the risk factors for JIA complicated with hyperuricemia included the following: slightly high systolic pressure, obesity (high BMI), older age, active sacroiliitis status, and SASP application. After the incidence of hyperuricemia, the Scr level was relatively higher, but not beyond the normal upper limit, which indicated a potential risk of renal impairment. The urate crystals gradually formed after 6 months of hyperuricemia, indicating a higher risk of gout.

Due to the limited sample size, the 5 factors significantly related to the groups of interest could not be further analyzed through logistic regression to observe whether they were correlated.
The increase in the systolic pressure and obesity can be treated as predictive risk factors for hyperuricemia; which has also been mentioned as the risk factors by several large data epidemiological investigations associated with adult and child hyperuricemia cases\cite{2,3}. The food intake of obesity patients is greater than their calorie consumption, which results in the accumulation of excessive fat in the subcutaneous, abdominal, or internal organs, which in turn may add to the total amount of nucleic acid to be processed through purine metabolism that may lead to increase in the UA synthesis\cite{4}. The incidence of hyperuricemia may affect the renal functions, as has also been reported by several local and remote studies\cite{5,6}. High UA level leads to systemic hypertension and high pressure, high perfusion, and renal fibrosis in glomerulus through RAS, which ultimately results in renal impairment \cite{7,8}. In this study, after 6 months of hyperuricemia, the dual-energy CT examination of pediatric gout with diagnostic value revealed a gradual formation of urate crystals; despite the lack of symptoms, the examination predicted the development of gout.

However, no incidence of hyperuricemia in JIA active sacroiliitis individuals and pediatric patients with SASP treatment has yet been reported in local or foreign studies, which is consistent with our clinical findings. Since the majority of non-biological DMARDs selected for the JIA active sacroiliitis group was SASP, we inferred that the real cause leading to hyperuricemia is SASP instead of the active sacroiliitis group. Furthermore, because this JIA group included older patients, age was not an independent risk factor.

SASP is an azo complex of 5-aminosalicylic acid (5-ASA) and a sulfa pyridine, after it was applied orally and reached the colon, the azo bond cleaved subject to the effect of the intestinal bacterium– azoreductase. The released 5-ASA is the main active component of SASP, but approximately 80% of it remains in the colon where it plays the role of mucosal antibacterial anti-inflammation and immunological suppression, as well as exhibits anti-inflammatory effect by inhibiting the synthesis of prostaglandin and other inflammatory mediators such as leukotriene, leukocytes IL-1. Most of the released sulfa pyridine are absorbed into the colon, and, after the acetylation in the liver, they are excreted with the urine in the form of free sulfonamide, acetylation, hydroxylation, or glucuronic acid derivatives \cite{10}. This phenomenon may be attributed to the excretion of several acidifying substances competing against UA from the urine, which leads to an increase in the UA level. In case of insufficient water consumed during this period, which is necessary to maintain the high urine flow, it may lead to the incidence of crystalluria and aggravate the renal impairment. Therefore, excretion of UA is reduced. The specific mechanism involved in this phenomenon remains to be clarified.

The appropriate therapeutic program for JIA pediatric patients with obesity and high blood pressure was applied to reduce the application of SASP or the addition of alkalizing urine drugs as much as possible so as to reduce the incidence of hyperuricemia, renal impairment, and accumulation of urate crystal at the joints, which together further aggravate joint symptoms.

**Abbreviations**
JIA Juvenile idiopathic arthritis

HUA hyperuricemia.

GLU Glucose

ALB Albumin

ALT Alanine aminotransferase

AST Aspartate transaminase

TG Triglyceride

TC Total cholesterol

LDL-C Low-density lipoprotein cholesterol

HDL-C High-density lipoprotein cholesterol

Scr Serum creatinine

BUN Blood urea nitrogen

NSAIDs Non-steroidal anti-inflammatory drugs

MTX Methotrexate

SASP Salicylazosulfapyridine

TNF-α Tumor necrosis factor-alpha

GC Glucocorticoid

ILAR International League of Associations for Rheumatology

BMI Body mass index

5-ASA 5-aminosalicylic acid

**Declarations**

**Availability of data and materials**

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.
Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee of Ningbo Women and Children's Hospital (2018-LSZ-22). All patients and their parents provided written informed consent for their data to be used in analyses and reported.

Consent for publication

Yes.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

LW and YLC was responsible of the collection of clinical information on KD patients, statistical analyses, figures, data interpretation and manuscript preparation. LW and YYL were responsible for critical review of the statistical analyses and the manuscript. LW and JPW contributed in the writing of the manuscript and its scientific content. YZD is the project leader of the study; she is involved in the conceptualization of the project, the study design and preparation of the manuscript. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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