Original Paper

Algorithm for Growth Evaluation in Juvenile Idiopathic Arthritis

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ABSTRACT: Juvenile Idiopathic Arthritis (JIA) includes a range of inflammatory conditions that exhibit chronic arthritis with various clinical presentations. The disease's heterogeneity leads to different impacts on children's health, both short and long-term. Compromised growth, seen as growth retardation and delayed puberty, is a common complication in children with JIA, severely impacting their quality of life. This impairment is linked to disease duration and activity, with severe cases in systemic and polyarticular subtypes. Literature reports growth retardation incidence from 8% to 41%, but data on pubertal impairment is lacking. Growth in children is influenced by systemic and local mechanisms. Chronic inflammation, prolonged glucocorticosteroid (GCS) use, and nutritional issues contribute to growth stunting and pubertal delays. Chronic inflammation in JIA flattens growth curves, while steroid treatment impairs growth and causes weight gain. Disruption of the GH/IGF1 axis is known, but data on systemic hormonal resistance in JIA are insufficient. Optimizing JIA treatment, including biological therapies, is expected to improve growth velocity and reduce long-term impacts by better disease control and reduced GCS doses. Thyroid function also influences growth and puberty, but comprehensive studies on thyroid involvement in JIA are lacking. Given the early onset of chronic inflammatory consequences, preventive auxological screening measures are necessary for children with JIA. Early detection of developmental disorders can enhance therapeutic management. This article summarizes information from a cohort study on growth in children with JIA and proposes a diagnostic algorithm for clinical use.

KEYWORDS: *Growth impairment, juvenile idiopathic arthritis, algorithm, children.*

Introduction

Juvenile idiopathic arthritis (JIA) refers to a collection of persistent arthritis conditions lasting more than six weeks, with an unknown cause.

It is not a single disease but a collection of related immunoinflammatory disorders that are genetically heterogeneous and phenotypically diverse, affecting the joints as well as other tissues and organs, potentially triggered by contact with one or more external antigens [1,2].

JIA is relatively common, but its true prevalence is not fully known and is likely underdiagnosed according to some studies [3].

Globally, approximately 3 million children and young adults suffer from JIA, with higher prevalence rates consistently observed in girls [4].

Epidemiological studies show that the incidence of JIA ranges from 1.6 to 23 per 100,000 children annually, while its prevalence in Europe is approximately between 3.8 and 400 per 100,000 children [5].

It is essential to specify that JIA is not a homogeneous entity.

There is no specific symptom or laboratory test for JIA, and the diagnosis is established through exclusion and differentiation [6,7].

The first diagnostic criteria were formulated and proposed in the 1970s.

Currently, the limitations of the ILAR classification scheme are relevant, including the lack of connection to pathogenesis, molecular pathways, and therapeutic response.

The ILAR criteria were meant to be revised as new information became available.

Numerous suggestions have been collected, and the proposed modifications have been tested in international cohorts.

A new classification should be able to differentiate arthritis cases typical in children from those occurring in both pediatric and adult populations [8-10].

Growth impairment is a common complication among JIA patients [11].

A retrospective study by Alsulami et al. found that 1 in 3 children with JIA experience some form of growth retardation [12].

Some studies indicate that the prevalence of short stature in JIA ranges from 10.4% in children with polyarticular disease to 41% in those with the systemic form.

In contrast, oligoarthritis is mainly associated with excessive localized bone growth in the affected limb, resulting in limb asymmetry [13,14].

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Furthermore, depending on the geographical area, diagnostic and treatment options, studies report different prevalence rates of growth disorders in children with JIA.

Chronic inflammatory conditions are often linked to growth insufficiency, ranging from a slight decrease in height velocity to severe stunted patients [16,17].

The etiology of growth delay in JIA is multifactorial, involving frequent infections, chronic disease stress, inflammation, malnutrition, body composition changes, adverse therapy effects (including GCS treatment), delayed puberty onset, and slow pubertal progression.

These factors impede linear growth by influencing the GH/IGF-1 axis, gonadotropin-releasing hormone (GnRH), and growth plate function.

JIA causes notable changes in the joint microenvironment, with immune cell proliferation leading to localized hypoxia and decreased pH, which affect osteoblast function and bone mineralization.

Any disruption in the growth plate cartilage can negatively affect longitudinal bone growth [17-19].

The epiphyseal growth plate is the key organ for growth regulation mechanisms.

Growth hormone (GH) impacts the growth plate both directly and indirectly by stimulating IGF-1 production and chondrocyte hypertrophy [20,21].

Pro-inflammatory cytokines such as TNFα and IL1β directly influence chondrocyte dynamics and longitudinal bone growth, while IL6 affects growth through systemic mechanisms [22].

TNFα, IL1β, and IL6 are known to trigger apoptosis in growth plate cartilage, hindering bone growth.

Prolonged exposure to these cytokines is linked to diminished chondrogenesis recovery and longitudinal bone growth, explaining the more severe growth disturbances in children with extended, severe, and uncontrolled disease [18,23].

An inverse correlation between serum IGF-1 and IGFBP-3 levels with serum IL6 in children with systemic JIA indicates a direct link between inflammation and the GH-IGF-1 axis [11,18].

Locally, TNF and IL-1β work together to delay growth by inhibiting chondrocyte proliferation and differentiation, as well as inducing apoptosis in growth plate chondrocytes, as demonstrated in cultured fetal rat metatarsal bones [23].

The aim of this paper is to illustrate the growth patterns and velocity according to age, gender, subtype, onset, duration, and disease activity in juvenile idiopathic arthritis.

Based on these findings, it presents a diagnostic algorithm for growth impairment in juvenile idiopathic arthritis.

Material and Methods

We conducted an analytic cohort study in the department of pediatric rheumatology from the Mother and Child Institute in Chisinau, Moldova.

Thus, were included 52 prepubertal and 45 pubertal children with JIA selected from admission lists.

Inclusion and Exclusion Criteria

Children diagnosed with juvenile idiopathic arthritis according to ILAR/ACR criteria, onset before age 16, parental and/or caregiver consent (children older than 14 also required consent), were included.

Exclusion criteria encompassed other connective tissue diseases, endocrine pathologies, and refusal to participate.

Data Collection and Analysis

We employed epidemiological observation and various data accumulation methods, including direct methods like observation, investigation, and interviews, as well as indirect methods.

Data management utilized a comprehensive 129-question patient examination questionnaire covering general, diagnostic, clinical, endocrine, laboratory, and imaging aspects.

The research protocol of the current study was approved by the University's research ethics committee.

Relevant data from patient’s anamnesis, risk assessment, laboratory tests, and patient evolution were monitored prospectively at 6, 12, and 18 months, exploring the link between arthritis inflammation and hormonal-dependent development.

Statistical Analysis

Data were processed using descriptive, dispersion, and correlational analysis, employing Microsoft Excel, Visual Studio Code, and

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statistical libraries like NumPy, SciKit Learn, Altair.

Statistical tests (t-Student, one-way ANOVA) were considered significant different for a value of $p<0.05$.

Meanwhile, through correlation coefficients (Pearson's r) and ROC analysis was assessed the predictive value.

Results Interpretation

Laboratory data analysis, comparison with international databases, and centile graph development facilitated interpretation and diagnostic algorithm creation, enhancing endocrine comorbidity diagnosis in children with chronic diseases.

Results

The study included 97 children, comprising 52 patients in the cohort of prepubertal children (group L1-prepubertal) and 45 patients in the cohort of pubertal children (group L2-pubertal).

The average age of patients in the general group is 10.66 years±4.53 years (Me=10.89 years, Q1=7.25 years, Q3=14.72 years).

The average age at onset in the general study group is 6.73 years±4.08 years (Me=6.29 years, Q1=3.35 years, Q3=10.25 years).

The average duration of the disease in the general group is 3.96 years±3.91 years (Me=2.93 years, Q1=0.62 years, Q3=6.29 years).

Regarding gender distribution in the general group, we enrolled 54.63% girls (95% CI: 44.73%, 64.54%) compared to 45.36% boys (95% CI: 35.45%, 55.26%).

According to the ILAR classification, the most frequent subtype of onset of JIA in the general study group was the oligoarticular form, found in 44.33% of cases (95% CI: 34.44%, 54.21%), followed by the polyarticular seronegative form in 36.08% of cases (95% CI: 26.52%, 45.63%), and the systemic onset of JIA diagnosed in 12.37% of cases (95% CI: 5.81%, 18.92%).

Based on age, the L1-prepuberty group exhibited the most frequent oligoarticular onset in 63.46% compared to the seronegative polyarticular onset (53.33%) in the L2-puberty group ($\chi2=19.72$; gl=5; $p=0.001$).

Clinical severity of JIA was quantified using several clinical tools, including DAS28 activity scores and JADAS71 score.

For the first time, we analyzed the incidence and distribution of reserved prognostic factors of JIA in a cohort of children.

The analysis of growth impairment forms revealed that among the children examined, 15.46% exhibited hypostature (z score<-1.5 SD), while another 10.31% had a z score between-1.5 SD and-1.0 SD.

In terms of weight assessment, undernutrition conditions were suspected in 20.62% of children with weight indices lower than-1.5SD for age and sex, and in 8.25% of them, nutritional disorders such as overweight and/or obesity were suspected.

The analysis of BMI data confirmed that 30.93% of the children were undernourished, while 9.28% were overweight.

For the first time, we present the evaluation data of the triponderal index (TPI) studied in a cohort of patients with chronic rheumatic pathology, on the model of children with JIA.

TPI was analyzed in children with JIA older than 10 years.

With a statistically significant difference, we observed that when TPI is applied, the rate of undernutrition and overweight, respectively previously known by applying BMI, decreases in the general study group ($\chi2=13.64$; gl=3; $p=0.003$) and in the case of boys ($\chi2=11.34$; gl=3; $p=0.009$).

The comparative analysis of BMI versus TPI among girls did not reveal statistically significant differences ($\chi2=3.11$; gl=3; $p>0.05$).

The area under the ROC curve is insignificantly higher when evaluating BMI than in the case of TPI.

The study findings suggest that BMI and TPI are significantly associated with nutritional disorders in children with JIA.

However, BMI is a better predictor of nutritional disorders than TPI among children and adolescents aged 10-18 years (Figure 1).

According to age, sex, and puberty (L1 and L2 research groups), we observed that the mean value of waist circumference at research enrollment was lower (-0.336 SD±1.03 SD) in children from the L1 group compared to subjects from the L2 group (-0.252 SD±1.51 SD), where growth may already be influenced by the pubertal growth spurt.

Boys, unlike girls, presented a negative value of SD for waist circumference (-0.37 SD±1.33SD versus-0.23 SD±1.23 SD) but without significant statistical differences (Z test=0.50, $p>0.05$).

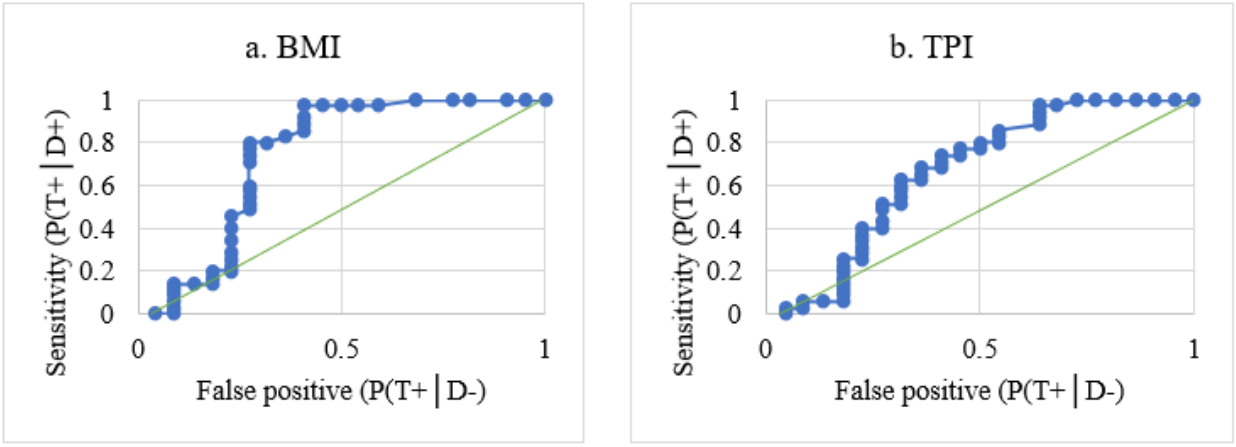

Figure 1. ROC curve for BMI (a.) and TPI (b.) in children with JIA (>10 years).

Depending on the age at the onset of the disease, lower values of the means of the standard deviations for weight and height were determined in those children with the onset of the joint syndrome before the age of 3 years compared to those with the onset after the age of 3 years (Z-test=-0.96; p>0.05 for mass, and for waist (Z-test=-1.23; p>0.05; critical Z 1.95).

Concerning the JIA subtype (Figure 2), the Z score for weight assessment was statistically significantly lower in subjects with systemic onset of JIA compared to those with oligoarticular onset (p<0.05) and seronegative polyarticular onset (p<0.05).

Additionally, the Z score for weight assessment was statistically significantly lower in subjects with systemic onset of JIA compared to those with oligoarticular onset (p<0.001) and seronegative polyarticular onset (p<0.01).

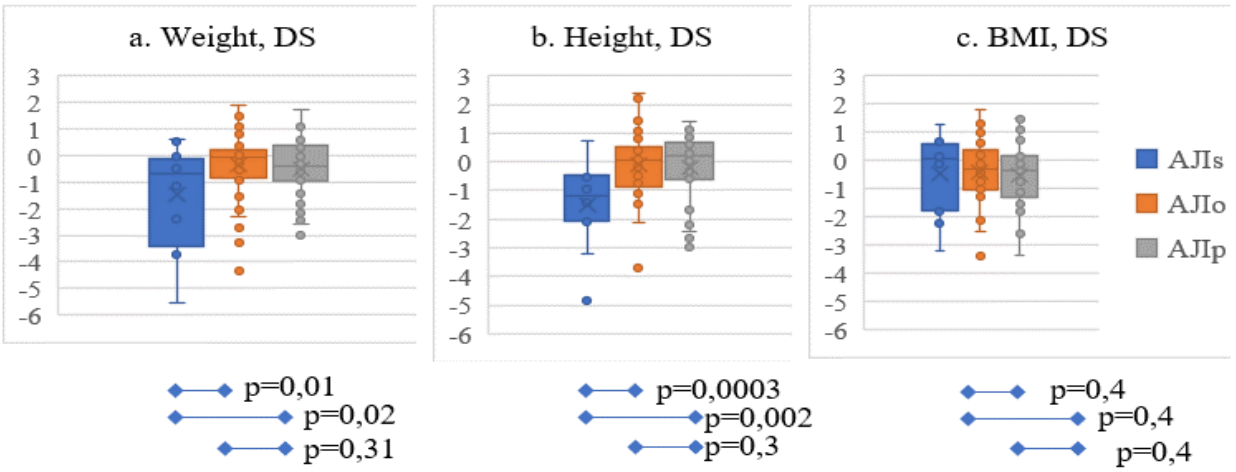

Figure 2. Evaluation of anthropometric indicators (weight, height) and BMI according to JIA onset subtype, SD.

Based on the duration of the disease, it was observed that the mean waist circumference in the group of children with a prolonged period of the disease (more than 1 month) was -0.42 SD±1.41 SD, compared to 0.01 SD±0.80 SD in children with a newly established diagnosis (treatment <1month), p<0.05.

Although only 15.46% of children exhibited clinically compromised values of anthropometric indicators, low serum levels of insulin-like growth factor 1 (IGF1) were detected in 41.24% of cases.

Among these, 27.84% had values corresponding to the centile range of 0.1-5, while 13.40% had values lower than the 0.1 percentile.

Conversely, serum values of IGF transport protein 3 (IGF-BP3) were elevated in 43.30% of cases, exceeding the 90th percentile.

Statistical analysis using the Pearson test revealed a strong positive correlation between these two variables (r=0.84).

Our study aimed to evaluate the incidence of central autoimmune damage in children with JIA and growth retardation.

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The evaluation of antipituitary antibodies was performed using the indirect immunofluorescence method, resulting in negative results for the presence of antipituitary antibodies in 100% of cases.

Therefore, we conclude that our study, conducted for the first time, does not confirm the hypothesis of central hypothalamic-pituitary autoimmune dysfunction in children with JIA.

We employed a linear regression model to verify the prediction model of the analyzed parameters.

A statistically significant correlation was found in the evaluation of serum IGF1 levels against the age of the subjects and, respectively, the absolute values of the anthropometric indicators (Table 1).

Table 1. Evaluation of the influence of anthropometric indicators on the serum value of IGF1 by the method of logistic regression.

Parameter	*Statistical indicator*						
	r	r^2	*ß*	*ES*	*t stat*	*p*	*IÎ 95%*
Age (years)	0,67	0,44	13,48	1,53	8,79	**0,0000** (6,15E-14)	10,43; 16,52
Weight (kg)	0,69	0,48	3,76	0,4	9,37	**0,0000** (3,67E-15)	2,96; 4,56
Height (m)	0,72	0,53	255,6	24,6	10,36	**0,0000** (2,74E-17)	206,7; 304,64
BMI (kg/m^2)	0,48	0,23	15,52	2,85	5,44	**0,0000** (4,11E-07)	9,85; 21,18

The relationship between IGF1 levels and age is well-documented in the literature, and our results are consistent with those previously described in this field.

Adjusting the interpretation of IGF1 values according to age, weight, and height is essential for the correct interpretation of the data.

Age at onset also exhibits a direct proportional correlation with IGF1, indicating its potential as a predictor for growth disorders in children with JIA (r=0.47; p=0.0000).

Furthermore, we observed a highly statistically significant, directly dependent correlation between the age of the research subjects and the serum value of IGF-BP3 (r=0.575).

In comparison to anthropometric indicators, there is a statistically significant correlation, directly proportional with both weight (r=0.619), waist circumference (r=0.616), and the absolute value of BMI (r=0.517).

However, regarding the clinical, laboratory, and activity indicators of JIA, no statistically significant correlations with IGF-BP3 were identified.

Discussion

According to our study, chronic autoimmune inflammatory processes in the JIA model were reflected in the hypothalamic-pituitary-GH/IGF axis, resulting in growth retardation in 15.46% of cases (95% CI: 8.26%, 22.65%), malnutrition in 20.62% of cases (95% CI: 12.56%, 28.66%), and overweight in 9.28% of cases.

We found a lower average value of DS for waist according to age in prepubertal children and according to sex in boys, in those children with a longer duration of the disease, systemic onset of JIA, and elevated proinflammatory activity, respectively.

Additionally, we observed an improvement in growth towards 18 months of follow-up, indicating good disease control allowing the growth process to recover.

Regarding growth evaluation and monitoring, existing literature presents similar studies correlating these cases with the long period until diagnosis is established, and an intensely expressed inflammatory process affecting the growth plate [14,15].

Anthropometric measurements are reliable, low-cost, non-invasive, and can be performed without high-tech equipment by personnel with minimal training.

Our data align with similar studies published in recent years.

For instance, Mondal et al. (2014) reported significant differences in height (p=0.011), weight (p=0.005), and growth velocity (p=0.005) between JIA onset subtypes but not in body mass index [24].

Additionally, by integrating clinical variables with laboratory research, healthcare providers can streamline the diagnostic process and tailor treatment strategies to meet the unique needs of children with JIA.

This holistic approach allows for a more comprehensive understanding of the disease and

facilitates early intervention, ultimately improving patient outcomes [25,26].

Currently, the cornerstone of managing JIA-associated growth retardation lies in effectively controlling inflammation using available pharmacotherapy options while optimizing treatment duration and dosage [27].

This proactive approach not only alleviates symptoms but also minimizes the detrimental impact of chronic inflammation on growth potential.

Recognizing the critical window of opportunity, early diagnosis is paramount as it enables timely initiation of interventions aimed at preserving bone growth before epiphyseal closure occurs [28].

In the diagnostic evaluation of young or slow-growing children suspected of having growth hormone deficiency, serum IGF-1 emerges as a crucial component of laboratory screening [29].

Serving as the primary indicator, its assessment guides clinicians in identifying potential hormonal imbalances early on, paving the way for targeted interventions and personalized care plans tailored to each child's specific needs.

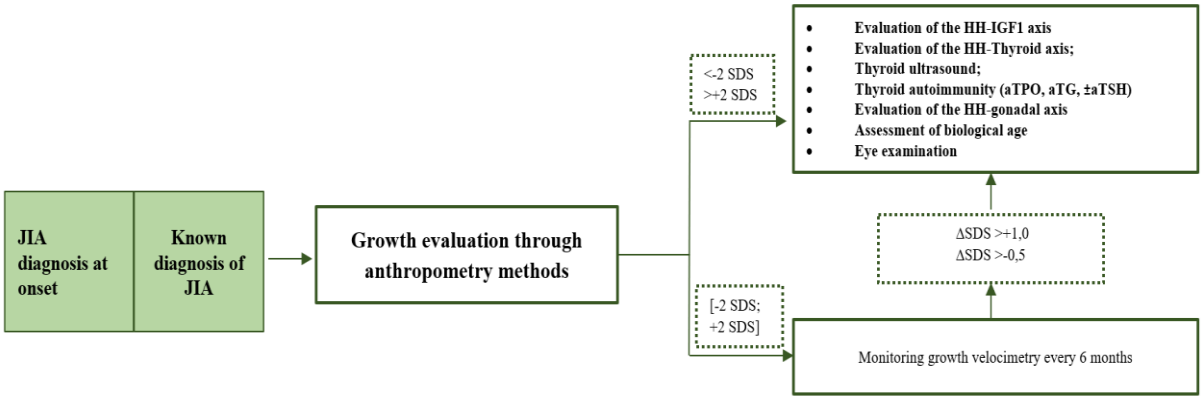

Figure 3. Proposed algorithm for the diagnosis and management of growth impairment in JIA.

We propose an algorithm (patented by authors) aimed at optimizing the growth trajectory of children with JIA (see Figure 3).

To proactively address growth impairment risks, we advocate for routine assessment of anthropometric indices, nutritional status, and pubertal development every six months at the primary care level.

Upon identification of growth and/or puberty disorders, prompt referral to a specialist, such as a rheumatologist-pediatrician or endocrinologist-pediatrician, is recommended to ascertain the underlying disease complication.

At the specialized medicine level, we emphasize the importance of evaluating hormonal profiles, including the hypothalamic-pituitary-peripheral axes, tailored to the patient's age and gender.

Interpretation of laboratory test results should be based on reference values derived from percentiles or standard deviations corresponding to the patient's demographic characteristics.

By implementing this algorithm, healthcare providers can promptly detect and address growth-related issues in children with JIA, ensuring timely intervention and personalized management plans.

Conclusion

The chronic autoimmune inflammatory processes inherent in the JIA model can profoundly impact the hypothalamic-pituitary-GH/IGF axis, potentially leading to endocrine complications and comorbidities.

In light of these complexities, we advocate for the widespread adoption of the algorithm developed in this study.

By implementing this algorithm, healthcare providers can proactively screen for and identify endocrine complications in patients with JIA, facilitating earlier diagnosis and intervention.

This proactive approach not only enhances treatment response and outcomes but also ensures that patients have timely access to high-quality care.

In conclusion, the application of our algorithm marks a significant advancement in the management of JIA, providing a systematic framework for identifying and addressing endocrine-related issues.

By prioritizing early detection and intervention, we can enhance the overall management and well-being of children living with JIA.

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Conflict of interests

None to declare.

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