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ARAŞTIRMA / RESEARCH

Growth parameters of Turkish children with juvenile idiopathic arthritis

Juvenil idiopatik artritli Türk çocukların büyüme parametreleri

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Abstract

Purpose: Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in childhood which could results in growth retardation. With the present study, we aimed to investigate the growth parameters in Turkish children with JIA.

Materials and Methods: Clinical and laboratory data, weight, height, and body mass index of 233 JIA patients were retrospectively collected from medical files. Growth parameters and z-scores were calculated by anthropometric references in Turkish children. The patients were diagnosed according to the International League of Associations for Rheumatology classification criteria.

Results: The frequency of female patients was 59.2% (138). The mean age at diagnosis was 7.40±4.54 years, the mean age at the study time was 11.20±4.45 years. While mean initial visit weight and BMI z-scores were significantly improved at last visit, initial mean height z-score was significantly decreased. The frequency of short stature at last visit was 7.3% (number, 17). Acute phase reactants, including erythrocyte sedimentation rate, C-reactive protein levels were significantly lower at last visit than initial. Last visit growth parameters did not differ according age at diagnosis, disease duration and presence or absence of remission, relapses, corticosteroid usage, and biologic agent usage.

Conclusion: Suppressing ongoing inflammation in JIA patients improves both weight and BMI z-scores of those patients, however, it may be insufficient to prevent short stature.

Keywords:. Growth, children, juvenile idiopathic arthritis, corticosteroid

Öz

Amaç: Juvenil idiopatik artrit (JIA) çocukluk çağında en sık görülen romatizmal hastalıktır ve büyüme geriliği ile sonuçlanabilmektedir. Bu çalışma ile JIA'lı Türk çocuklarında büyüme parametrelerini araştırmayı amaçladık.

Gereç ve Yöntem: Juvenil idiopatik artrit tanılı 233 hastanın klinik ve laboratuvar verileri, vücut ağırlığı, boy ve vücut kitle indeksi (VKI) **bilgileri h**astaların tıbbi dosyalarından geriye dönük elde edildi. Büyüme verileri ve z-skorları Türk çocuklarının antropometrik referans değerlerine göre hesaplandı. Hastalara International League of Associations for Rheumatology sınıflama kriterlerine göre tanı kondu.

Bulgular: Hastaların %59,2'si (sayı, 138) kız hastaydı. Ortalama tanı yaşı 7.40±4,54 yıl ve çalışma esnasında ortalama yaş 11.20±4,45 yıldı. Ortalama ilk vizit vücut ağırlığı ve VKI z-skorları son vizit değerlere göre istatistiksel anlamlı olarak düzeldi. Ortalama ilk vizit boy z-skoru ise istatistiksel anlamlı olarak geriledi. Son vizitte kısa boy sıklığı %7,3 (sayı, 17) idi. Eritrosit çökelme hızı, C-reaktif protein düzeyleri dahil olmak üzere akut faz reaktanları son vizitte ilk vizit değerlerine kıyasla anlamlı olarak düşüktü. Son vizit büyüme parametreleri tanı yaşı, hastalık süresi, remisyon ve relaps durumu, kortikosteroid ve biyolojik ajan kullanımına göre farklılık göstermemekteydi.

Sonuç: JIA hastalarında devam eden inflamasyonun kontrol altına alınması ile vücut ağırlığı ve VKI z-skorları düzelebilir, fakat bu durum boy kısalığını önlemek için yeterli olmayabilir.

Anahtar kelimeler: Büyüme, çocuk, juvenile idiopatik artrit, kortikosteroid

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INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in childhood[1,2]. JIA encompasses several subgroups that all manifesting joint inflammation but present with various clinical characteristics and outcomes, requiring different treatment modalities[3]. Proinflammatory cytokines that play a role in JIA pathogenesis are interleukin-1β (IL-1β) and interleukin-6 (IL-6). These cytokines lead to chronic inflammation by local and systemic effects[4]. Chronic inflammatory process, which is the leading pathological mechanisms of JIA, and long-term corticosteroid usage result in growth abnormalities as well as poor weight gain in JIA patients[5]. In children suffering from JIA, the frequency of growth impairment ranges from 7-20% of patients, in which the most affected children are JIA patients with systemic and polyarticular subgroups[5].

The treatment modalities of JIA have been changed over the past decades which results in better controlling disease activity, increased life span, and quality of life[2]. Growth is an important indicator of well-being in children. Therefore, in this article, we aimed to investigate the growth parameters in a sample of Turkish children with JIA and to compare the growth parameters of JIA patients according to the gender, remission status, disease duration and prescribed medications, particularly corticosteroid.

MATERIALS AND METHODS

This retrospective study includes 233 Turkish children with JIA. The patients were under control for at least 6 months, and their anthropometric data were available at baseline. The patients were diagnosed according to the International League of Associations for Rheumatology (ILAR) classification criteria as oligoarticular JIA, rheumatoid factor (RF) positive polyarticular JIA, RF-negative polyarticular JIA, systemic-onset JIA (soJIA), enthesitis-related arthritis (ERA), juvenile psoriatic arthritis (JPsA), and undifferentiated JIA[3]. The data including gender, age at disease onset and diagnosis, JIA subgroups, clinical and laboratory characteristics, and medication data were retrospectively collected from medical files. Laboratory parameters, including whole blood counts, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) were noted.

The clinical states of JIA patients were defined as inactive disease, clinical remission on medication, and clinical remission off medication according to the Wallace criteria [6]. Inactive disease includes the following items: no active arthritis; no fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA; no active uveitis; normal ESR or CRP; and physician's global assessment of disease activity indicates no activity. According to the criteria, six continuous months of inactive disease on medication indicates clinical remission on medication and 12 months of inactive disease without all medications, including medications for uveitis, indicates clinical remission off medication[6]. The ethical approval was obtained from Cukurova University Medical Faculty Ethical Committee (Number: 82, Date: 2 November 2018). Written informed consent was obtained from the parents of each patient prior to the study.

Anthropometric data

The height in centimeters (cm) and weight in kilograms (kg) of all children were measured routinely at each visit by the same operator with the same type of stadiometer (Harpender). Body Mass Index (BMI) was calculated as weight (kg) divided by height (meters) squared. Weight (kg), height (cm), and BMI were collected, then, z-scores were measured by utilizing anthropometric references in Turkish children[7]. Short stature was defined as a height z-score < -2.

Statistical analysis

SPSS 20.0 statistical software (IBM SPSS Statistics) was utilized for all statistical analysis. Continuous variables were summarized as mean (standard deviation; SD) and as median, minimum-maximum where appropriate. Categorical variables were presented as percentages. The normality of distribution for growth parameters was confirmed with the Kolmogorov-Smirnov test, stem-and-leaf diagram, and the histogram. For comparison of continuous variables between two groups, the Student' t-test was utilized. Moreover, a paired-sample t-test was used for comparing two dependent variables in the same study group. The one-way analysis of variance (ANOVA) is used to determine whether there are any statistically significant differences between the means of two or more independent subgroups. The statistical level of significance for all tests was defined to be 0.05.

RESULTS

General demographic features and subgroups of 233 JIA patients are presented in Table 1. Initial and last visit laboratory parameters were compared. Acute phase reactants (APRs), including ESR, CRP levels were significantly lower at last visit than initial, which were given in Table 2 elaborately.

Table 1. General demographic features, subgroups and treatment modalities of juvenile idiopathic arthritis patients.

Demographic features	
Female/Male, n (%)	138 (59.2)/95 (40.8)
Age at diagnosis, years, mean (SD)	7.40 (4.54)
Diagnostic delay, months, median (range)	3.02 (0.46-59.9)
Age at study time, years, mean (SD)	11.20 (4.45)
Disease duration, years, mean (SD)	4.46 (3.27)
JIA subgroups	
Oligoarticular, n (%)	104 (44.6)
RF-positive, n (%)	10 (4.3)
RF-negative, n (%)	35 (15)
Systemic onset, n (%)	47 (20.2)
Enthesitis-related arthritis, n (%)	34 (14.6)
Juvenile psoriatic arthritis, n (%)	3 (1.3)
Treatments	
NSAIDs, n (%)	100 (100)
Corticosteroid, n (%)	56 (24)
Biologic agents, n (%)	117 (50.2)
DMARDs, n (%)	224 (96.1)

SD; Standard deviation, JIA; Juvenile idiopathic arthritis, RF; Rheumatoid factor, NSAID; Non-steroid anti-inflammatory drugs, DMARDs; Disease modifying antirheumatic drugs.

Table 2. Comparison of initial and last visit laboratory parameters of 233 juvenile idiopathic arthritis patients.

Laboratory data	**Initial visit**	**Last visit**	**p**
WBC; mm3, mean±SD	11400±5768	7775±2369	0.001
Hematocrit; %, mean±SD	33.9±4.7	37.9±3.1	0.001
Platelet count; mm3, mean ±SD	436000±149404	315000±84010	0.001
ESR; mm/h, median (min-max)	35 (2-140)	11 (2-119)	0.001
CRP; mg/dl, median (min-max)	2.2 (0-53.6)	0.2 (0.1-9.2)	0.001

WBC; White blood cell, SD; Standard deviation, ESR; Erythrocyte sedimentation rate, CRP; C-reactive protein; Paired t-test was utilized for comparison of parametric data and Wilcoxon signed rank test was used for non-parametric data, significant p values are presented in bold.

Initial and last visit growth parameters were compared. While mean initial visit weight and BMI z-scores were significantly improved at last visit, initial mean height z-score was significantly decreased. The frequency of last visit height z-score below -2 was 7.3% (number, 17) and the frequency of BMI score equal and above 25 was 6% (number, 14).

Initial and last visit growth parameters of patients were not statistically significant between genders. Moreover, there was not a relationship between delay in diagnosis and initial and last visit growth parameters. Comparison of initial and last visit growth parameters of the patients were given in Table 3.

Table 3. Comparison of initial and last visit growth parameters of 233 juvenile idiopathic arthritis patients.

Growth parameters	**Initial visit**	**Last visit**	**p**
Weight z-score (mean±SD)	-0.77±3.74	-0.26±1.32	0.026
Height z-score (mean±SD)	0.07±1.40	-0.10±1.36	0.023
BMI z-score (mean±SD)	-0.71±1.62	-0.07±1.71	0.001

SD; Standard deviation, BMI; Body Mass Index; Paired t-test was utilized for comparison of data; significant p values are presented in bold.

Initial and last visit growth parameters of patients with oligoarticular JIA, RF-negative polyarticular JIA, and soJIA subgroups were compared. One-way Anova revealed no statisticaly significant difference between these subgroups. However, post-hoc analysis performed by Tukey's HSD test showed that last visit weight z-score was significantly lower in RF-negative polyarticular JIA subgroup than patients with oligoarticular JIA (p=0.048). Comparison of initial and last visit growth parameters of JIA subgroups were presented in Table 4.

Table 4. Comparison of initial and last visit growth parameters of juvenile idiopathic arthritis patients with oligoarticular, rheumatoid factor negative polyarticular, and systemic onset subgroups.

Growth parameters (mean±SD)	**Oligoarticular**	**RF-negative polyarticular**	**Systemic onset**	**p**
Initial weight z-score	-0.94±3.20	-.086±1.57	-0.84±1.42	0.987
Initial height z-score	0.17±1.52	-0.26±1.40	0.15±1.16	0.198
Initial BMI z-score	-0.66±1.75	-0.82±1.52	-1.24±1.40	0.140
Last weight z-score	-0.16±1.37	-0.71±1.25	-0.32±1.17	0.062
Last height z-score	0.01±1.25	-0.37±1.28	-0.09±1.14	0.222
Last BMI z-score	-0.06±1.29	-0.48±1.31	0.13±2.81	0.228

RF; Rheumatoid factor, SD; Standard deviation, BMI; Body Mass Index; One-was Anova was utilized for comparison of data.

We compared the last visit growth parameters of JIA patients according to the presence or absence of remission as well as relapses. The differences between growth parameters were not statistically significant in the both scenarios, except mean BMI z-score of JIA patients without relapses was significantly lower. Comparison of last visit growth parameters of juvenile idiopathic patients according to the presence or absence of remission, relapses were presented in Table 5, in detail.

Table 5. Comparison of last visit growth parameters of juvenile idiopathic arthritis patients according to the presence or absence of remission, relapses.

	Remission (n, %)		
Growth parameters	Presence (207, 89)	Absence (26, 11)	p
Weight z-score (mean±SD)	-0.22±1.33	-0.64±1.19	0.121
Height z-score (mean±SD)	-0.05±1.36	-0.49±1.33	0.124
BMI z-score (mean±SD)	-0.12±1.33	0.32±3.51	0.207
	Relapses (n, %)		
Growth parameters	Presence (60, 26)	Absence (173, 74)	p
Weight z-score (mean±SD)	-0.03±1.39	-0.34±1.29	0.120
Height z-score (mean±SD)	0.06±1.35	-0.15±1.37	0.268
BMI z-score (mean±SD)	0.32±2.57	-0.21±1.26	0.035

SD; Standard deviation, BMI; Body mass index.; Student's t-test was used for the comparison of data. Significant p values (<0.05) are presented in bold.

Table 6. Comparison of last visit growth parameters of juvenile idiopathic arthritis patients according to the presence or absence of corticosteroid treatment, and at least one biologic agent.

	Corticosteroid (n, %)		
Growth parameters	**Presence (56, 24)**	**Absence (177, 76)**	**p**
Weight z-score (mean±SD)	-0.34±1.06	-0.24±1.39	0.606
Height z-score (mean±SD)	-0.06±1.09	-0.11±1.44	0.840
BMI z-score (mean±SD)	0.06±2.58	-0.11±1.33	0.496
	Biologic agent (n, %)		
Growth parameters	**Presence (117, 50.2)**	**Absence (116, 49.8)**	**p**
Weight z-score (mean±SD)	-0.30±1.45	-0.23±1.17	0.698
Height z-score (mean±SD)	-0.12±1.34	-0.08±1.39	0.825
BMI z-score (mean±SD)	0.00±2.12	-0.14±1.16	0.522

SD; Standard deviation, BMI; Body mass index; Student's t-test was used for the comparison of data. Significant p values (<0.05) are presented in bold.

The patients were grouped according to the age at the time of diagnosis as follows: Group 1; ≤8 years, Group 2; >8 years. The last visit growth parameters were compared between the two groups. The differences between groups were not significant.

The patients were once more grouped according to the disease duration as follows: Group 1; ≤5 years, Group 2; >5 years. The last visit growth parameters were compared between the two groups. The differences between groups were not significant.

The last visit growth parameters were also compared according to the presence or absence of corticosteroid treatment, and at least one biologic agent, however, the differences between the last visit growth parameters were not statistically significant. Comparison of the last visit growth parameters of juvenile idiopathic patients according to the presence or absence of corticosteroid treatment and at least one biologic agent was showed in Table 6.

DISCUSSION

In the present report, we have investigated the growth parameters of 233 JIA patients. Mean weight and BMI z scores of the patients were significantly improved at last visit. However, the mean height z-score was significantly lower at last visit than initial. Moreover, laboratory parameters including APRs were also significantly improved at last visit. Improving laboratory parameters at last visit in patients with JIA means suppressing ongoing inflammation which may explain the significant improvements in both weight and BMI z-scores at last visit. However, suppressing ongoing inflammation was not solely enough to prevent diminishing the last visit height z-score. The frequency of short stature was 7.3% at last visit. The last visit growth parameters did not differ according to presence or absence of remission and relapses, age at the time of diagnosis and the duration of disease. Furthermore, the last growth parameters were also compared according to the presence or absence of corticosteroid treatment, at least one biologic agent. Only 24% of JIA patients received systemic corticosteroid. Last visit growth parameters did not differ in patients with and without corticosteroid treatment and at least on biologic agent. However, mean last visit BMI z-score of patients with relapses was significantly higher than those without. This finding led us to think that JIA patients with relapses might require more corticosteroid treatment with long-term usage. However, because the data on the length and dose of corticosteroid usage was not available, we could not analyze the relationship of corticosteroid dose and length with BMI z-scores.

Chronic inflammation in rheumatic diseases cause growth retardation in children[8,9]. Juvenile idiopathic arthritis is a well-known chronic inflammatory disease, causing growth retardation which are associated with overproduction of proinflammatory cytokines such as interleukin-1β (IL-1β), IL-6 and tumor necrosis factor-α[5,10]. Over the last decades the treatment modalities of JIA have been greatly improved which affect the controlling the chronic inflammation of the disease and in return positively affect the growth parameters in those patients[11-13].

There are several studies investigating growth patterns of JIA patients[13,14]. In 2017, Guzman et al have investigated the growth and weight gain in 1147 Canadian children with JIA. Mean height z-scores of the whole cohort remained unchanged and short stature was identified in 3.4% of the patients. However, mean height z-score of soJIA patients decreased and did not return to baseline in 3 years follow-up (9.3%). The frequency of short stature among corticosteroid users was significantly higher than non-users within 3 years. Moreover, systemic corticosteroid usage was related to the higher BMI z-scores[14]. The negative impact of corticosteroids on growth of particularly soJIA patients is well-described in previous publications[15,16]. However, it remains unclear whether this effect is solely due to the negative effect of corticosteroid on growth or simply due to the severe disease activity. In the present study we have found that children with JIA faced decreased mean height z-score compared to the baseline parameter. However, the mean height z-scores did not differ according to the presence of absence of corticosteroid usage. Initial and last visit growth parameters did not differ between patients with oligoarticular JIA, RF-negative polyarticular JIA, and soJIA subgroups.

Growth retardation have also been reported in 11.3% and 23.5% of soJIA patients in two previous studies from Turkey, respectively[17,18]. Moreover, one of which have reported the longer duration of corticosteroid and methotrexate treatment in soJIA patients with growth retardation.

In a previous publication, growth patterns of 568 JIA patients were investigated[13]. Median height z-score significantly decreased within 3 years compared to

baseline and 7% of the patients had short stature after 3 years follow-up. Although decrease in height z-score was identified among all JIA subgroups, it was greatest in soJIA patients. Median BMI z-score remained unchanged during within 3 years. They also concluded that corticosteroid usage was associated with growth restriction[13]. Similar to the previous study, the short stature was identified in 7.3% of the whole JIA patients.

Previous publications showed that growth of JIA patients affected by disease duration, disease activity, age at the disease onset, dose and length of corticosteroid usage, JIA subgroup with different results[13-20]. Moreover, previous reports have suggested that anti-TNF treatments, particularly etanercept have significantly positive effect on growth of JIA patients[21,22]. However, in a more recent study, it was concluded that in particularly soJIA patients who required more than one biologic agents, therapy with biologics may be insufficient to improve normal growth[20].

In the present study, growth parameters of Turkish children with JIA were analyzed. We have suggested that with suppressing inflammation mean weight and BMI z-scores of JIA patients improved significantly; however, diminished mean height z-score of the patients remained a problem to be solved which highlights the need for early aggressive treatment modalities. Although the absence of significant association between corticosteroid usage in our study was in contrast with some previous studies[13,14], was also in line with other previous studies[20,23]. Corticosteroid treatment may both help and restrict the growth of JIA patients by positive effect in reducing inflammation and negative effect of long-lasting corticosteroid therapy on growth.

There are several limitations of the present study. We have analyzed growth parameters of JIA patients with collecting data from medical files. Relatively small number of patients did not allow us to compare the growth parameters between all subgroups. Pubertal maturation of the patients and factors that could affect the growth of children such as nutritional status of the patients could not be reached from the medical files. Moreover, retrospective design of the study prevented us to obtain information on growth hormone levels of the patients which may also be affected in JIA patients due to the inflammatory nature of the disease. Furthermore, we also could not obtain record of parental height for measuring parent-adjusted height z-scores.

In conclusion, identification of growth restriction in the early presentation of the disease is important to children with JIA because growth retardation, particularly short stature has significant effect on both physical and psychosocial health of children with chronic diseases which may further affect the long-term educational and social outcomes. Therefore, further prospective, multicenter studies including more patients with JIA subgroups, exploring patterns of growth restriction, and measuring parent-adjusted height z-scores would add important information to the literature.

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