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The role of Paraoxonase 1 in Alopecia Areata, a Marker and a Severity Index

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Abstract

Background: Alopecia areata (AA) is an immune-mediated form of hair loss that affects all ages and both sexes. Paraoxonase 1 (PON1) is an esterase enzyme that has lipophilic antioxidant power; it is one of the endogenous free-radical-scavenging systems in the human body. This work was to detect serum PON1 level in patients with alopecia areata.

Methods: 60 subjects, 30 AA patients and 30 controls. Full history, general and local clinical examination, clinical assessment of the degree of AA and collection of blood for investigations and paraoxonase1 measurement were to participants.

Results: The study revealed significant decrease in serum PON1 level in AA patients (54.083 ± 25.464 µg/L) in comparison to controls (69.479 ± 17.012 µg/L). This decrease was more in male than female.

Conclusions: Serum PON1 levels are lower in AA patients. An association between oxidative stress and pathogenesis of this auto immune disease is identified. Attenuation of oxidative stress might be a relevant therapeutic approach and it would be useful to recommend additional drugs with antioxidant effect for treatment.

Keywords: Alopecia areata; Paraoxonase1; Oxidative stress.

Introduction

Alopecia areata (AA) is a common autoimmune-mediated form of nonscarring alopecia that typically presents with sudden-onset hair loss in solitary patches, diffuse bands, or rarely, the full scalp (ie, alopecia totalis) or full body (ie, alopecia universalis). Disease severity correlates with early age of onset, rapid onset of diffuse hair loss, and total alopecia. The pathogenesis of AA remains unknown.[1]

AA is associated with autoimmune thyroiditis and vitiligo, and males and females are affected equally. The lifetime risk of AA has been calculated as approximately 1.7%, making it one of the most common autoimmune conditions.[2]

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Paraoxonase-1 (PON1) is a member of a family of proteins that also includes PON2 and PON3, the genes for which are clustered in tandem on the long arms of human chromosome 7 (q21.22).[3]

Paraoxonase-1 (PON1) is an enzyme synthesized in liver and has lactonase and esterase activities towards lipid peroxides and circulates in plasma bound to high-density lipoproteins (HDL).[4]

HDL-associated PON1 has been frequently shown to have anti-oxidant and anti-inflammatory potential mainly by protecting lipids of HDLs and low-density lipoproteins (LDL) from oxidative modifications.[5]

The aim of` our work is to detect serum paraoxonase 1 (PON1) level in patients with AAin comparison to controls, in an attempt to detect its role in the pathogenesis of AA which might help in treatment.

Subjects and Methods

Subjects

The study included 60 subjects, 30 AA patients: 26 males (86.67%), 4 females (13.33%) with ages ranging from 20-48 years (mean 33.567 ± SD 7.655) and 30 healthy controls: 23 males (76.67%) and 7 females (23.33%) with ages ranging from 20-50 (mean 32.33± SD 8.755). They were collected from dermatology outpatient clinic of AL-zhraa university hospital and Houd El Marsoud public hospital during the period of December 2012 till June 2013.

This study included 30 patients with AA (Group I) and 30 normal healthy controls (group

1. Clinical criteria:

The patients were selected with localized AA: single, few or multiple patches.

2. Exclusion criteria:

- Any patient who was experiencing spontaneous regrowth of terminal hair at time of presentation.
- Patients using systemic treatment like steroids and immunosuppressive drugs likely to cause regrowth of hair within the last 3 months.
- All associated diseases that alter blood paraoxonase (1) level as vitiligo, psoriasis, thyroid, liver, renal, cardiovascular and diabetes.
- Other conditions that affect blood paraoxonase (1) level as pregnancy and smoking.
- Children less than 18yrs and adults more than 50 yrs.

Methods

All subjects in this study were subjected to Full history taking, General and local clinical examination, Clinical assessment of the degree of AA and Collection of 5 c.c. blood for investigations and paraoxonase1 measurement.

1. History:

Personal history: name, age and sex, History of the present illness: onset, course, duration, no of episodes of AA, precipitating factors, previous medications and the date of discontinuation if any, Family history of AA or other skin or systemic disease affecting blood paraoxonase1 level as previously mentioned.

2. General and local clinical examination:

A. General examination was done to exclude systemic diseases.

B. Local examination to confirm the diagnosis of AA.[6,7]

3. Clinical assessment of the degree of AA:

This was determined according to the Severity of Alopecia Tool or SALT score.[8]

4. Collection of 5cc blood for investigations and paraoxonase1 measurement:

Venous blood samples were collected from each subject participating in this study. Determination of serum PON1 had been carried out using ELISA kits supplied from wuhan EIAab science CO., ltd with catalog no: E0243h.

Ethical statement:

All adults who provided informed consent were invited to participate. This study was approved by

Ethical committee of faculty of medicine at Al-azhar University for girls, Cairo, Egypt.

Statistical Analysis

Statistical Package for social science (SPSS) program version 9.0 was used for analysis of data. P-value is considered significant if < 0.05.

Results and Discussion

AA is an inflammatory autoimmune disease characterized by scarless hair loss of scalp or body hair anywhere. The exact etiology is unknown, and research is focusing on genetic factors, autoimmune factors, drugs, trauma, infections, psychological factors and oxidative stress.[9]

Paraoxonase-1 (PON1) plays a role in contribution to innate immunity processes and antioxidant properties of HDL have been attributed, at least partially, to PON1.[10]

Oxidative stress is one of the possible mechanisms involved in the pathogenesis of AA. Studies of enzymes with antioxidant effect as PON1 appear to be of great importance, so the idea of this study to find a role of (PON1) in the pathogenesis of AA and hence to help in the management of this distressing disease.[11]

This work was performed on 30 patients with AA and 30 age and sex matched controls to detect their serum PON1 level. A highly significant decrease of mean serum PON1level was found in patients than in the control group (54.083 ± 25.464 versus 69.479 ± 17.012µg/L, p=0.008). II).

In group I, patients were 26 males (86.67%) and 4 females (13.33%) with ages ranging from 20 to 48 years with mean ±SD=33.567±7.655. The duration of the disease was minimum of 0.01 years and maximum of 18. Family history of AA was positive in 6 patients (20%). In group II, controls were 23 males (76.67%) and 7 females (23.33%). Their ages range from 20 to 50 (mean ±SD=32.33 ±8.755)

Regarding SALT score, 21 patients (70%) were S1, 5 patients (16.67%) were S2, and 4 patients (13.33%) were S3. Body hair loss was Bo in 21 patients (70%) and B1 in 9 patients (30%) in the eye brows and beard area. Nail affection was No in 23 patients (76.67%), N1 in 7 patients (23.33%) and N1a in 2 patients (Table 1).

Table 1: Demographic data of the studied groups

Groups					**T-test and Chi-square**	
		Patients		**Controls**	**t**	**P-value**
Age	**Range**	20-48		20-50	0.722	0.473
	Mean±SD	33.567±7.655		32.033±8.755		
Sex	**Female**	4(13.33%)		7(23.33%)	1.012	0.314
	Male	26(86.67%)		23(76.67%)		
		N	%			
S	**S1**	21	70.00%			
	S2	5	16.67%			
	S3	4	13.33%			
Body	**B0**	21	70.00%			
	B1	9	30.00%			
Nail	**N0**	23	76.67%			
	N1	7	23.33%			
Family history	**Negative**	24	80.00%			
	Positive	6	20.00%			
Stress	**Negative**	15	50.00%			
	Positive	15	50.00%			
Previous attack	**Negative**	23	76.67%			
	Positive	7	23.33%			

Groups					T-test and Chi-square	
		Patients		Controls	t	P-value
Duration	<3m.	10	33.33%			
	3-12m.	9	30.00%			
	12-24m.	5	16.67%			
	24-60m.	1	3.33%			
	>60m.	5	16.67%			

On comparing serum PON1 level between both groups, Serum PON1 level showed a significant decrease in patients with AA with mean ± SD=54.083 ± 25.464 when compared with normal controls with mean ± SD =69.479 ± 17.012) (Table 2).

Table 2: Comparison between serum PON1 level of patients and controls

Groups	PON1						T-test	
	Range			Mean	±	SD	t	P-value
Patients	16.000	–	97.500	54.083	±	25.464	-2.754	0.008*
Controls	40.900	–	99.900	69.479	±	17.012		

P – Value is significant if < 0.05.

Regarding the severity of AA (SALT score), Patients were divided into three groups according to the severity of AA:

Group 1 is S1 which is the mild form of AA due to less than 25% hair loss. It consisted of 21 patients with mean ± SD of (PON1) = 61.97 ± 34.063 µg/L. Group 2 is S2 which is the moderate form of the disease with 25-49%hair loss. It consisted of 5 patients with mean ± SD of (PON1) = 55.140± 29.907 µg/L. Group 3 is S3 which is the severe form of the disease with 50-74% hair loss. It consisted of 4 patients with mean ± SD of (PON1) = 52.329 ± 23.902µg/L.

In accordance to our results, only one study which done on paraoxonase 1 and showed significant low serum PON1 level in patients with AA in relation to control were reported by.[12]

Amirnia et al.[13] found that the serum level of SOD, GPX-Px were significantly lower and level of MDA were higher among patients with AA compared to controls (P<0.05). These results suggest that lipid peroxidation and alterations in the oxidant and antioxidant enzymatic system may play a role in the pathogenesis of AA. Decreased (GSH-Px) activity was also found in AA patients in comparison to controls by.[14]

In a study of **Naziroglu and Kokcam**[15], decreased levels of beta-carotene and GSH-Px, indicating a decrease in the antioxidant effect, as well as increased levels of lipid peroxidation products, indicating an increased oxidant effect, in the plasma and RBCs were found, thus shifting the OST/AOS balance in favor of stress leading to DNA damage or apoptosis of hair follicles. Based on these findings, they suggested that antioxidant therapy using beta-carotene, vitamin E and Se in patients with alopecia may decrease inflammation of the skin by inactivating the effect of free radicals and conferring stability of cell membranes thus preventing epidermal structure destruction including the hair.

In **Koca et al**. study[16] on the comparison of serum levels of antioxidants in the patients with alopecia and normal people following results were obtained: serum level of MDA was meaningfully higher in the patients compared to the normal people. The activity level of super oxidase dismutase enzyme was also meaningfully lower compared to the normal people. This study suggests that the increase in peroxidation of the fats in the patients with AA is in relation with degrees in the activity of super oxidase enzyme and therefore fat peroxidation is a key factor in AA pathogenesis.

Akar et al.[11] found significantly increased SOD and GSH-Px levels in the scalp of patients with AA indicating increased antioxidation in response to the

excessive free radical generations as indicated by the increased lipid peroxidation. This finding could not protect the patients from ROS due to inability of antioxidants to lower the lipid peroxidation products in AA.

Lymphocytes and plasma from patients with AA showed a lower total antioxidant status (TAS) levels than the controls[17], suggesting the presence of a generalized decrease in antioxidant status in the patients which may be attributed to the utilization of body antioxidants in neutralizing the increased endogenous free radicals. These observations might explain the low serum PON1 level found in our study due to the presence of increased ROS in lesions of AA lead to excess free radical formation which neutralized by utilization of body antioxidants.

On comparing serum PON1 level of the 2 groups, no statistical significance was found between the extent of AA and serum PON1 level (P- value is 0.794). (Table 2).

Regarding sex of the patients, Serum PON1 level showed a significant decrease in males when compared with females (Table 3). By studying the correlation between serum PON1 level and age or NO of patches, duration of disease and family history, we did not find any significant correlation (Table 4).

Table 3: Comparison between serum PON1 level of patients in relation to severity of disease

	N	PON1			ANOVA	
		Mean	±	SD	F	P-value
S1	21	61.975	±	34.063	0.233	0.794
S2	5	55.140	±	29.907		
S3	4	52.329	±	23.902		

P – Value is significant if < 0.05.

Table 4: Comparison between serum PON1 levels of patients included in the study in relation to sex

Sex	PON1						T-test	
	Range			Mean	±	SD	t	P-value
Female	16.900	–	97.500	58.242	±	23.995	2.474	0.020*
Male	16.000	–	54.700	27.050	±	18.587		

Table 5: Correlation between serum PON1 level of patients included in the study in relation to duration of disease

Duration		PON1		ANOVA	
	N	Mean	Std. Deviation	F	P-value
<3m.	10	62.630	19.738	1.412	0.259
3-12m.	9	38.433	23.334		
12-24m.	5	55.080	23.831		
24-60m.	1	53.300	.		
>60m.	5	64.320	36.077		

P – Value is significant if < 0.05.

In this study, a decrease in the serum PON1 level was noted in the patient group with the more severe form of AA with extent >50% (N=4, 52.329 ± 23.902µg/L.) when compared with the less severe forms with extent <25% (N=21, 61.97 ± 34.063 µg/L.) and with extent between 25-50% (N=5, 55.140± 29.907 µg/L.). The difference was not significant (p=0.0794) most probably due to the lower number of patients with the severe form of AA (N=4) as compared to less severe forms. The decrease of serum PON1 level in the more severe forms of AA seems logic as extensive lesions produce more endogenous free radical which utilizes more (PON1) as antioxidants in neutralizing this excess free radicals.

As regards the relation between serum PON1 level and sex; there is significant decrease of (PON1) in males than females. A higher mean value of serum PON1 activity in females has been found by **Mueller et al.** study.[18] Statistically insignificant correlations were detected to sex, severity of disease and family history regarding PON1.[12]

Costa et al.[3] found that the anti-inflammatory glucocorticoid dexamethasone caused an 8 fold increase in PON1. This elevation may be an additional explanation to the beneficiary effect of systemic corticosteroids in the management of resistant forms of AA.

Conclusion

Serum PON1 levels are lower in AA patients. An association between oxidative stress and pathogenesis of this auto immune disease is identified.

Conflict of interest:

None

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