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PARTICULARITIES OF GROWTH IN CHILDREN OF PREPUBERTAL AGE WITH JUVENILE IDIOPATHIC ARTHRITIS

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REZUMAT

PARTICULARITĂȚILE CREȘTERII LA COPIII DE VÂRSTĂ PREPUBERTARĂ CU ARTRITĂ JUVENILĂ IDIOPATICĂ

Introducere. Efectul inflamației determină o creștere deficitară a copiilor ce variază de la o scădere ușoară a vitezei de creștere până la hipostatură severă. Nu există date suficiente pentru a elucida rezistența hormonală periferică în stagnarea creșterii la copiii cu artrită idiopatică juvenilă (AJI).

Scopul lucrării. A evalua velocimetria creșterii la copiii cu subtipuri diferite de debut al AJI și corelarea datelor clinice obținute cu rezultatele imunologice hormonale și autoimune hipofizare.

Material și metode. Studiul prospectiv a inclus analiza datelor a 45 de pacienți cu vârsta mai mică de 11 ani cu diagnosticul confirmat de AJI, la înrolare, și în dinamică la 6, 12 și 18 luni. Analiza auxologică și velocimetria creșterii au fost exprimate prin Z-score, conform bazei statistice OMS 2007. Profilul hormonal a inclus determinarea serică a hormonilor centrali și periferici și evaluarea imunologică hipofizară.

Rezultate. Analiza datelor demografice a relevat: vârsta medie 6.95±0.49 ani; vârsta medie la debut a fost de 4.31±0.46 ani; raportul de sex M:F =1:1,36. Cea mai frecventă categorie AJI a fost oligoartrita (51,11%). La înrolare, scorul Z pentru talie a fost -0,53±0,14 DS (IÎ: −2.98, +0.99). Aproximativ 18% subiecți au fost diagnosticați cu retard al creșterii (scorul Z < −2 DS), iar 14 % cu valori scăzute ale factorului de creștere a insulinei [IÎ: 37,4; 79,2]. Supravegherea în dinamică a scorului Z pentru talie la 6, 12 și 18 luni a evidențiat valori între -0,42 și -0,49. În studiu, nu au fost depistate tulburări care implică proteina 3 de transport al factorului de creștere a insulinei și prezența anticorpilor antihipofizari.

Concluzii. Forma cu debut sistemic a AJI și vârsta mică la debut determină cea mai severă stagnare a creșterii. Proces autoimun hipofizar nu a fost depistat la copiii cu AJI complicată cu retard al creșterii.

Cuvinte-cheie: stagnarea creșterii, anticorpi antihipofizari, artrită juvenilă idiopatică.

РЕЗЮМЕ

ОСОБЕННОСТИ РОСТА У ДЕТЕЙ ПРЕДПУБЕРТАЛЬНОГО ВОЗРАСТА С ЮВЕНИЛЬНЫМ ИДИОПАТИЧЕСКИМ АРТРИТОМ

Введение. Эффект воспаления вызывает задержку роста у детей с ювенильным идиопатическим артритом, от легкой до очень выраженной. Данные для выяснения периферической гормональной резистентности в процессе задержки роста у детей с ювенильным идиопатическим артритом (ЮИА) ещё недостаточные.

Цель иследования было оценить скорость роста у детей с разными подтипами ЮИА и сопоставить клинические данные с показателями иммунологической гормональной и аутоиммунной активностью гипофиза.

Материалы и методы. В исследование включены данные 45 пациентов младше 11 лет с подтвержденным диагнозом ЮИА, на исходном уровне и при последующем наблюдении через 6, 12 и 18 месяцев. Согласно статистической базе данных ВОЗ за 2007 год, ауксологический анализ и скорость роста выражались Z-баллом. Гормональный профиль включал определение в сыворотке крови центральных, периферических гормонов и аутоантител гипофиза.

Результаты. Анализ демографических данных выявил: средний возраст 6,95 ± 0,49 года; средний возраст начала заболевания составил 4,31 ± 0,46 года; соотношение полов Ж:М=1,36:1. Наиболее частой категорией ЮИА был олигоартрит (51,11%). При зачислении Z-балл для роста был -0,53 ± 0,14 СД (ДИ: -2,98, +0,99). Почти 18% субъектов были установлены с задержкой роста (оценка Z <-2 СД) и 14% - с низкими значениями фактора роста инсулина [ДИ: 37,4; 79,2]. Последующее наблюдение по Z-баллу для роста через 6, 12 и 18 месяцев составило -0,42 и -0,49. Самые низкие значения были при ЮИА с системным началом, до -1,21 стандартного отклонения. В ходе исследования не было обнаружено никаких нарушений, связанных с 3 белком транспортирующим фактор роста инсулина, и наличием антигипофизарных антител.

Выводы. ЮИА с системным началом и более молодой возраст в начале заболевания определяют наиболее тяжелые нарушения роста. У детей с ЮИА, осложненным задержкой роста, аутоиммунный процесс гипофиза не выявлен.

Ключевые слова: задержка роста, антигипофизарные антитела, ювенильный идиопатический артрит.

Introduction

Juvenile idiopathic arthritis (JIA) is the most common joint disorder in developing children. [1,6,9]

The effect of chronic arthritis on bone and joint development often results in impaired growth in children, ranging from a mild decrease in growth velocity to severely short stature. Over the long term, inflammation can cause stiffening and deformation of the affected joints, and can lead to significant growth retardation. Factors responsible for growth retardation in chronically ill children include frequent infections, primary and secondary malnutrition, long-term stress related to being chronically ill or handicapped, and side effects of therapy. [7,8]

Short stature in patients with JIA is usually due to reduced growth in the lower extremities, and only rarely due to reduced growth in the spinal column. [1,3]

Growth retardation in children with JIA is especially severe when auto-immunological activity has been elevated over a long period, which is associated with high levels of the pro-inflammatory cytokines IL-1, IL-6 and TNF-α. These cytokines reduce secretion of growth hormone from the pituitary gland, and also act directly on the growth plates of the long bones. In laboratory experiments, IL-1 and TNF-α have been found to reduce proliferation and differentiation in chondrocytes in the growth plates, to induce death in chondrocytes, and to disrupt the synthesis of type II collagen and proteoglycans.[3,7,9] However, it is insufficient data to elucidate systemic hormonal resistance to growth failure in children with juvenile idiopathic arthritis.

Aim of the research is to study the impact of the autoimmune inflammatory processes on different levels: clinical, laboratory, hormonal disorders such as hypothalamic-pituitary-peripheral features in prepubertal children with idiopathic juvenile arthritis

Material and methods

The subjects of the study were selected within the Rheumatology unit of the Mother and Child Institute based on the admission on the nominal lists and the informed consent of the parents. Participation in the study was voluntary, based on informed consent, signed by parents / caregiver and the consent of children over 14 years of age. The research protocol was performed using different methods: observation method, survey, interview, laboratory testing and monitoring over 6, 12 and 18 months.

The diagnosis of juvenile idiopathic arthritis was established based on ILAR criteria - the International League for Combating Rheumatism, which provide for the onset of the disease until the age of 16, the duration of the disease of at least 6 weeks and the exclusion of other potential pathologies. According to ILAR / ACR recommendations, patients were grouped into the following subtypes of JIA: systemic onset form with active arthritis, systemic onset form without active arthritis, oligoarticular form (persistent or extensive), seropositive polyarticular form (RF +), seronegative polyarticular form (RF-) or other forms (psoriatic form, arthritis associated with enthesitis or undifferentiated). The duration of the disease was calculated in months. Patients are grouped into 2 subgroups: those with early onset (<1 month) and those with established JIA, who receive treatment lasting more than 1 month. [4,5]

Anthropometric data were collected personally at the time of enrollment in the study and at each mandatory repeated visit - 6, 12 and 18 months. They were then analyzed according to the WHO 2007 statistical base, as a reference system for all age groups and sex. For the objective analysis of the data we calculated the Z-score depending on age and sex (0 = average of healthy children, 1 = a standard deviation in the population of healthy children), for weight, height and body mass index (BMI). Dynamics during monitoring was expressed as ΔSDS for height and BMI. ΔSDS, was assessed based on the mathematical calculation ΔSDS = SDS1-SDS2, where SDS1 is the value for the current measurement of height or BMI (at 6, 12 or 18 months), and SDS2 - the value measured at the time of enrollment in the study. [2]

The hormonal biochemical investigations performed

were indicated depending on several factors: sex and age of the subjects, as well as the analysis of the collected auxological data - patients with growth retardation or spective study, estimates the duration of the disease at 2,73±0,43 years, [CI: 0,04; 8,27]. All detailed data is presented bellow in Table 1.

Table 1.

Characteristic of the general group and study subgroups

	Average age (years)	Average age at disease onset (years)	Duration of the disease (years)	Weight, Z-score, DS[1]	Height, , Z-score, DS	BMI[2], , Z-score, DS
Lot of study n[3]=45	6,95±0,49 [1,56; 10,95]	4,31±0,46 [0,51; 10,37]	2,73±0,43 [0,04; 8,27]	-0,5±0,16 [-2,72; 1,1]	-0,53±0,14 [-2,98; 0,99]	-0,25±0,18 [-3,37; 1,32]
a) according to gender distribution						
Girls (n=26)	6,09±0,68 [1,56; 10,95]	2,85±0,47 [0,51; 7,2]	3,23±0,63 [0,06; 8,09]	-0,93±0,29 [-2,72; 1,1]	-0,81±0,27 [-2,98; 0,66]	-0,56±0,32 [-3,37; 1,29]
Boys (n=19)	7,73±0,66 [2,62; 10,57]	5,60±0,62 [2,03; 10,37]	2,27±0,57 [0,04; 8,27]	-0,15±0,12 [-1,53; 0,64]	-0,30±0,13 [-1,31; 0,99]	0,003±0,18 [-1,44; 1,32]
b) according to the age at disease onset						
Children younger <3y.o.	5,15±0,78 [1,56; 10,3]	1,78±0,17 [0,51; 2,74]	3,37±0,84 [0,04; 8,27]	-0,78±0,29 [-2,72; 1,1]	-0,76±0,29 [-2,98; 0,59]	-0,37±0,28 [-2,13; 1,29]
Children older >3y.o.	8,10±0,5 [2,78; 10,95]	5,91±0,48 [3,15; 10,37]	2,32±0,43 [0,05; 7,38]	-0,32±0,18 [-2,31; 0,64]	-0,38±0,15 [-1,63; 0,99]	-0,17±0,23 [-3,37; 1,32]
c) according to disease duration						
Duration <1year	5,36±0,93 [1,56; 10,51]	5,10±0,88 [1,49; 10,22]	0,25±0,07 [0,04; 0,9]	-0,44±0,25 [-2,31; 0,24]	-0,35±0,21 [-1,26; 0,99]	-0,43±0,36 [-3,37; 1,29]
Duration >1year	7,65±0,52 [2,34; 10,95]	3,95±0,52 [0,51; 10,37]	3,81±0,46 [0,72; 8,27]	-0,53±0,21 [-2,72; 1,1]	-0,61±0,19 [-2,98; 0,66]	-0,17±0,2 -2,13; 1,32
d) according to disease subtype						
Oligoarticular JIA[4]	6,9±0,62 [1,91; 10,95]	4,6±0,61 [1,25; 10,37]	2,43±0,61 [0,04; 8,27]	-0,49±0,20 [-2,72; 1,1]	-0,42±0,16 [-2,11; 0,99]	-0,37±0,24 [-3,37; 1,29]
Polyarticular JIA (RF[5] negative)	7,04±1,13 [1,56; 10,95]	3,58±0,75 [0,51; 7,2]	3,45±0,76 [0,06; 7,38]	-0.63±0.36 [-2.43; 0,59]	-0,6±0,39 [-2,98; 0,66]	-0,33±0,32 [-1,63; 1,32]
Systemic onset JIA	5,35±0,96 [3,9; 7,18]	2,47±0,51 [1,56; 3,36]	2,86±0,75 [1,38; 3,81]	-0,45±0,55 [-1,12; 0,64]	-1,2±0,46 [-2,1; -0,53]	0,6±0,4 [-0,12; 1,28]

[1] DS – deviation standard; [2] BMI – body mass index; [3]n – number of subjects; [4] JIA – juvenile idiopathic arthritis, [5] RF – rheumatoid factor.

normal growth. In normal-growing children were evaluated: insulin-like growth factor 1 (IGF-1), insulin-like growth factor 3 transporter protein (IGF-BP3), prolactin (PRL), thyroid hormone (TSH), and free thyroxine. fT4), free triiodothyronine (fT3), anti-thyroglobulin antibodies (anti-TG) and anti-thyroperoxidase antibodies (anti-TPO). In addition, in children with growth impairment were assessed growth hormone (GH) and the anti-pituitary antibodies. The analysis of anti-pituitary antibodies was examined by the indirect immunofluorescence (IIF) method. The test was performed at a serum dilution of 1:10. The norm variant was considered the negative result, and pathological in case of a positive result.

The study was approved positively by the Research Ethics Committee of the State University of Medicine and Pharmacy "Nicolae Testemitanu", through the issued document no. 53 of April 12, 2018.

Results and discussions

General demographic data analyse highlights pre-schoolers more susceptible to develop JIA, thus the average age at disease onset is 4,31±0,46 [CI: 0,51; 10,37]. Our pro-

Gender distribution in this population with JIA is 1,36 to 1, female to male ration. Data analyse according to gender distribution, identified some key-moments: girls are younger at the onset of the disease (2,85±0,47y.o. vs 5,60±0,62 y.o.). Also, girls are thinner and shorter than boy's presentation at baseline (see Table 1, part a).

Analysing growth in relation with age, set some risk factors which can impair growth process in children. Those are: younger age at onset of the disease and longer duration of the inflammatory process itself. Thus, children younger than 3-years-old at the onset present worst parameters for height and weight, as well. The SD for height at baseline for children <3 years old id -0,76±0,29 SD by comparison with -0,38±0,15 SD for children >3-years-old. Similarly, children with disease duration longer than 1 year-old have their baseline height at -0,61±0,19 SD vs -035±0,21 SD in shorter duration of the disease (Table 1, part b and c).

According to disease subtype, we observed that children diagnosed with systemic onset of JIA are the youngest one and, also, those more affected by growth impairment. Thus, average age at onset for systemic onset JIA

is 2,47±0,51 years-old versus 4,6±0,61 y.o. and 3,58±0,75 y.o. for oligoarticular and, respectively, polyarticular RF negative. Subsequently, Z score for height was calculated in systemic JIA at -1,2±0,46 SD [CI: -2,1; -0,53], but in other two forms: -0,42±0,16 SD and -0,6±0,39 SD.

Similar studies, like the one conducted by Ansell and Laaksonen consider that the duration of the disease is an important negative factor that significantly influences the growth in children. Polito et al., revealed a significant statistical correlation between the duration of the disease and the z-score of the body's height/length. According to Jarosova et al. the correlation between the age at the onset of the disease and some somatic parameters with significant correlation was found only in patients with polyarticular onset subtype. [1,7,8]

In Table 2, is presented the growth velocity during our ongoing study. As we proposed, we tried to monitor how our patients will grow at 6, 12 and 18 months. From our baseline group, 43 of patient were assessed during those periods. We try to analyse their velocity depending on different key-elements: age, duration of the disease, activity, comorbidities and treatment as well. For the general group of study, we observed tendency to keep Z-score for height at -0,49 SD. However, female patients have more negative values than boys on similar period of time – at 6 months from baseline -0,76±0,27 SD vs -0,26±0,12 SD; at 12 months -0,81±0,26 SD vs -0,2±0,12 SD and at 18 months -0,65±0,24 SD vs -0,21±0,1 SD.

The younger age at the disease onset still influence the growth velocity during time. Thus, our patients <3y.o. at onset have smaller Z-score at each of this period of times by comparison to subgroup >3 y.o. at onset (data presented in Table 2, part b). However, we didn`t identify any differences in the subcategory of disease duration.

Oligoarticular JIA has better Z-score for height at baseline, and during the follow-up. In this subgroup, we noticed lower values in children who undergo intraarticular corticosteroid treatment. Children with polyarticular JIA have SD value intermediary, depending more on the disease activity. Those children with high activity and moderate activity of the disease, respectively JADAS score higher than 20 and DAS28 >3.7 have lower value for their Z score. The higher activity of the disease is, the ΔSDS at 6,12 and 18 months is lower than 0 value. Growth impairment is more pronounced in systemic onset of JIA, which is noticed also in growth velocity. Thus in the first 6 months after onset we have worst values of the Z-score for height (-1,21±0,62 SD), which could be explained by the intensive inflammatory process, also higher doses of corticosteroid treatment until the achievement of disease control through DMARD therapy. During time, at 12 months and, further, at 18 months we observe a positive tendency by achieving similar values from oligoarticular or polyarticular subtypes of JIA.

In 8 patients (17,7%) were assessed low values of insulin growth factor according age and gender [range: 37.4;

Table 2.

Growth velocity at 6, 12 and 18 months

	Height at 6 months, Z score, DS	D	Height at 6 months, Z score, DS	D	Height at 6 months, Z score, DS	D
Lot of study n=45	-0,49±0,14	0,05±0,05 [-0,9; 1,15]	-0,49±0,14	0,05±0,06 [-0,9; 0,88]	-0,42±0,13	0,14±0,07 [-0,78; 1,29]
a) according to gender distribution						
Girls (n=26)	-0,76±0,27	0,04±0,09 [-0,5; 1,15]	-0,81±0,26	0,001±0,11 [-0,9; 0,88]	-0,65±0,24	0,15±0,11 [-0,78; 1,29]
Boys (n=19)	-0,26±0,12	0,06±0,07 [-0,41; 0,87]	-0,2±0,12	0,10±0,08 [-0,51; 0,73]	-0,21±0,1	0,13±0,09 [-0,75; 0,83]
b) according to the age at disease onset						
Children younger <3y.o.	-0,75±0,28	0,007±0,11 [-0,5; 1,15]	-0,825±0,28	-0,06±0,13 [-0,9; 0,88]	-0,63±0,24	0,13±0,12 [-0,78; 1,29]
Children older >3y.o.	-0.323±0,13	0,09±0,06 [-0,41; 0,87]	-0,25±0,13	0,13±0,07 [-0,51; 0,73]	-0,27±0,13	0,15±0,09 [-0,75; 0,84]
c) according to disease duration						
Duration <1year	-0,45±0,19	-0,03±0,1 [-0,41; 0,53]	-0,47±0,18	-0,04±0,13 [-0,8; 0,62]	-0,45±0,19	-0,04±0,18 [-0,78; 0,84]
Duration >1year	-0,51±0,19	0,09±0,07 [-0,5; 1,15]	-0,49±0,19	0,09±0,08 [-0,9; 0,88]	-0,4±0,17	0,22±0,07 [-0,35; 1,29]
d) according to disease subtype						
Oligoarticular JIA[4]	-0,39±0,15	0,06±0,07 [-0,41; 1,15]	-0,37±0,14	0,08±0,07 [-0,51; 0,88]	-0,38±0,13	0.07±0.08 [-0,75; 0,84]
Polyarticular JIA (RF negative)	-0,52±0,38	0,07±0,13 [-0,5; 0,87]	-0,65±0,42	-0,10±0,17 [-0,9; 0,65]	-0,46±0,39	0,13±0,12 [-0,78; 0,43]
Systemic onset JIA	-1,21±0,62	-0,01±0,15 [-0,32; 0,2]	-0,87±0,57	0,32±0,23 [-0,07; 0,73]	-0,59±0,3	0,7±0,37 [0; 1,29]

79,2]. However, none disturbances involving the insulin growth factor binding protein 3 were registered. Those values were correlated with age at onset of the disease, disease duration and disease activity of each patient. All children presenting growth delay were investigated for growth hormone level and for the presence of antihypophisary antibodies. All those tests from IIF were obtained as negative one.

The data literature analysis in this topic remains brief and varied as the incidence of the growth retardation is estimated from 8 to 41%. Some studies specify only the severe subtypes of the disease, others reporting in all juvenile idiopathic arthritis subtypes. [1,2,9]

Laboratory findings revealed hyperprolactinemia in 6,7% cases. Clinical manifestations of specific conditions with hyperprolactinemia (galactorrhea, disturbance of visual field, pituitary tumor syndrome) have not been identified. Serum prolactin abnormalities correlate with disease activity (JADAS score> 25 points in all cases with hyperprolactinemia) and low onset age (1.76y.o.). According to literature data, prolactin along with estrogen is pro-inflammatory hormones, and high levels in women explain the high proportion of women: men. Prolactin maintains cartilage maintenance, osteogenesis, growth, proliferation and apoptosis as well as the release of proinflammatory mediators by immune cells – events that can both induce and prevent rheumatic diseases. [3,9]

It has been suggested that excessive prolactin secretion may contribute to the pathogenesis of juvenile idiopathic arthritis. However, the correlation of hyperprolactinemia with the indices of the activity of many rheumatologic conditions are still contradictory. Both hypo- and hyperprolactinemia induce immunocompromised conditions. TNFα and IL-6 have the potential to stimulate prolactin secretion, which is another cause of hyperprolactinemia in patients with rheumatic diseases. [7,9]

Paraclinically, an increase in the free fraction of triiodothyronine has been noted. Contrary to the data in the literature, the presence of antithyroid autoantibodies was found in only 4/45 patients in the case of antiTPO and only in 1 patient was antiTG found. Ultrasound abnormalities in the thyroid gland were found in every third patient included in the study. The ultrasound examination of thyroidal gland revealed abnormalities in 33% cases, most of them cystic changes (28,6%) and hypo-echogenicity (23,33%). According to literature data, rheumatic conditions can be associated with both hypothyroidism and hyperthyroidism.[3,9]

Conclusions

Identifying the endocrine comorbidities in idiopathic juvenile arthritis aims to prevent and limit the impact of the disease on the child's development. Thus, it would be necessary in the practice of the paediatrician – an active follow up through a clinical monitoring of the growth pattern, laboratory and investigations at intervals of 6-12-18 months, inclusively in the absence of clinical manifestations.

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