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Growth and Final Height in Children with Autoimmune Hepatitis; A long term observation

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Abstract

Background: Abnormal growth in children with autoimmune hepatitis (AIH) is anticipated, either due to hepatic affection or the growth inhibitory effects of corticosteroids. We aimed to describe children's anthropometry with AIH, and study the factors affecting height.

Methods: The present observational study investigates the anthropometric measures of 28 children with AIH followed at a university hospital for 9.5±3 years. We calculated the initial AIH score, the Child-Pugh score, and the pediatric end-stage liver disease score (PELD), follow-up anthropometry, and corticosteroid history. We defined abnormal growth as under nutrition (underweight, wasting, stunting), short stature, overweight, and obesity.

Results: At AIH diagnosis, children had a mean age of 7.4±3.1 years, ranging from 2 to 13.8; among whom ~20% had ascites, ~79% had jaundice, and ~82% had type 1 AIH, ~70% had a definite diagnosis of AIH, ~64% were Child-Pugh Score B, ~64% showed severe fibrosis/cirrhosis, and the median PELD score was 8.1 (0.1-12.1). At follow-up, their mean age was 15.9±1.6 years, with mean corticosteroid duration of 7.1±3.1 years, and remission occurred in 50%. We observed a significant improvement in the initial rates of underweight (46.4% vs. 17.8%), mainly stunted, and increased rates of overweight/obesity (14.3% vs. 32.2%). The final rates of height affection without weight affection were comparable to the initials (28.6% vs. 32.1%). Cases with abnormally low final height had significantly more frequent Child-Pugh Score B, higher PELD score, and severe hepatic fibrosis at presentation, with no difference regarding the continuation/ total duration of steroids.

Conclusion: the final height in children with AIH is significantly affected by the disease severity at presentation and not the continuation or the duration of corticosteroids use.

Key Words: Autoimmune hepatitis, Corticosteroids, Growth, final height, Liver cirrhosis/fibrosis.

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1- INTRODUCTION

Autoimmune hepatitis (AIH) is one of the most challenging hepatic diseases in children, although being a rare condition. Its prevalence in the pediatric population is variable, ranging between ~3 to ~10 per 100,000 children. The rates of AIH vary according to the genetic background of each individual. It is mainly an inflammatory process of the hepatic and or biliary system, resulting in the end-stage liver disease. It can affect all ages and any ethnic group (1-3). AIH has a peak in the pediatric age group at about ten years (4), and it is more common in the female gender (5). The pathogenesis of AIH is a defect in the immune system, where people with genetic susceptibility cannot tolerate the self-hepatic antigens triggered by environmental factors (1, 2).

AIH has variable modes of presentation ranging from an asymptomatic child with abnormal hepatic functions, acute onset, the stigma of chronic liver disease, to a child with cirrhosis. Diagnosis is somewhat problematic, relying on clinical manifestations, high γ-globulins, the presence of specific antibodies, interface hepatitis on hepatic histology, and noticeable response to corticosteroids, excluding other hepatic diseases (5, 6). Compared to adults, AIH in children has more severe presentations and is usually associated with primary sclerosing cholangitis (3).

AIH is a unique situation among hepatic diseases in children that has an effective therapy modifying the disease progression, and improving the patient's quality of life and survival. Corticosteroids with or without azathioprine have been the standard care for children in the last decades, showing considerable efficacy in induction of remission (2, 3). Remission is defined by normalized transaminases and immunoglobulin values (3, 5), reflecting an underlying histological remission (7).

In children with chronic liver disease, abnormal growth is a common observation with multifactorial etiologies, i.e., malnutrition (8), functional disorders of the growth hormone (9, 10), and corticosteroids use (11). The earlier the age at onset of AIH, the likelier the child will suffer from growth retardation (12).

We aimed to describe the patients' anthropometric measurements at diagnosis and follow-up, and to study the characteristics affecting the final height in a group of children with AIH receiving continuous or interrupted corticosteroid therapy.

2- MATERIALS AND METHODS

The present observational study investigates the anthropometric measures of children with AIH at presentation and after years of treatment. It was conducted at the outpatient clinic of the Pediatric Hepatology Unit, at Cairo University hospital, Cairo, Egypt. We enrolled children with confirmed AIH who were followed up between 2005 and 2018 and agreed to come for anthropometry.

AIH was classified as type 1 when antinuclear antibodies (ANA) and/or anti-smooth muscle antibodies (SMA) tested positive, and type 2 when anti-liver kidney microsomal type 1 (anti-LKM-1), or anti-liver cytosol type 1 (anti-LC1) antibodies and/or anti-LKM3 antibodies tested positive. Antibody positivity was considered in dilutions > 1/40. The patients who tested negative for autoantibodies were not classified.

2-1. Data at AIH diagnosis from the patients' files, included

a) Demographic data, age at diagnosis, other autoimmune conditions, type of AIH, and the treatment initiation time;

b) Anthropometry data of weight, height, and Body Mass Index (BMI);

c) Examination and ultrasound findings, mainly for stigmata of liver disease; and

d) Laboratory data of liver functions, immunoglobulins, autoantibodies, and liver biopsy results.

2-2. Inclusion and Exclusion criteria

Initial diagnosis of AIH at our site relies on the exclusion of known causes of liver disease, including viral hepatitis (hepatitis A-E, Epstein-Barr and cytomegalovirus infections in acute cases and hepatitis B and C in chronic cases), alpha-1-antitrypsin deficiency, Wilson disease, drug-induced hepatitis as well as biliary anomalies and obstruction, besides the presence of high gamma-globulin, positive autoantibodies, and positive liver biopsy findings when feasible. Children with other conditions affecting growth (e.g., skeletal or chromosomal abnormalities) were excluded from the study.

2-3. Calculated scores

i. AIH score was calculated using the Simplified Autoimmune Hepatitis score (13) as an accurate positive test for diagnosis in children (14). An aggregate score >7 before therapy constitutes a definite diagnosis of AIH and 4-6 a probable diagnosis.

ii. Child-Pugh score was calculated for every patient with "A" reflecting the slightest and "C" the most severe affection. Its value is to assess the severity of AIH (15).

iii. PELD score (Pediatric End-stage Liver Disease, assigned for children <12 years) was used for the younger children to determine their need for liver transplantation and to assess its reflection on growth. Its value is to assess the mortality rate expected due to hepatic affection.

2-4. Follow-up data

We reported the duration of follow-up, the number of relapses, and corticosteroid history. Conditions of corticosteroids withdrawal were absence of clinical symptoms, normal transaminase, normal IgG levels, and negative or very low levels of autoantibodies, without reactivation (negative monthly investigations for three months after withdrawal).

Anthropometric measures: children were requested to come for an anthropometric assessment. We measured weight using a digital scale. We measured height using a stadiometer, with the child barefoot in light clothing with head, shoulder blades, buttocks, and heels touching the board and head in the Frankfurt plane. BMI was calculated as the child's weight in kilograms divided by his height squared in meters. In patients with ascites, we subtracted 10% to assess the dry body weight. The indicators of anthropometric measures presented as percentiles and Z scores were calculated online (16), using the CDC growth charts for ages 2-20 years.

2-5. Definition of abnormal anthropometric measures (17)

a) Low weight-for-age: <-2 Z score is underweight & < -3 Z score is severely underweight.

b) Low height-for-age:

- In cases with low weight-for-age, < -2 Z score is stunting & < -3 Z score is severely stunting.
- If weight-for-age is not low, < -2 Z score is short stature.

c) Low BMI: < -2 Z score is wasting & < -3 Z score is severely wasting.

d) Overweight or obese: Considering the percentiles for age and sex, > 85th is overweight & >95th is obesity

2-6. Ethical considerations

Ethics approval of this non-funded study was obtained from the University of Cairo. The protocol was approved by the site's research ethics committee and carried out

following the Helsinki declaration. Enrollment was done after receiving informed consent for participation and publication from one of the parents if above 18 years or from the participants reaching 18 years of age.

2-7. Statistical Analysis

Data were tabulated and analyzed using SPSS for Windows 7. We presented continuous data as mean ± SD and categorical data as numbers and percentages. We used the chi-squared test, paired t-test, and Wilcoxon Signed Ranks Test-related samples to compare anthropometric measures when appropriate. The chi-squared was tested in tables 3 and 4 using the online calculator for the 2x2 contingency table (18). Boxplots were used to present the difference in Z scores between the initial and follow-up measures. A two-tailed p-value <0.05 was considered statistically significant.

3- RESULTS

Among 44 children with AIH registered at the study site, we included 28 children who were still reachable. About 70% of them were females. Children's characteristics are shown in **Table 1.** Type 1 AIH was diagnosed in 23 (~82%) of the cases, type 2 was not identified, and 5 (~18%) children had no significant antibody titer at diagnosis.

The anthropometric measures and the percentage of children fulfilling the definitions of abnormal weight, height, and BMI at diagnosis and follow-up are shown in **Table 2.**

At the initial diagnosis, all patients received an initial dose of prednisone (2 mg/kg/day) for 2-3 weeks until normal or near-normal liver enzymes, then tapering begun with the introduction of azathioprine. Prednisone was maintained at the lowest dose that prevented relapse (5 mg every other day for one year).

At follow-up, the mean age was 15.9±1.6 years, and the mean duration of follow-up was 9.5±3 years (4- 14). The mean duration of corticosteroid therapy was 7.1 ± 3.1 years. Corticosteroids were stopped in 50% and continued in 50% of cases. Biochemical relapse occurred in 19 children, at a median of 2 (1-3).

We compared anthropometric measurements and children's characteristics at the diagnosis and follow-up regarding the continuation of corticosteroids **(Table 3** and **Fig. 1)**. In cases where steroids could be withdrawn, significant improvements in the weight and height Z scores were observed at follow-up. In children with a continuation of steroids, a considerable improvement in the weight Z score was noticed. The frequencies of abnormal follow-up measures showed no significant difference in both groups. All cases showed improved weight Z scores regardless of the degree of hepatic fibrosis. Height Z score showed a considerable increment in subjects with severe fibrosis. No significant difference was observed in the frequencies of abnormal measures between the two groups at the follow-up. The comparisons regarding the degree of fibrosis are shown in **Table 4.**

Comparing the anthropometric measurements and children's characteristics regarding the final height showed that children with average height at follow-up were less common in the child B group of severe disease category, with lower PELD score values. The initial presentation as jaundice, ascites, and liver size or AIH type showed no significant difference between the groups (**Table 5**).

Interestingly, in half of the group having finally average heights, it improved to normal in 32.1%, and maintained in the standard range in10.7% . In the other half, 10.7% decreased from standard to more than -2 Z score, while 39.3% maintained in the abnormally low height.

Table-1: Characteristics of the study sample at the diagnosis of Autoimmune Hepatitis (N=28)

Variable		Values
Age in years; mean ± SD (min-max)		7.4 ± 3.1 (2-13.8)
Gender; N (%)	Females	20 (71.4)
	Males	8 (28.6)
Ascites; N (%)		6 (21.4)
Jaundice; N (%)		22 (78.6)
Hepatic size; N (%)	Enlarged	11 (39.3)
	Shrunken	4 (14.3)
Biopsy; N (%)	Mild/moderate fibrosis	10 (35.7)
	Severe fibrosis/cirrhosis	18 (64.3)
AIH score	4-6: probable diagnosis	8 (28.6)
	≥ 7: definite diagnosis	20 (71.4)
Child-Pugh Score; N (%)	Child A	10 (35.7)
	Child B	18 (64.3)
PELD score; median (IQR) (min-max)		8.1 (0.1-12.1) (0 – 19)

AIH: Autoimmune Hepatitis, PELD: Pediatric End-stage Liver Disease score.

Table-2: A Comparison of the anthropometric measurements of our study sample at diagnosis and follow-Up (N=28)

Anthropometric Measurements	At diagnosis	At follow-up	P value
Weight; mean ± SD	19.1 ± 6.3	50.3 ± 8.7	0.000*
Weight percentiles; median (IQR)	2.7 (13.4 - 0.03)	27 (52.5 – 8.1)	0.001*
Weight Z score; median (IQR)	-1.9 (-1.1 - -3.3)	-0.6 (0.06 - -1.4)	0.000*
Weight >-2 Z score; N (%)	13 (46.4)	5 (17.8)	0.04* (OR 4)
Underweight (-2 to > -3)	4 (14.3)	3 (10.7)	
Severely underweight (> -3)	9 (32.1)	2 (7.1)	
Height; mean ± SD	108.9 ± 16.96	152.6 ± 10.3	0.000*
Height percentiles; median (IQR)	0.6 (3.5 – 0.03)	2.8 (13.3 – 0.4)	0.02*
Height Z score, median (IQR)	-2.6 (-1.8 - -3.3)	-1.9 (- 1.1 - -2.7)	0.007*
Height > -2 Z score; N (%)	20 (71.4)	14 (50)	0.2
-Stunting (with underweight)	12 (42.9)	5 (17.8)	0.08
Stunted (-2 to > -3)	4 (14.3)	2 (7.1)	-
Severely stunted (> -3)	8 (28.6)	3 (10.7)	-
-Short stature (no underweight)	8 (28.6)	9 (32.1)	0.9
BMI; mean ± SD	15.7 ± 1.7	21.7 ± 3.5	0.000*
BMI percentiles; median (IQR)	30.6 (67 – 11.25)	52 (86 – 29.4)	0.04*
BMI Z score, median (IQR)	-0.5 (0.44 - -1.2)	0.05 (1.08 - -0.5)	0.03*
BMI >-2 Z score; N (%): Severely wasting (> -3)	1 (3.6)	0	0.5
Overweight/obese (BMI>85th percentile); N (%)	4 (14.3)	9 (32.2)	0.2

BMI, Body Mass Index. OR: Odds Ratio. P is considered significant at < 0.05.

Table-3: Differences in children's characteristics and abnormal growth considering the continuation of corticosteroids (N=28)

Variable	Steroids Stopped (N=14)			Steroids continued (n=14)		P value
Age at diagnosis; mean± SD	6.5 ± 2.5			8.3 ± 3.5		0.1
Gender (female/male); N (%)	11 (78.6)/ 3(21.4)			9 (64.3)/ 5(35.7)		0.7
Marked fibrosis; N (%)	10 (71.4)			8 (57.1)		0.4
AIH score; mean± SD	6.7 ± 1.3			7.5 ± 1.2		0.09
Child B; N (%)	7 (50)			11 (78.6)		0.1
PELD score; median (IQR)	8 (0-14)			8 (3.7-11.5)		0.8
Follow-up; mean± SD	10.4 ± 2.3			8.7 ± 3.4		0.1
Duration of steroids; mean± SD	5.5 ± 1.5			8.7 ± 3.4		0.004*
Relapses; median (IQR)	1 (0 - 2)			1 (0 – 3.3)		0.4
Azathioprine; N (%)	6 (42.9)			9 (64.3)		0.3
Anthropometric measurements	At diagnosis	At follow-up	P value	At diagnosis	At follow-up	P value
Weight <-2 Z score; N (%)	8 (57.1)	3 (21.4)		5 (35.7)	2 (14.3)	0.4
- Underweight	3 (21.4)	3 (21.4)	0.2	1 (7.1)	0	
- Severely underweight	5 (35.7)	0		4 (28.6)	2 (14.3)	
Height <-2 Z score; N (%)	10 (71.4)	6 (42.9)		10 (71.4)	8 (57.1)	0.8
- Stunting (with underweight)	7 (50)	3 (21.4)	0.4	5 (35.7)	2 (14.2)	0.4
• Stunted	2 (14.3)	1 (7.1)	0.3	2 (14.3)	1 (7.1)	
• Severely stunted	5 (35.7)	2 (14.3)	0.9	3 (21.4)	1 (7.1)	
- Short stature	3 (21.4)	3 (21.4)		5 (35.7)	6 (42.9)	0.9
BMI Z score; median (IQR)	-0.6 (-1.3 – 0.1)	0.04 (-0.7 – 1.1)	0.08	-0.3 (-1.3 – 0.5)	0.2 (-0.6 – 1.1)	0.2
BMI <-2 Z score; N (%) Severely wasting	1 (7.1)	0	0.9	0	0	NA
BMI>85th percentile; N (%)	2 (14.3)	4 (28.6)		2 (14.3)	5 (35.7)	0.4
• Overweight	0	4 (28.6)	0.7	1 (7.1)	5 (35.7)	
• Obese	2 (14.3)	0		1 (7.1)	0	

AIH: Autoimmune Hepatitis, BMI, Body Mass Index, NA: Not Applicable, PELD: Pediatric End-Stage Liver Disease score. P is considered significant at < 0.05.

Table-4: Differences in children's characteristics and abnormal growth considering the degree of hepatic fibrosis (N=28)

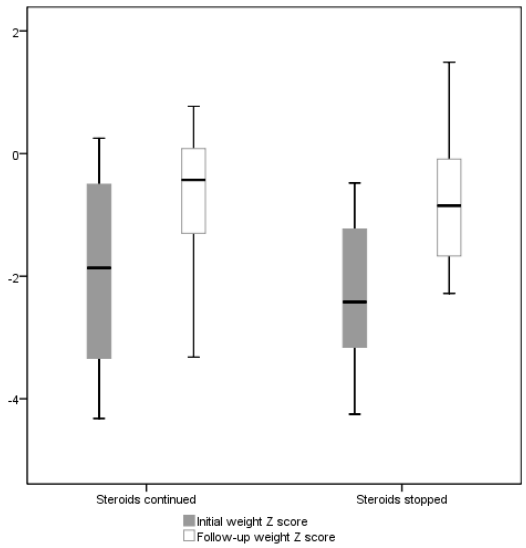
Variable	Mild/moderate fibrosis (no=10)			Severe fibrosis/cirrhosis (no=18)		P value
Age at diagnosis; mean± SD	7.1 ± 3.1			7.6 ± 3.1		0.7
Gender (female/male); N (%)	6 (60)/4 (40)			14(77.8)/4 (22.2)		0.3
AIH score; mean± SD	7.1 ± 1.3			7.1 ± 1.3		0.9
Child B; N (%)	6 (60)			12 (66.7)		0.7
PELD score; median (IQR)	8 (0.1-10.5)			12.9 (2.2-18.5)		0.3
Follow-up; mean± SD	11 ± 2.9			8.7 ± 2.8		0.05*
Continued steroids; N (%)	4 (40)			10 (55.6)		0.4
Duration of steroids; mean± SD	7.2 ± 3.7			7.1 ± 2.8		0.9
Relapses; median (IQR)	1 (0 – 3.3)			1 (0-2.3)		0.7
Azathioprine; N (%)	4 (40)			11 (61.1)		0.3
Anthropometric measurements	At diagnosis	At follow-up	P value	At diagnosis	At follow-up	P value
Weight Z score; median (IQR)	-2.6 (-3.5 – -0.6)	-0.9 (-1.8 – 0.3)	0.01*	-1.9 (-2.9- -1.2)	-0.6 (-1.3 - -0.07)	0.001*
Weight <-2 Z score; N (%) • Underweight • Severely underweight	6 (60) 1 (10) 5 (50)	2 (20) 1 (10) 1 (10)	0.2	7 (38.9) 3 (16.7) 4 (22.2)	3 (16.7) 2 (11.1) 1 (5.6)	0.3
Height Z score; median (IQR)	-2.8 (-3.5- -1.9)	-1.5 (-3 - -0.9)	0.06	-2.4 (-3 - -1.4)	-2.1 (-2.6 - -1.3)	0.04*
Height <-2 Z score; N (%) -Stunting (with underweight) • Stunted • Severely stunted -Short stature	7 (70) 5 (50) 1 (10) 4 (40) 2 (20)	4 (40) 2 (20) 1 (10) 1 (10) 2 (20)	0.4 0.2 - - 0.9	13 (72.2) 7 (38.9) 3 (16.7) 4 (22.2) 6 (33.3)	10 (55.6) 3 (16.7) 1 (5.6) 2 (11.1) 7 (38.9)	0.5 0.3 - - 0.9
BMI <-2 Z score; N (%); Severely wasting	1 (10)	0	0.9	0	0	NA
BMI>85th percentile; N (%) • Overweight • Obese	3 (30) 0 3 (30)	4 (40) 4 (40) 0	0.9	1 (5.6) 1 (5.6) 0	5 (27.8) 5 (27.8) 0	0.2

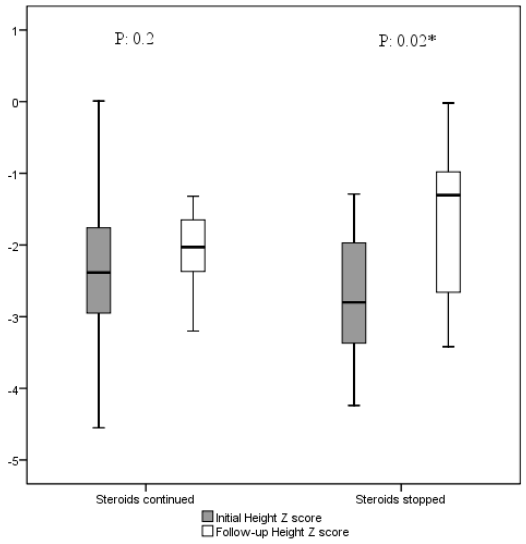
AIH: Autoimmune Hepatitis, BMI: Body Mass Index, NA: Not Applicable, PELD: Pediatric End-Stage Liver Disease score. P is considered significant at < 0.05.

Table-5: Differences in children's characteristics and abnormal growth considering the final height (N=28)

Variable	Final height		P Value
	Normal (N=14)	More than -2 Z score (N=14)	
Age in years; mean ± SD	6.6 ± 2.7	8.2 ± 3.3	0.2
Gender (female/male); N (%)	9 (64.3)/5 (35.7)	11 (78.6)/3 (21.4)	0.4
Severe fibrosis; N (%)	8 (57.1)	10 (71.4)	0.4
AIH score; mean± SD	6.7 ± 1.4	7.5 ± 1	0.1
Child-Pugh Score B; N (%)	6 (42.9)	12 (85.7)	0.02*
PELD score; median (IQR)	7.4 (0-8.6)	12.1 (6.7-17.5)	0.04*
Follow-up years; mean ± SD	10.2 ± 3	8.8 ± 2.9	0.2
Continue on steroids; N (%)	6 (42.9)	8 (57.1)	0.4
Duration of steroids; mean± SD	6.4± 2.9	7.7±3.1	0.3
Relapses; median (IQR)	1 (0-1.3)	1.5 (0-4)	0.4
Azathioprine; N (%)	7 (50)	8 (57.1)	0.7
Initial weight <-2 Z score; N (%) • Underweight • Severely underweight	4 (28.5) 1 (7.1) 3 (21.4)	9 (64.3) 3 (21.4) 6 (42.9)	0.2
Initial Height <-2 Z score; N (%) - Stunting (with underweight) • Stunted • Severely stunted - Short stature	9 (64.3) 3 (23.4) 1 (7.1) 2 (14.3) 6 (42.9)	11 (78.6) 9 (64.3) 3 (21.4) 6 (42.9) 2 (14.3)	0.1 0.05 0.2
Initial BMI <-2 Z score; N (%); Severely wasting	1 (7.1)	0	0.4
Initial BMI>85th percentile; N (%) • Overweight • Obese	3 (21.4) 1 (7.1) 2 (14.3)	1 (7.1) 0 1 (7.1)	0.5

AIH: Autoimmune Hepatitis, PELD: Pediatric End-Stage Liver Disease score. P is considered significant at < 0.05.





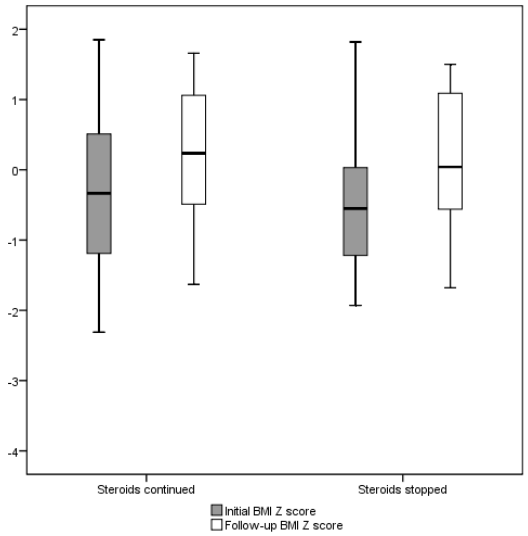


Fig. 1: Differences in anthropometric measurements considering the continuation of corticosteroids

4- DISCUSSION

This study presented the growth pattern of 28 children with AIH at their initial presentation and after a mean follow-up of 9.5±3 years. Our studied group was first diagnosed with AIH at a mean age of 7.4 ± 3.1 years (range 2-13.8), and about two-thirds had severe hepatic fibrosis/cirrhosis at presentation. AIH-remission was achieved in 50% with discontinuation of corticosteroids. We used undernutrition (underweight, wasting, stunting), short stature, overweight, and obesity to describe anthropometric growth. To our knowledge, our study is one among the few that describe anthropometry in children with AIH over a long follow-up duration.

Among our study group with AIH, females represented 71.4% of the cases, with a female: male ratio of 2.5:1. The preponderance of the female gender in children with AIH is generally accepted. Close to our results, the female gender was observed in 79.9% among a cohort of more than 800 children with AIH (19). The ratio varies from one report to another; a female: male ratio of 1.5:1 was observed previously, with more prevalent females in those above ten years of age (20).

Based on our observations, ~82% of children were type 1, ~18% had no detected antibodies, and none were type 2. We studied the growth in the whole group without any types-related classification. According to our results, the domination of type 1 in children has been reported in 89.6% of AIH cases (19). The latest research studies, based on evidence of changing antibody profile during the disease course, have recommended considering AIH collectively without type-classification (21).

At the time of diagnosis, about half of our samples were underweight; and 28.6% had short stature. About 2/3 of our studied AIH-children were presented with severe disease category, i.e., Child-Pugh Score "B", with severe hepatic fibrosis/cirrhosis. Unlike our findings, some other studies have reported that children with AIH did not have a higher chance of abnormal anthropometric measurements (22, 23). Delayed diagnosis of AIH could be the reason for the prolonged burden of AIH over children's growth in our group, which is a common scenario in countries with limited medical facilities. Delayed diagnosis of AIH is a multifactorial issue, related to a challenging presentation, low incidence of antibodies, low immunoglobulin-G levels, delayed biopsy decision, etc. (5, 6).

The description of the studied children at diagnosis was as follows: 46.4% were underweight; among whom 42.9% experienced stunting, and 3.6% wasting. All weight indicators increased significantly at follow-up, reducing the underweight rates to 17.8%, mainly in the stunted group. Similar to the observed rates after the treatment, undernutrition has been reported as about 25% in children with chronic liver diseases (24). Children with chronic liver disease are frequently presented with weight affection followed secondarily with height affection due to malnutrition (25, 26). Combined factors contributing to malnutrition include limited intake of nutrients (8, 22), malabsorption (9), dietary restrictions, disturbed hepatic metabolic functions (27, 28), increased energy needed for growth (10, 22), and the resistance to growth hormone (29).

We observed a significant improvement in height indicators at follow-up. Differently, Sogo et al. (20) reported a considerable decline in height Z-score after the corticosteroids therapy. Also, Cortez et al. (22) said that in 10.5% of the studied children with AIH, height declined below -2 Z score. They relate this decline to the cumulative doses of steroids used.

Despite the improved height indicators at follow-up, about one-third of our group had short stature with no weight affection, comparable to the initial frequency (28.6% vs. 32.1%). The impaired linear growth in AIH-children, without underweight, reflects an etiology other than malnutrition. Two explanations are reasoning, growth hormone resistance (9, 10), and prolonged corticosteroids therapy (11). Glucocorticoid therapies are incriminated in growth retardation in children with the chronic liver disease due to reduce in growth hormone secretion and direct inhibition of the growth of bone and connective tissues (30, 31). Extra-physiologic doses of steroids can negatively affect skeletal growth by inhibiting osteoblastic activity, increasing bone resorption, and interfering with normal bone metabolism (32). Linear growth of the whole studied group was abnormally low at 50%. Cases with a final height > -2 Z score were 39.3% who maintained their initial impaired height, and 10.7% declined from normal. Having a final abnormal height was not related to the disease severity or the continuation of steroids. The target height could be affected permanently even after steroids withdrawal (33) and after successive liver transplantations in 15% of children (34). The burden of corticosteroids on children's growth is related to both its duration and dose-intensity; even 3-5 mg/m2/day can inhibit growth (22; 35).

Our sample received corticosteroids at diagnosis, and those who showed remission were maintained on alternative days' low steroid doses. Among the studied samples, 32.1% could achieve a final average height after an initial impaired one, and 10.7% maintained their average height. Many scientists preferred the alternate-day steroids regimen to lessen their negative effect on the child's growth, with a higher tendency for disease relapse. Similar to our results, previous studies have reported that alternative-day regimens can only decrease but cannot eliminate the risk of growth suppression (35, 36). Differently, Maggiore and colleagues (37) reported resumed growth rates in children with AIH on alternative day's corticosteroid therapy. Other scientists believed that small daily doses could control the disease severity, induce remission, and decrease the negative effect of continuous high amounts on the child's final height. They believed that a long-term prednisolone use in AIH-children does not interfere with their targeted final height, based on their genetic potential (38). Mieli-Vergani and colleagues (39) observed that 56% of children with AIH maintained their initial height-percentiles or went up, 38% dropped down one centile line, and only 6% showed growth failure after five years of continuous treatment.

After a long-term follow-up of our AIH-children, we observed a significant improvement in underweight rates, mainly in the stunting group (42.9% vs. 17.8%), with no difference regarding the continuation of corticosteroids or the degree of hepatic fibrosis. The associated increase in the BMI indicators may be a conflicting factor explaining the improved weight of the malnourished children. Still, the increased height of stunted children is a clinical clue for a real improved growth rate and resumed height. They had a 50% remission rate that can reflect corticosteroid efficacy, with or without azathioprine, in controlling the disease severity and calming the hepatic inflammatory process in children with AIH, directing them to a healthier growth pattern. The utility of corticosteroids in managing AIH in children had been proven previously, with more than 2/3 achieving disease remission (19). Corticosteroid therapy can reduce liver affection progression and improve children's quality of life (2).

In children with chronic liver disease, linear growth is used as an overall

indicator of growth. These children usually have edema, ascites, organomegaly, and are prone to malnutrition. So, continuous monitoring of their heights is crucial for detecting early growth failure; this explains its incorporation in the PELD score for selecting transplantation candidates (40).

On follow-up, we observed an increment in BMI indicators and an increment in rates of overweight/obesity (14.3% vs. 32.2%), especially in cases with mild hepatic fibrosis. The continuation of steroids was not associated with higher rates of overweight/obesity. It is well established that corticosteroids cause weight gain and obesity (41). Meanwhile, the current obesity pandemic observed, with estimated rates of 18% among children aged 5-19 years in 2016, maybe another risk factor for duplication of the incidence of overweight/obesity in the studied adolescents.

The limitations of this study included the low number of participants, along with the fact that the patients had not maintained their birth data of weight and height.

5- CONCLUSION

All indicators of weight, height and BMI improved significantly over the follow-up duration. We observed a significant improvement in under-nutrition rates, mainly in the stunting group. During the follow-up, the prevalence of short stature remained almost the same, and overweight/obesity rates doubled. The final height in children with AIH is significantly affected by the disease severity at presentation and not the continuation or the duration of corticosteroids use.

6- CONFLICT OF INTEREST

None.

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