Screening Of Growth Impairment In Juvenile Rheumatoid Arthritis, Systemic Lupus Erythematosus And Autoimmune Chronic Liver Disorders

Dr.Hanan Abd-Allah El-Gamal
Professor of Pediatrics Department of Medical Studies for Childern Institute of Post- Graduate Childhood Studies Ain Shams University
Dr.Manal Mohamed Ali Hassan Abd El- Gwad
Assistant professor of pediatrics Faculty of Medicine Alexandria University
Mourad Abd El- Hamid Mohamed Ahmed Kassem

Abstract

Introduction: Autoimmune diseases are frequently associated with growth impairment. This may be a consequence of the inflammatory process associated with disease activity and is also caused by the high- dose corticosteroids that are often used for treatment.

Aim: Screening of growth impairment in juvenile rheumatoid arthritis, systemic lupus erythematosus and autoimmune chronic liver disorders.

Subjects and methods: One thousand cases of school age children of both sexes of juvenile rheumatoid arthritis, systemic lupus erythematosus and autoimmune chronic liver disorders, the study will be conducted in the 4 main pediatric hospitals in Alexandria, to detect growth impairment in those children as indicated by auxological parameters from June 2010 to August 2015.

Results: In the studied juvenile rheumatoid arthritis (No. 593) group of school male (No. 118) and female (No. 475) children <3rd- <10th height for age percentile category (short stature) the percentage in males and females were 51.7 and 46.5 respectively, which were the highest percentages are statistically significant and in the studied autoimmune chronic liver disorders (ACLD) group of school age female (No. 69) children and adolescents in the short stature category (<3rd- <10th height for age percentile) a high percentage was observed which was 45.5 that is statistically significant. Pubertal assessment (Tanner staging) of the studied systemic lupus erythematosus (SLE) group of school age male children and adolescents (No. 69) shows that 48% of cases were in the Tanner stage 1 category is statistically significant which means delayed puberty was in a large number of this cases.

Conclusion: Juvenile rheumatoid arthritis, systemic lupus eryth- ematosus and autoimmune chronic liver disorders are frequently associated with growth impairment and delayed puberty. It is important to regularly monitor physical development and control inflammation associated with disease activity.

Key words: Growth Impairment, Delayed puberty, Short Stature, Under- Weight.

مسح لنقص النمو فى الروماتويد الطفولى والذئبة الحمراء والالتهاب الكبدى المناعى الذاتى المزمن

المقدمة: أمراض المناعة الذاتية من الأسباب التى تسبب الوفاة فى النساء صغيرات السن ومتوسطات العمر ومعدل انتشارها يختلف بين الأمراض المختلفة ويتراوح بين أقل من ٥ حالات لكل ١٠٠٠٠٠ فى (الالتهاب الكبدى المزمن النشط) إلى أكثر من ٥٠٠ حالة لكل ١٠٠٠٠٠ فى (مرض الروماتويد). تمثل النساء ٨٥% من الحالات وبالرغم من أن أكثر هذه الأمراض تحدث فى أى عمر إلا أن بعض الأمراض تحدث فى الأطفال والمراهقين. وتضم أمراض المناعة الذاتية فى الأطفال: مرض الروماتويد الطفولى ومرض الذائبة الحمراء وأمراض المناعة الذاتية الكبدية المزمنة بين أمراض أخرى كثيرة. وفى الأطفال المصابين بأمراض روماتزمية شديدة يكون العلاج بالكورتيزنات ضرورياً وهو مرتبط بنقص النمو وضعف العظام، والعلاج بهرمون النمو من الممكن أن يحسن النمو وكذلك كتلة الجسم لكن هذه الفوائد تختفى عندما يتوقف العلاج بهذا الهرمون.

المنهجية: دراسة مقطعية مستعرضة. والحالات ١٠٠٠ حالة مصابه بالروماتويد الطفولى والزئبة الحمراء والالتهاب الكبدى المناعى الذاتى المزمن. تم القيام بهذه الدراسة فى أربعة مستشفيات أطفال رئيسية فى الإسكندرية وهى مستشفى الشاطبى الجامعى ومستشفى الأنفوشى للأطفال مستشفى أطفال الرمل ومستشفى الطلبة للتأمين الصحى لاختيار الأطفال المصابين بأمراض المناعة الذاتية خاصة الروماتويد الطفولى والذئبة الحمراء وأمراض الكبد المناعية الذاتية وذلك لاكتشاف نقص النمو فى هؤلاء الأطفال عن طريق قياس النمو لمدة ثمانية عشرة شهرا.

التحليل الاحصائى: جمع البيانات وجدولتها وتحليلها البيانات وفقا للبرنامج الاحصائى (SPSS version 22).

النتائج: نسبة حالات التهاب المفاصل التلقائى مع التاريخ السلبى لنقص الوزن عند الولادة ٥٢,٦ مقابل ٤٧,٤ مع التاريخ نقص الوزن عند الولادة إيجابي. وهذاالفرق ذو دلالة إحصائية. وكانت النسبة المئوية لحالات التهاب المفاصل التلقائى مع التاريخ السلبى لنقص التغذية وتأخر النمو خلال السنة الأولى ٦٠ مقابل ٤٠ وجود تاريخ إيجابي. وهذاالفرق ذو دلالة إحصائية. النسبة المئوية لحالات التهاب المفاصل التلقائى مع التاريخ السلبى لسوء التغذية كان ٨٠,٨ مقارنة بـ١٩,٢ وجود تاريخ إيجابي. وهذاالفرق ذو دلالة إحصائية و. توزيع اضطرابات الكبد المزمنة المناعة الذاتية مجموعة من الأطفال الذكور فى سن المدرسة والمراهقين وفقا لمعايير البلوغ [مرحلة تانر] معارض وكانت أعلى نسبة بين الإناث فى المرحلة١ (٣٠,٣) متبوعا بالمرحلة ٢ (٢٤,٢) تدعم هذه البيانات العلاقة بين اضطرابات الكبد المزمنة المناعة الذاتية وتأخر سن البلوغ.

Introduction:

Autoimmune diseases are a group of diseases in which the body produces antibodies against its own tissue not against infective agents. It is characterized by severe inflammation and widespread tissue damage (Eaton et.al., 2007).

Autoimmune diseases are among the leading causes of death in young and middle- age women. Prevalence rates range from less than 5 per 100.000 (chronic active hepatitis) to 500 per 100.000 (rheumatoid arthritis). Females are mostly affected in 85% of cases. Although most diseases can occur at any age, some disease primarily occur in childhood and adolescence (Cooper and Stroehla, 2003).

Autoimmune diseases in children include juvenile Rheumatoid arthritis (JRA), systemic lupus erythematosus (SLE) autoimmune chronic liver disorders among many others (Rose and Mackay, 2007).

Juvenile rheumatoid arthritis (JRA) is the most common chronic rheumatic disorder of childhood. (Carrasco et.al., 2008). In which an inflammatory process may lead not only to fixed deformities but also to growth inhibition (Bartnicka et.al., 2007).

SLE is a systemic autoimmune disease characterized by the production of autoantibodies against a spectrum of nuclear antigens. The auto antibodies are immunoglobulins that bind via the combining sites of antigens originating in the same individual or species (Kotzin, 1996 and Elkon, 1998).

Liver disorders with likely autoimmune pathogenesis in childhood include autoimmune hepatitis, autoimmune sclerosing cholangitis and autoimmune hepatitis after liver transplantation (Mieli- Vergani and Vergani, 2009).

Many autoimmune diseases are chronic illness which may lead to growth retardation either because of illness itself or because of treatment required for it. Short statue is commonly perceived to be associated with social or psychological disadvantage (Voss, 2001).

In children with severe rheumatic disorders, treatment with glucocorticorids is frequently needed and is associated with growth retardation and osteopenia. Growth hormone (GH) treatment may improve growth and lean body mass but these benefits disappear when GH therapy is stopped (Grote, 2006 and Bechtold et.al., 2004).

Short stature frequently occur in children suffering from juvenile idiopathic arthritis. The potential of disturbance of linear growth is greater in children with systemic or non- systemic polyarticular disease of long duration (Bechtold et.al., 2004).

Aim Of The Study:

Screeing of Growth Impairment In Juvenile Rheumatoid Arthritis, Systemic Lupus Erythmatosus And Autoimmune Chronic Liver Disorders. So, it is important to use every effort to explore the relation between autoimmune disease in children and growth impairment.

Subjects And Methods

Type Of Study:

Cross Sectional Study.

Subjects:

Cases: one thousand cases of which 593 Juvenile Rheumatoid Arthritis, 305 Systemic Lupus Erythematosus and 102 Autoimmune Chronic Liver Disorders.

The study was conducted in the 4 main pediatric hospitals in Alexandria namely: El Shatby pediatric university hospital, El Anfoshy, El Ramelh pediatric hospitals and El Talaba health insurance hospital in Alexandria to select children with autoimmune diseases particularly JIA, SLE and autoimmune liver diseases to detect growth impairment in those children as indicated by auxological parameters from June 2010 to August 2015.

1. Inclusion Criteria:
   a. Children with autoimmune disease.
   b. School age children and adolescents.
   c. Both Sexes Are Included
2. Exclusion Criteria:
   a. Growth Hormone Deficiency.
   b. Hypothyroidism
   c. Inborn Errors Of Metabolism
   d. Chronic Hemolytic Anemia
   e. Undernutrition/ malnutrition (PFM)

Methods:

All children enrolled in the study will be subjected to the following

1. Complete medical history including:
   a. Birth Weight.
   b. Nutrition and growth during the first year.
   c. Nutrition History.

   According to the rheumatology sheet from El Shatby pediatric university hospital.
2. Auxoliogical parameters including:
   a. Measurement of basic parameters:
      - Height
      - Weight
   b. Plotting of this measurements using Egyptian growth charts to compare with children of same age and sex in normal population. (Cairo university, 2002)
   c. Calculating the body mass index (BMI):
      - > 95: Obese
      - 85- 95: overweight
      - < 25: Underweight
      - <10: Severe underweight
   d. Pubertal assessment in adolescent age group using Tanner staging (Tanner, 1962)
3. Investigations:
   a. Erythrocyte sedimentation rate (ESR) (Westergren method)
   b. C- Reactive protein (Latex agglutination test)
   c. Rheumatoid factor (RF) (latex or Rosewaller agglutination test)
   d. Anti- nuclear antibody (ANA) (ELISA technique).

e. Complete blood count (CBC) (automated cell counter machines)
f. Anti- Smith antibody (ELISA technique) if needed.
g. Anti- double strand DNA (ELISA technique) if needed.
h. Alanie transaminnase (ALT), aspartate transaminnase (AST), alkalaine phosphatese. (Enzymatic colorimetric chemical analysis)
i. Total Serum bilirubin and direct bilirubin (colorimetric chemical analysis).

Limitations Of The Study:

1. Availability Of Cases.
2. Parents Refusing To Cooperate.

Statistical Analysis:

Statistical analysis and data management the collected data was analyzed and expressed as follows: Qualitative data will be expressed as percentage while quantitative data will be expressed as mean +/- SD. All statistical analysis will be using SPSS software version 22 (IBM Corp, 2013)

Ethical Considerations:

Ethical considerations is followed according to WMA declaration of Helsinki- ethical principles for medical research (Finland, 2014) involving human subjects and according to ethical principles of ethical scientific committee of the high institute of childhood studies.

Results:

1. The percentage of juvenile idiopathic arthritis cases with negative history of LBW was 52.6 versus 47.4 with positive LBW history. The difference is statistically significant.
2. The percentage of JIA cases with negative history of under- nutrition and growth retardation during the first year was 60 compared with 40 having positive history. The difference is statistically significant.
3. The percentage of JIA cases with negative history of malnutrition was 80.8 compared with 19.2 having positive history. The difference is statistically significant.

   It is evident from the distribution tables that medical history in infancy or childhood has no effect in the future growth of the studied JIA group. this means other factors may be involved in growth retardation.

   Similarly, systemic lupus erythematosus (SLE) and autoimmune chronic liver disorders medical history in infancy or childhood has no effect in the future growth.
4. The percentage of SLE cases group of school age male children and adolescents $<3^{rd}<10^{th}$ weight percentile was 40.6versus 36.2 in$<10^{th}<50^{th}$ weight percentile and 23.7 in$<50^{th}<97^{th}$ weight percentile. The difference is statistically significant. This means a higher percentage of SLE cases are under- weight than those in the normal weight group.
5. The percentage of SLE cases group of school age male children and adolescents$<3^{rd}<10^{th}$ height percentile was 44.9versus 37.7in $<10^{th}$ $<50^{th}$ weight percentile and 17.4in$<50^{th}<97^{th}$ weight percentile. The difference is statistically significant. This means a higher percentage of SLE cases has short stature than those in the normal height group.
6. The percentage of SLE cases $<3^{rd}<10^{th}$ BMI percentile was 49.3 versus 30.4 in$<10^{th}<25^{th}$ BMI percentile and 20.3 in$<25^{th}<85^{th}$ BMI percentile. The difference is statistically significant. This means a higher percentage of SLE cases were in the severely underweight group than in the underweight group.

   Similarly, juvenile idiopathic arthritis and autoimmune chronic liver disorders a higher percentage of JIA and ACLD cases Were in the severely underweight group than in the underweight group.
7. Distribution of the studied Juvenile idiopathic arthritis (JIA) group of school age male children and adolescents according to auxiological parameters (Tanner stage) shows the highest percentage among the studied JIA males was 33.9 in stage 1 followed by stage 2 (29.7) this data support the association between JIA and delayed puberty.
8. Distribution of the studied SLE group of school age male children and adolescents according to auxiological parameters (Tanner stage) shows the highest percentage among the studied SLE male cases was 48in stage 1 followed by stage 2 (20.2) this data support the association between SLE and delayed puberty.
9. Distribution of the studied SLE group of school age female children and adolescents according to auxiological parameters (Tanner stage) shows the highest percentage among the studied SLE female cases was 42 in stage 1 followed by stage 2 (26.3) this data support the association between SLE and delayed puberty as most cases were in the stage 1 group.
10. Distribution of the studied autoimmune chronic liver disorders (ACLD) group of school age male children and adolescents according to auxiological parameters (Tanner stage) shows the highest percentage among the studied ACLD females was 30.3in stage 1 followed by stage 2 (24.2) this data support the association between ACLD and delayed puberty as most cases were in the stage 1 group.

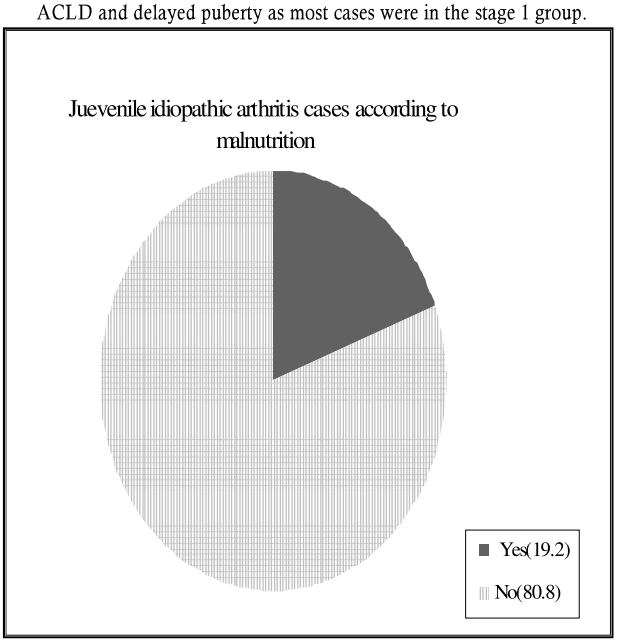

Figure (1) Showing distribution of juvenile idiopathic arthiritis cases of school children and adolescents (both sexes) according to history of malnutrition in the first year

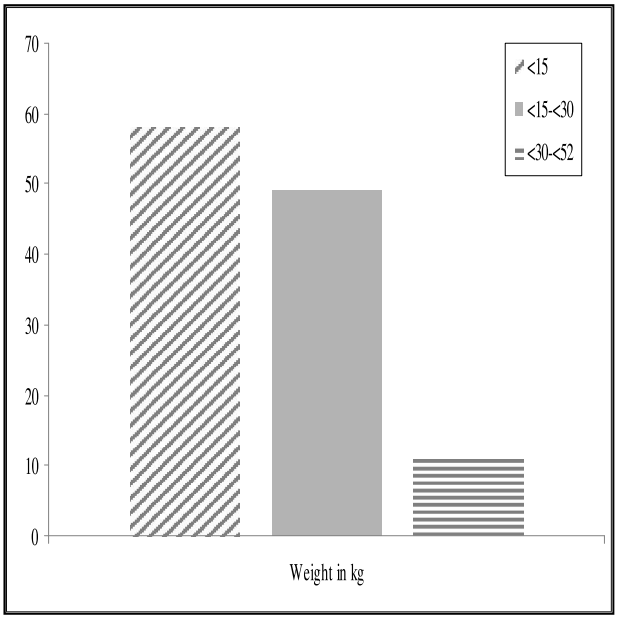

Figure (2) Showing distribution of systemic lupus erythrematosus group of school age female children and adolescents according to weight.

Discussion:

Autoimmune diseases are chronic illness which may lead to growth retardation either because of illness itself or because of treatment required for it. Short statue is commonly perceived to be associated with social or psychological disadvantage (Voss, 2001).

The results revealed that the percentage of Juvenile idiopathic arthritis (JIA) group of school age male and female children and adolescents who were severely under- weight was 49.2 and 44.8 respectively and those in< 3rd< 10th height for age percentile category (short stature) was 51.7 in males and 46.5 in females.

The above findings support the study of Giannini, Mohn and Chiarelli (2014) who stated that children and adolescents with chronic inflammatory diseases and especially JIA have largely documented an increased risk of developing growth alterations during childhood and adolescence. Growth alterations are often characterized by general growth retardation which may range from mild decreases in growth velocity to severe forms of short stature (Giannini C, Mohn A, Chiarelli F, 2014).

MacRae, Farquharson and Ahmed (2013) also concluded The development of abnormal growth patterns in children with inflammatory diseases such as JIA may be modulated by proinflammatory cytokines through both systemic effects and effects acting locally at the level of the growth plate (MacRaeV, Farquharson C and Ahmed S, 2005).

The results revealed that the percentage of systemic lupus erythematosus (SLE) group of school age male and female children and adolescents who were severely under weight was 40.6 and 44.5 respectively and those in <3rd- <10th height for age percentile category (short stature) was 44.9 in males and 46 in females.

The above findings are supported by the analysis of 1.015 Patients With juvenile- onset systemic lupus erythematosus which stated that Children and adolescents may experience growth retardation as a result of high- dose corticosteroid therapy, although growth may catch up significantly once steroid doses are lowered. The degree of permanent growth retardation is variable and has been insufficiently studied. A high frequency of short stature (38%) (Gutierrez- Suarez et.al., 2006)

The results revealed that the percentage of autoimmune chronic liver disorders (ACLD) group of school age male and female children and adolescents who were severely under- weight was 42.4 and 43.5 respectively and those in <3rd- <10th height for age percentile category (short stature) was 36.4 in males and 46.4 in females.

The above findings support the study which stated that autoimmune diseases are chronic illness which may lead to growth retardation either because of illness itself or because of treatment required for it. Short statue is commonly perceived to be associated with social or psychological disadvantage (Voss, 2001).

Pubertal assessment of Juvenile idiopathic arthritis (JIA) group of school age male and female children and adolescents using Tanner staging, the results showed that puberty is delayed in 33.9% of males and 35% of females.

The above finding found support in the study which stated that Sexual development is also delayed in children with JIA. In children with chronic arthritis, there is a strong association between the activity of the disease and the age of puberty. In girls with JIA, menstruation occurs almost two years later than in healthy children. In boys, delayed puberty is caused by reduced testosterone production by the testicular leydig cells.

Pubertal assessment of systemic lupus erythrematosus (SLE) group of school age male and female children and adolescents using Tanner staging reveals that that puberty is delayed in 48% of males and 42% of females.

The above results agreed with the analysis of 1.015 Patients With juvenile systemic lupus erythematosus which stated that delayed puberty is frequent and significant sources of damage specific to pediatric SLE patients and delayed puberty a temporary phenomenon but it may have irreversible consequences because it may prevent some important physiologic events, such as growth spurt. These losses may not be regained once puberty develops and may lead to final short stature and premature osteoporosis. Delayed puberty may also cause important emotional and social difficulties (Gutierrez, Suarez et.al., 2006).

Conclusion:

Juvenile rheumatoid arthritis (JIA), systemic lupus erythematosus (SLE) and autoimmune chronic liver disorders (ACLD) are frequently associated with growth impairment and delayed puberty. It is important to regularly monitor physical development and control inflammation associated with disease activity.

The severity of growth alteration in children and adolescents with these chronic diseases is variable, ranging from mild reductions in growth velocity to severe forms leading to an impaired final height.

Reduction of growth retardation in children with JIA, SLE and ACLD is to control inflammation with the help of currently available drugs, while reducing the duration and dosage of treatment with corticosteroids.

Further improvements to the treatment protocol depend on continued

research involving pediatricians and rheumatologists.

The statistical analysis detected the following results:

1. A significantly high percentage of severely under- weight was among JIA male children and adolescents (49.2).
2. A significantly high of short stature was among JIA male children and adolescents (51.7).
3. Pubertal assessment of systemic lupus erythrematosus (SLE) group of school age male children and adolescents using Tanner staging reveals that that puberty is delayed in 48% of males.

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