AJMAS
https://journal.utripoli.edu.ly/index.php/Alqalam eISSN 2707-7179

Original article

Serum Ferritin Level and Alopecia Areata in Pediatric Patients

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ARTICLE INFO

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Received: *10-10-2022* ***Accepted:*** *28-10-2022* ***Published:*** *30-10-2022*
Keywords: *Pediatric, Hair Loss, Alopecia Areata, Serum Ferritin, Severity, Duration.*

ABSTRACT

Background and aims. *Alopecia areata (AA) is a non-cicatricial type of hair loss, it presents clinically by well-circumscribed single or multiple patches affecting hair bearing body areas making the affected area completely devoid of hair, although the exact etiology is not well known, genetic and immunological factors are the main players in disease pathogenesis. The aim of this study was to evaluate serum ferritin in alopecia areata in children and to estimate the relation between serum ferritin and disease duration and severity.* ***Methods****. An observational cross section study was carried out on 50 clinically diagnosed alopecia areata pediatric patients; serum ferritin levels were measured and compared according to clinical types, disease severity and duration.* ***Results****: There was low serum ferritin in patients with patchy alopecia areata (p value =0.016), also, it was low in ophiasis pattern (p value=0.008). About 86.66% of patients who had severe disease were with serum ferritin below the lower recommended value and patients who with longer disease duration had lower serum ferritin.* ***Conclusion****. Serum ferritin plays a role in AA presentation pattern and its can be considered as a prognostic factor as its low level are associated with increased disease severity and longer disease duration. Further studies are needed to evaluate whether ferritin level correction can change the course of the disease.*

Cite this article. *Abdaljawad S, Qiteesh H, Abdelgader A, Saed W. Serum Ferritin Level and Alopecia Areata in Pediatric Patients. Alq J Med App Sci. 2022;5(2):527-533. https://doi.org/10.5281/zenodo.7264077*

INTRODUCTION

Alopecia areata (AA) is an immune-mediated hair loss disorder that affects 1.7% of the general population. It is prevalence ranges from 0.1–0.2% worldwide [1]. There is no known race, sex, predilection for the development of alopecia areata, Alopecia areata can occur at any age with a mean age of onset of 20 years [2]. It is characterized by a well-defined single patch or multiple patches of non-scarring alopecia that may extend leading to total scalp alopecia and/or lead to total body hair loss [3].

Alopecia areata is frequently associated with autoimmune diseases like vitiligo, thyroid disease, pernicious anemia, and diabetes mellitus [4]. The disease course is unpredictable, spontaneous remission can occur, but chronic course with treatment resistance is possible [5]. AA considered as an autoimmune disease with multiple players and a complex immune-pathogenesis. A lot of molecular mechanisms and factors are implicated in AA pathogenesis [5,6].

Serum ferritin is a molecule that have different roles, it is the main storage form of iron and is a detrimental for iron homeostasis, it has a role as a signaling molecule, and it is considered as a modulator of the immunological responses, The expression of ferritin is regulated by levels of iron, cytokines, hormones and oxidative stress, it was found to be an acute - phase reactant in many autoimmune diseases [6]. They found that low serum ferritin and increased incidence of iron deficiency anemia has been documented in female patients with telegon effluvium, with established relation between chronic telegon effluvium and lower ferritin levels [7,8].

Many studies have been conducted regarding iron and ferritin levels in patients with AA, ferritin considered the main transport protein for functional iron to the hair follicle, and they relate a low ferritin level with AA cases [9]. In pediatric age group it was found that low serum ferritin considered significantly low if below 30mg/L and it recommended to starting

iron treatment even if not associated with low hemoglobin, iron deficiency ranging from iron store depletion to iron deficiency anemia , in iron depletion body iron store is so low but functional iron within normal levels while in iron deficiency anemia all iron depleted [10]. WHO guide line recommend that if hair loss an issues in children it is appropriate to raise serum ferritin up to 30Mg/L [11], at levels of ferritin above the recommended values for each age group more follicles in anagen regrowth phase with less ligands exposed to autoimmunity and more perfect antioxidant processes.
Hair loss in children can be caused by different diseases while AA considered as the commonest cause of hair loss among children, clinical presentation of child with alopecia areata ranges from subtle to disfiguring, while, patchy type considered the commonest presentation in children, early presentation age can associated with poor respond to management especially with severe clinical types, while later presentation in adolescent can lead to more psychological disturbance, ranging from just stress to depression [4,12]. The aim of this study is to find if there is relation between serum ferritin and the different types of AA, duration of AA and severity in pediatric age group to, analyze if low serum ferritin have a prognostic importance regarding the clinical presentation and durability of the disease specifically in children.

METHODS

Study design and setting

A cross- sectional, observational study was carried out in the pediatric outpatient department and dermatological outpatient department in Al-Bayda medical center over a one-year period.
Detailed history was taken from all patients including personal data, disease onset, and duration, family history of AA, autoimmune diseases and atopic diseases, and drug history. All patients participating in the study were examined by a pediatrician to exclude any other medical conditions especial focusing on autoimmune, endocrine, atopic disorders, and any dysmorphic features in order to exclude any patient with multifactorial hair loss rather than alopecia areata.
A dermatologist examined all participants and diagnosis of Alopecia areata was made clinically by examination of scalp, hairy body skin, lashes, nails and confirmed using a dermoscope, size, site and number of patches were detected.

Inclusion criteria

Pediatric age group under 16 years newly diagnosed with alopecia areata both males and females not receiving any medication.

Exclusion criteria

AA patients on treatment, the other causes of alopecia, chronic infection, other chronic illness, patient taking iron supplement, patient with abnormal thyroid function test.
Informed consent was obtained from children‘ s parents.
The severity of the disease classified as follows [13]; 1) Mild cases: patients with three or less patches of alopecia with a widest diameter of three cm or less. 2) Moderate cases: patients with more than three patches of alopecia or a patch larger than three cm at the widest diameter. 3) Severe cases: Alopecia totalis, and alopecia universalis. 4) Ophiasis: a band-like loss of hair usually on the side of the scalp.
Venous blood samples were collected to analyzes, ferritin, the other investigations performed were CBC, TFT. Serum ferritin was evaluated by electro-chemiluminescent immunoassay method. The accepted lower cut-off value for serum ferritin in children is<30 Mg/l [11].

Statistical analysis

The data were fed to the computer and analyzed using IBM SPSS software package version 20.0 (Armonk, NY: IBM Corp.). The Qualitative data were described using number and percent while Quantitative data were described using range (minimum and maximum), mean, and standard deviation, median and interquartile range (IQR). Chi-square test was used for categorical variables, to compare between different groups, Mann Whitney test was used for abnormally distributed quantitative variables, to compare between two studied groups, Kruskal Wallis test was used for abnormally distributed quantitative variables, to compare between types of AA and serum ferritin, the results are considered statistically significant if P value is < 0.05.

RESULTS

This study is a cross-sectional, observational study included 50 children, the age of the study population ranged from 3 to 16 years old with (mean 9.52 _+ 3.58) years. A negative family history of AA was recorded in 30 patients (60%) while 20

patients (40%) had a positive family history. Number of patients with alopecia areata was 35 (70%), 8 (16%), 4 (8%), 3 (6%) of patients have alopecia areata, totalis, universalis and ophiasis pattern respectively.
Of total 27 (54%) were female, and 23 (46%) were male, with statistically non-significant gender distribution, AA patchy type was found in 35 patients (70%), 20 of them were females and 15 males, alopecia totalis was found in 8 patients (16%), 4 of them were females and 4 were males, alopecia univerrsalis was found in 3 patients (6%), 1 was a female and 2 were males and ophiasis pattern was found in 4 patients (8%), 2 of them were females and 2 were males (Table 1).

Table 1. Relation between type of alopecia and serum ferritin in each category

Serum ferritin Mg/L	**Type of alopecia**				**H**	**p**
	Patchy Alopecia areata	Alopecia totalis	Alopecia universalis	Ophiasis patarene		
Total (n= 50)	(n= 35)	(n= 8)	(n= 3)	(n= 4)		
Min. – Max.	6.30 – 83.0	8.0 – 33.54	12.50 – 70.0	6.71 – 13.30	9.069*	0.028*
Mean ± SD.	37.35 ± 26.46	17.13 ± 8.70	32.28 ± 32.68	9.0 ± 3.02		
Median	28.10	14.55	14.35	8.0		
Male (n= 23)	(n= 15)	(n= 4)	(n= 2)	(n= 2)		
Min. – Max.	3.60 – 80.22	8.0 – 33.54	12.50 – 14.35	8.90 – 13.30	2.53	0.522
Mean ± SD.	34.75 ± 28.32	20.21 ± 10.67	13.43 ± 1.31	11.10 ± 3.11		
Median	25.32	19.65	13.43	11.10		
Female (n= 27)	(n= 20)	(n= 4)	(n= 1#)	(n= 2)		
Min. – Max.	8.17 – 83.0	9.70 – 23.10		6.70 – 7.10	2.253	0.522
Mean ± SD.	39.29 ± 25.55	14.05 ± 6.12	70.0	6.91 ± 0.28		
Median	36.60	11.70		6.91		

H: for kruskal wallis test

When we considered the level of 30 Mg/l as a low cut off value, we found that about 31 children (62%) has a low reference and 19 children (38%) has a high serum ferritin reference with a median 22.15 (Table 2).

Table 2. Distribution of the studied cases according to serum ferritin

Serum ferritin Mg/L	**No.**	**%**
≤30 (low reference)	31	62.0
>30 (high reference)	19	38.0
Min. – Max.	6.30 – 83.0	
Mean ± SD.	31.54 ± 25.31	
Median (IQR)	22.15(11.70 – 55.20)	

Serum ferritin levels were compared between the four groups of AA; the patchy alopecia has a median ferritin level of 28 Mg/l and this was statistically significant with a P value= 0.016. In addition, it is statistically significant in ophthiasis pattern with a median 22.8 and a P value 0.008. However, neither alopecia totalis nor alopecia universalis was statistically significant by using this relation (Table 3).

Table 3. Relation between types of alopecia and serum ferritin (n=50)

Type of alopecia	N	Serum ferritin			U	p
		Min. – Max.	Mean ± SD.	Median		
Patchy alopecia						
No	15	6.71 – 70.0	17.99 ± 16.11	12.50	148.50*	0.016*
Yes	35	6.30 – 83.0	37.35 ± 26.46	28.10		
Alopecia totalis						
No	42	6.30 – 83.0	34.29 ± 26.54	24.0	116.50	0.176
Yes	8	8.0 – 33.54	17.13 ± 8.70	14.55		
Alopecia universalis						
No	47	6.30 – 83.0	31.49 ± 25.21	22.30	63.50	0.778
Yes	3	12.50 – 70.0	32.28 ± 32.68	14.35		
Ophiasis patarene						
No	46	6.30 – 83.0	33.50 ± 25.45	22.89	22.50*	0.008*
Yes	4	6.71 – 13.30	9.0 ± 3.02	8.0		

For more statistical analysis the percent for each type of AA around the accepted reference level 30mg/l measured, we found that : 18 out of 35 (51%) cases of patchy alopecia their serum ferritin level below 30Mg/l, and 7 out of 8 cases (87.5%) of Alopecia totalis their serum ferritin level was below 30 Mg/l, while in alopecia universalis 2 out of 3 cases (66.6%) has had a serum ferritin level below 30, and all the 4 cases of ophthiasis pattern (100%) their serum ferritin level was below 30 Mg/l. (table 4)**.**

Table 4. Percent distribution of types of alopecia around cutoff value of serum ferritin

Type of alopecia	Serum ferritin Mg/L			
	≤30 (low reference)		>30 (high reference)	
	No.	%	No.	%
Patchy alopecia	18	51%	17	49%
Alopecia totalis	7	87.5%	1	12.5%
Alopecia universalis	2	66.66%	1	33.33%
Ophiasispatarene	4	100%	0	0%

AA patients were sub-divided according to severity into two groups mild to moderate which includes (patchy alopecia) and severe type which includes the (Alopeciatotalis, universalis and ophiasis pattern). It was found that 86.66 % of patients with severe types have lower levels of serum ferritin as compared 51.42% of patients with mild type (Table 1& 5).

Table 5. Relation between severity and serum ferritin (n=50)

Serum ferritin Mg/L	Severity				χ^2	p
	Mild (n=35)		Sever (n=15)			
	No.	%	No.	%		
≤30 (low reference)	18	51.42	13	86.66	5.533*	0.018*
>30 (high reference)	17	48.57	2	13.33		

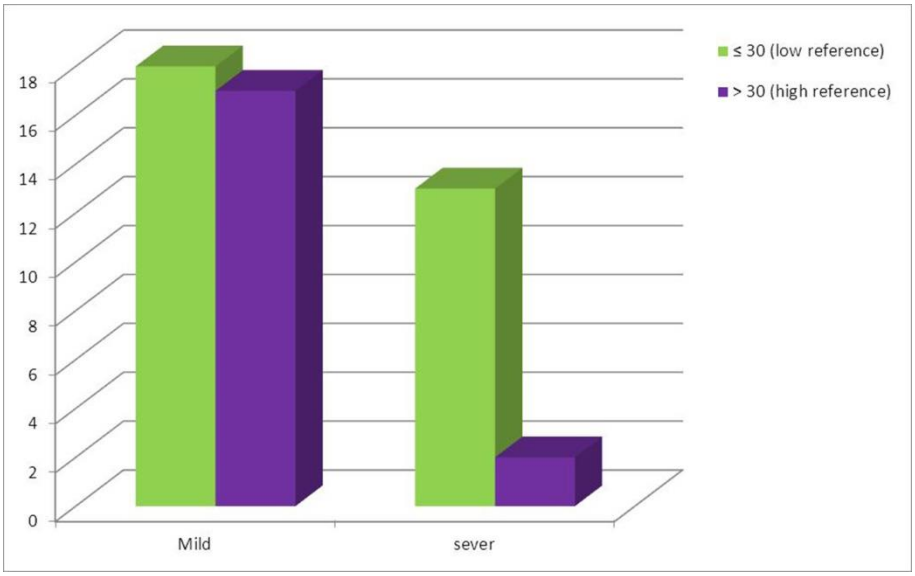

Figure 1. Relation between severity and serum ferritin

In our study, we found 56% of our study population has had AA for less than 6 months and 44% of them for more than 6 months. Higher serum ferritin levels were found in 53.6 % of patients with disease duration less than 6 months, while lower levels were found in 81.8% of patients with disease duration more than 6 months. (Table 6) (Figure 2)

Table 6. Relation between duration and serum ferritin (n=50)

Serum ferritin	Duration				χ^2	p
	< 6 months (n=28)		**>6month (n=22)**			
	No.	**%**	**No.**	**%**		
≤30 (low reference)	**13**	**46.4**	**18**	**81.8**	**6.549***	**0.010***
>30 (high reference)	**15**	**53.6**	**4**	**18.2**		

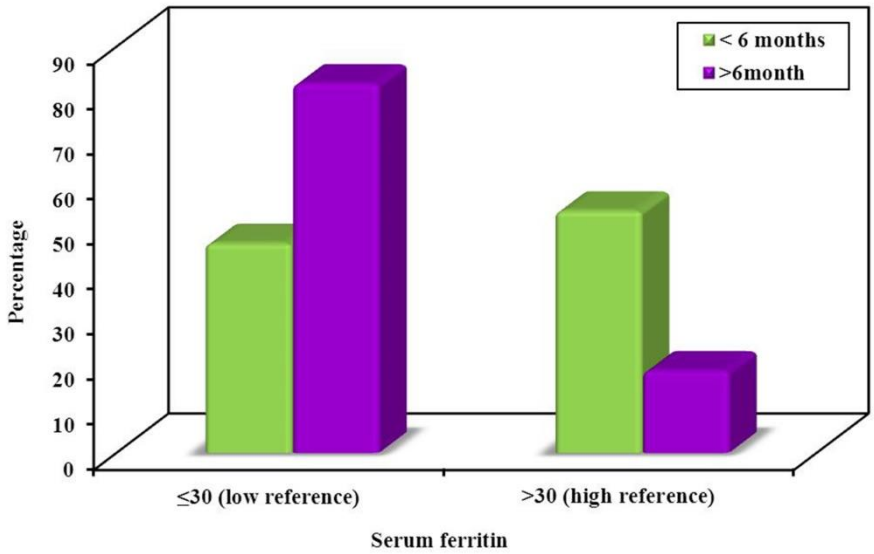

Figure 2. Relation between duration and serum ferritin

DISCUSSION

Our results suggest that low serum ferritin levels are a factor that can participate in AA presentation and can participate in longer disease duration, ferritin was significantly lower than the cutoff value in patchy alopecia areata p (0.016), 51% of patchy AA patients in our study with ferritin lower than 30Mg/L. In ophiasis pattern, also it was statistically significant (p=0.008). Longer disease duration related to lower ferritin levels (p=0.01), beside severe course was related to lower ferritin (p=0.018).

It is well known that AA is a multi-factorial disease with considerable role of autoimmunity in the disease pathogenesis, the main pathological process is a T lymphocytes mediated autoimmune reaction directed against hair follicles. Serum ferritin is considered as a marker for autoimmunity as it was found to be elevated in many autoimmune diseases. [6] while, in AA ferritin found to be low [9]. Oxidative stress is known to play a crucial role as one of the pathological mechanisms initiating AA associated with increased free radical production [14,15]. Ferritin is an important antioxidant [16]. Ferritin expression is regulated by various factors including iron, oxidative stress, some hormones, genes and cytokines (TNFα and IL-1α) [6]. ferritin is also involved in the cytokine mediated immune responses, it also regulates cytokine synthesis which plays a role in inflammatory and autoimmune diseases [17].

Serum levels of ferritin and iron have been evaluated in a several studies in patients with AA. Kantor et al measured ferritin levels in adult female patients with AA, telogen effluvium, and androgentic alopecia and they found that ferritin levels were lower in patients with AA and androgenetic alopecia, compared to controls [8]. In our study serum ferritin levels were found to be significantly lower in patients with patchy alopecia areata p(0.016), which is consistent with the literature, suggesting the association between low serum ferritin levels and AA, patchy alopecia type is the commonest presentation among children, and most of clinical types can start first with patchy type.[12] , low ferritin may the initiator of the processes that concomitant with Kantor who suggested that iron deficiency might has a role as an initiating factor for the disease [7,8]. Other studies were in contrast to our findings, Gonul et al, Esfandiarpour *et al*, and Aejaz et al all found no differences between serum ferritin and serum iron in AA patients vs. controls [7,19-20]. All these studies suggested that serum ferritin has no role in AA pathogenesis.

In our study we found that severe AA cases (86.66%) have lower serum ferritin levels than mild cases (51.42%), which was statistically significant (p=0.018). Devaraj et al suggested a possible role of serum ferritin in AA severity, he found that severe AA cases were associated with decrease serum ferritin [9], which is consistent with our study. Pradhan et al also found that serum ferritin measurements in AA cases was significantly lower as compared to normal controls [18], and was in agreement with our results. The possible explanation for that when the body stored iron depleted ferritin at hair follicle start to shifted to other biological functions that may affect the antioxidant protection mechanism at the hair follicle and so triggering hair loss by autoimmunity [16].

You HR et al reported that severe AA patients have longer disease duration in comparison with mild and moderate cases [21]. Treister et al, conclude that low ferritin have a relation with longer history of hair loss in women either their hair loss due to telegon effluvium or alopecia areata [8]. In our study, we found that patients with disease duration longer than six months have lower serum ferritin levels than patients with disease duration less than six months (p=0.01), that was statistically significant suggesting a possible connection between low serum ferritin and delayed recovery with increased severity.

CONCLUSION

Lower serum ferritin levels related to alopecia areata especially patchy type, which is the commonest type in children. Below reference readings for serum ferritin can lead to longer disease course and more severe presentations, ferritin level should bet requested for children who have AA, further study should be suggested to evaluate, if ferritin level correction affect AA prognosis.

Acknowledgments

The authors thank all patients who participate in the study. In addition, we thank all colleagues in dermatology and pediatric departments in Al-Bayda medical center for their help in collecting AA patients.

Disclaimer

The article has not been previously presented or published, and is not part of a thesis project.

Conflict of Interest
There are no financial, personal, or professional conflicts of interest to declare.

Funding
None

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