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Insulin Growth Factor-1 in Egyptian Children with Juvenile Idiopathic Arthritis: Correlation with Growth Pattern and Disease Activity

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ABSTRACT

Background: Juvenile idiopathic arthritis (JIA) is a systemic, chronic, inflammatory disease that affects patients under 18 years. Interactions between growth hormone (GH), insulin-like growth factor-1 (IGF-1), and the immune system are complex. Many studies found that chronic inflammation suppresses GH/IGF-1 axis.

Objective: To assess if there is correlation between the serum level of IGF-1 and the growth pattern in children with JIA in Egypt, and to evaluate the correlation between the serum level of IGF-1 and disease activity among these patients.

Patients and Method: The study was a case control study which included 80 patients with JIA and 40 normal children as a control. Their ages ranged from 5-15 years. All patients were subjected to full history taking from their care givers, clinical examination, growth assessment, and laboratory measurement of serum IGF-1 level, CRP, ESR, and CBC.

Results: There was a statistically significant decrease in serum level of IGF-1 among patients with JIA. There was a statistically significant positive correlation between serum level of IGF-1 with height, weight and BMI. There was a statistically significant difference between patients and controls regarding Height-for-Age-Z-Score (HAZ), 35% of patients had short stature. There was a statistically significant decrease in weight and BMI, 90% of patients were underweight. There was no statistically significant correlation between serum level of IGF-1 and the disease activity.

Conclusion: There was a statistically significant positive correlation between IGF-1 with height, weight and BMI. Short stature and underweight were common among JIA patients. There was no significant correlation between serum level of IGF-1 and the disease activity among JIA patients.

Keywords: Body mass index (BMI), Growth hormone (GH), Insulin-like growth factor-1(IGF-1), Juvenile idiopathic arthritis (JIA), Height-for-Age-Z-score (HAZ).

INTRODUCTION

Juvenile idiopathic arthritis (JIA) unifies all forms of chronic arthritis during childhood, affecting joints and extra-articular structures (including eyes, skin, and internal organs) and is leading to disability. It is defined as the presence of arthritis of unknown etiology that starts before the age of 18 and persists for at least 6 weeks [(1)]. The prevalence of JIA in Europe was reported as 0.07 - 4.01 per 1000 children and the annual incidence is 0.008 to 0.226 per 1000 children [(2)]. Although epidemiological studies are limited in Egypt, few data was reported to a similar range [(3)].

The pathogenesis of JIA is currently unknown, but it is a complex multifactorial origin due to a combination of environmental factors and specific immunogenic factors [(4)]. Genetic variants underlying JIA susceptibility have been reported [(5)].

The diagnosis of JIA requires the persistence of arthritis of at least one joint in a child less than 18 years old for more than 6 weeks after exclusion of other causes of arthritis [(6)]. Joint inflammation manifests with joint pain, effusion, decreased range of motion, or warmth over the joint [(7)].

Based on the predominant clinical and laboratory features presented during the first 6 months of the disease, the ILAR (the International League Against Rheumatism) defined the current classification of JIA categories [(8)].

Impaired linear growth is commonly encountered in children with chronic inflammatory diseases such as JIA [(9)]. Growth retardation may lead to short stature and a reduction in adult height despite the medical therapy [(10)]. Suboptimal nutrition, prolonged use of glucocorticoid, and chronic inflammation itself contribute to the underlying pathophysiology of growth retardation [(11, 12)]. This may be through effects on the growth hormone (GH) axis that regulates linear growth or through direct effects on the level of the growth plate [(13)]. Chronic inflammation may lead to a continuum of abnormalities in the systemic GH/IGF-1 axis, including relative GH insufficiency, GH/IGF-1 resistance due to impairment of IGF binding proteins (IGFBPs), down-regulation of GH/IGF receptors and/or impairment of local GH and IGF-1 signaling pathways [(14)].

The aim of the study was to assess the correlation between the serum level of IGF-1 and the growth pattern in children with JIA in Egypt, and to evaluate the correlation between the serum level of IGF-1 and disease activity among these patients.

PATIENTS AND METHODS

A case control study of 80 children diagnosed as JIA were recruited from pediatric outpatient clinic of Ain Shams University Hospitals during the period from

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2019 till 2021, their age's ranged from 5-15 years old. Forty healthy children were also involved as control group. Selection criteria for patients included diagnostic criteria for JIA according to **Petty *et al.*** [8]; age of onset from 5-15 years, arthritis in at least one joint, and arthritis last for at least 6 weeks. Exclusion criteria included associated other chronic diseases (as chronic renal, cardiac, chest or endocrinal disease etc.) that may interfere with normal growth, other causes of arthritis (as septic arthritis, rheumatic heart disease), acute infection or inflammation on the day of taking the blood sample, and genetic diseases.

Ethical approval:

Before enrollment, the care givers of children were informed about the nature of the study and a written informed consent was obtained from the care givers of all patients and controls in this study. The research was approved from Ethical Committee in Ain Shams University. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

All patients and controls were subjected to the following: 1- Complete history taking from their care givers (with special emphasis on age and gender, onset and duration of symptoms, duration of morning stiffness, number of active joints, number of affected joints, number of joints with limited range of motion, number of painful joints, history of medication particularly the steroids medication). 2- Past history to exclude; other chronic or genetic diseases, other causes of arthritis, collagen and endocrinal causes of growth retardation. 3- General clinical examination including: chest, cardiac, abdominal and neurological examination to exclude chronic or genetic diseases that may interfere with normal growth. 4- Local musculoskeletal and joint examination to detect active arthritis. 5- Growth assessment including; weight, height, and BMI. Each of these measurements was taken as the mean of three consecutive reading and was interpreted with reference to Egyptian growth charts using Height-for-Age-Z-score (HAZ) and Weight-for-Age-Z-score (WAZ). 6- Laboratory investigations to all patients and controls including; determination of serum level of insulin-like growth factors-1(IGF-1) and serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) to assess the disease activity, and complete blood count (CBC).

Blood samples were collected by a well-trained nurse from patients and controls. Five ml of venous blood samples were obtained and divided into EDTA tube (2.0 ml) with smooth shaking and vacutainer plain tube (3.0 ml). Vacutainer plain tubes were left for short time to allow blood to clot, and then clear serum samples were obtained by centrifugation (B. Bran-Sigma 2K15, USA) at 4000 rpm for 10 minutes. The separated serum was sealed and stored at -20 C^0 until the time of performing the analysis. The frozen serum samples were thawed at 4-8˚C then mixed by gentle shaking at room temperature prior to use. EDTA tube (whole blood samples), was used fresh for CBC and ESR tests. Insulin-like growth factors 1 (IGF-1) was measured by INOVA Human IGF-1 ELISA kits. It is an enzyme-linked immunosorbent assay for quantitative detection of human IGF-1. BioneovanCo., Ltd, No. 18, Keyuan Road, DaXing Industry Zone, Beijing, China. Measurement of human C-reactive protein (CRP) in serum was performed using the nephelometry.

Statistical analysis

The collected data were tabulated and analyzed using SPSS version 24 software (SPSS Inc, Chicago, ILL Company). Categorical data were presented as number and percentages. Chi square test (X^2) was used to analyze categorical variables. Quantitative data were tested for normality using Kolmogorov Smirnov test assuming normality at $P>0.05$. Quantitative data were expressed as range and mean ± standard deviation. Independent Student "t" test was used to compare normally distributed variables and Mann-Whitney test was used to compare abnormally distributed variables. Spearman's correlation coefficient (rho) was used to assess correlation between non parametric variables. $P<0.05$ was considered significant.

RESULTS

The demographic data of all participants was shown in table 1. There was no statistically significant difference between patients and controls regarding age and sex distribution (table 1). The clinical data among the patients group was illustrated in table 2. As regards the anthropometric measurements there was a statistically significant difference between patients and control as regards weight, height and BMI (table 3). There was a statistical significant difference between patients and controls regarding Height-for-Age-Z-score (HAZ) and Weight-for-Age-Z-score (WAZ) (table 4). There was a statistically significant increase in CRP (mg/L) and ESR (mm/hr) among our patients than controls. While, there was a statistically significant decrease in hemoglobin level (gm/dl) and IGF-1 (ng/ml) among patients than controls (table 5). There was a statistically significant positive correlation between IGF-1 (ng/ml) with weight (kg), height (cm), and BMI (Kg/m^2). But there was no statistically significant correlation between IGF-1 (ng/ml) and age, parameters of disease activity (CRP and ESR) or hemoglobin level (table 6).

Table (1): Demographic data of the patients and control

		Patients (NO.= 80)	Controls (NO.= 40)	P value
Age (years)	Range Mean ± SD	5.30 – 15 9.37 ± 1.86	5.20 – 15 8.48 ± 1.07	0.542
Sex	Female (NO. %)	56 70%	24 60%	0.468
	Male (NO. %)	24 30%	16 40%	
Consanguinity	NO. (%)	11 (13.75%)	5 (12.5%)	0.849
Family History with JIA	NO. (%)	18 (22.5%)	2 (5%)	0.015

JIA: Juvenile idiopathic arthritis.

Table (2): Clinical manifestations and complaints among the patients group

Clinical Manifestations and Complaint	(NO. = 80)	%
Morning Stiffness	56	70
Joint Pain	74	92.5
Fever	58	72.5
Siding	29	36.3

Table (3): Comparison between patients and controls regarding anthropometric measurements

Anthropometric Measurements		Patients (NO.= 80)	Controls (NO.= 40)	P value
Weight (Kg)	Range	14 - 30	22 – 42	<0.001
	Mean ± SD	21.28 ± 3.12	28.34 ± 5.34	
Height (cm)	Range	82 - 128	105 - 140	<0.001
	Mean ± SD	105.20 ± 4.36	121.14 ± 7.52	
BMI (Kg/m^2)	Range	14.03 – 21.92	18 – 25.67	<0.001
	Mean ± SD	17.38 ±1.62	20.85 ± 2.04	

BMI: Body mass index.

Table (4): Comparison between patients and controls regarding Height-for-Age-Z-score (HAZ) and Weight-for-Age-Z-score (WAZ)

			Patients (NO.= 80)	Controls (NO.= 40)	P value
HAZ score	HAZ score ≤ -2 SD	(NO. %)	28 (35%)	3 (7.5%)	0.002
	HAZ score > -2 SD	(NO. %)	42 (52.5%)	37 (92.5%)	
WAZ score	WAZ score ≤ -2 SD	(NO. %)	72 (90%)	3 (7.5%)	0.001
	WAZ score > -2 SD	(NO. %)	8 (10%)	37 (92.5%)	

HAZ: Height-for-Age-Z-score, WAZ: Weight-for-Age-Z-score

Table (5): Comparison between patients and controls regarding CRP, ESR, Hemoglobin level (Hb), and IGF-1

		Patients (NO.= 80)	Controls (NO.= 40)	P value
CRP (mg/L)	Mean ± SD	44.6 ± 7.31	10.54 ± 2.26	0.000
ESR (mm/hr)	Mean ± SD	14.55 ± 4.76	9.13 ± 1.50	0.001
Hb (g/dl)	Mean ± SD	9.62 ± 1.05	10.89 ± 1.41	0.000
IGF-1 (ng/ml)	Mean ± SD	94.45 ± 8.54	108.0 ± 5.2	0.02

CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, Hb: Hemoglobin, IGF-1: Insulin-like growth factor-1.

Table (6): Correlation between IGF-1 and other variables

Correlation with IGF-1 (ng/ml)	Pearson's Correlation	
	R	P
Age (years)	-0.056	0.658
Weight (Kg)	0.072	0.042
Height (cm)	0.028	0.028
BMI (Kg/m^2)	0.006	0.048
CRP (mg/L)	-0.095	0.396
ESR (mm/hr)	-0.132	0.285
Hb (gm/dl)	0.119	0.295

BMI: Body mass index, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, Hb: Hemoglobin, IGF-1: Insulin-like growth factor-1.

DISCUSSION

JIA is the most common rheumatologic disease in pediatrics and is one of the more frequent chronic diseases of childhood [15]. The etiology is not fully understood but is known to be multifactorial, with both genetic and environmental factors playing key roles. Without appropriate and early treatment, JIA may result in significant negative effects on growth and significant morbidity [16].

This study included 80 patients of both sexes with JIA, and 40 normal children as a control. Their ages ranged from 5-15 years. According to our results, there was no statistically significant difference between patients and controls regarding age and sex distribution. There was obvious female predominance (70% of patients were females and 30% were males). This is in agreement with **Al-Hemairi *et al.*** [17] who found female predominance among 82 total patients with JIA. It is well known that females are more commonly affected by JIA than males [18]. Our study showed positive consanguinity in 13.75% of patients and 22.5% of patients had positive family history of JIA. Genetic contributions and susceptibility of JIA and positive consanguinity with affected family members have been reported extensively in many studies as the study of **Prahalad and Glass** [19]. Our study revealed that fever was present in 72.5% of the patients, joint pain in 92.5%, and morning stiffness in 70% of patients. These findings were close to the findings of **Weakley *et al.*** [20] who reported similar results.

In our study, there was a statistical significant decrease in height among patients versus controls and there was a statistical significant difference between patients and controls regarding Height-for-Age-Z-score (HAZ), 35% of patients were short-statured while only 7.5% among controls. This was in agreement with **Aghamahdi *et al.*** [21], who found that 35% of their patients with JIA had short stature, while the study of **Uettwiller *et al.*** [22] reported lesser presence of short-statured among JIA patients. In addition, there was a statistically significant decrease in weight and BMI among patients versus controls using Weight-for-Age-Z-Score (WAZ), 90% of our patients were underweight. This is in agreement with the results of **Alsulami *et al.*** [23].

One of the main complications of JIA is growth retardation and is associated with significant impact on patient's physical and psychological health and overall quality of life [24]. Early treatment can improve the growth [25]. Many factors contribute to growth retardation in children with JIA such as; malnourishment, excessive cytokine and their proinflammatory action [26], prolonged use of corticosteroids [27], and hormonal and metabolic dysfunction (as parathyroid, sex steroids and vitamin D dysfunction) which lead to growth retardation by modulating GH/IGF-I axis, resulting in impaired bone growth. Malnourishment in children with JIA is induced by several factors including high levels of proinflammatory cytokines that reduce energy uptake and metabolism, even if the patient is on an appropriate diet. There was strong evidence indicating the modulating effect of cytokines (particularly IL-6) on growth plate of long bones [28]. In addition, cytokines have indirect action involving IGF -I and correlated to excessive production of IL-6 [24]. Malnourishment is also more common in children with inflammation of the maxillo-mandibular joint, and in children with affected digestive tract that nutrient assimilation is reduced. Coeliac disease, for example, is about seven times more common in children with JIA than in the general population. Many of the drugs used in treating the disease can also cause disturbances of the gastrointestinal tract. This is particularly true for methotrexate [29].

In the present work, there was a statistically significant decrease in hemoglobin concentration among patients versus controls. These results were in accordance with **Al-Hemairi *et al.*** [17] who found that anemia was the most common abnormal laboratory investigation and it was recorded in 80% of JIA patients. Anemia in JIA is commonly caused by iron deficiency or due to chronic inflammation [30]. Additionally, we found that there was a statistically significant increase in CRP and ESR levels among patients than controls and this was in agreement with **Rusonienė *et al.*** [31]**.** As regard the IGF-1, there was a statistically significant decrease in its serum level among our patients than controls and this was in agreement with the study of **Lundell *et al.*** [32].

Many studies reported interactions between IGF-1 and proinflammatory cytokines (particularly IL-6), which are commonly elevated in JIA patients. Inflammation-related cytokines (as TNF-α, IL-1β, and IL-6) have been shown to dysregulate IGF-1 downstream intracellular signaling in chondrocytes [33].

Also, systemic JIA patients who were treated with anti-IL-6 receptor antibody (tocilizumab) experienced a catch-up in growth and an increase in serum IGF-1 levels [34].

This study showed that there were statistically significant positive correlations between IGF-1 with weight, height and BMI. This was in agreement with the study of **Lundell *et al.*** [32]. The study that had done by **Bang *et al.*** [35], they revealed that deficiency of IGF- may be associated with serious clinical impacts in children leading to growth failure and short stature. This positive correlation explained as with more decrease in the serum level of IGF-1, the more is severity and chronicity of the disease and so on the more effect on the growth pattern. For that, with more decrease in the serum levels of IGF-1, a more affection of growth will be expected.

Finally, we found that no statistically significant correlation between IGF-1 and the parameters of disease activity (as CRP and ESR). Few studies have examined serum IGF-1 levels in relation to disease

activity in JIA. In a cohort study by **Benedetti *et al.*** [34] there was also a negative association, although not statistically significant, between IGF-1 levels and CRP.

CONCLUSION

There was a statistically significant positive correlation between IGF-1 with height, weight and BMI. Short stature and underweight were common among JIA patients versus controls. There was no significant correlation between the serum level of IGF-1 and the disease activity of JIA patients.

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