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Thyroid Dysfunction in Non-segmental versus Segmental Vitiligo

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ABSTRACT

Background: vitiligo is the most common pigmentation related disorder. Vitiligo is a one of the disorders of melanin pigmentation that affect approximately 0.5- 2% of the population. Both adults and children are affected with no predilection for sex or ethnicity. Although the pathogenesis of this disease is not fully understood, the autoimmune hypothesis is the most commonly accepted theory. The autoimmune thyroid abnormalities are the most common associations with NSV. One common feature of autoimmune thyroid diseases is the frequent presence of autoantibodies directed against thyroglobulin (TG) and thyroperoxidase (TPO). Associated thyroid dysfunction with NSV that may be at the subclinical or the clinical level, includes Graves' disease, Hashimoto's thyroiditis, hyper-thyroidism or hypothyroidism. Interestingly, vitiligo often precedes thyroid disease indicating a need for regular screening for thyroid dysfunction and thyroid-related antibodies.

Objective: this study aimed to shed a light on the association between SV, NSV and the presence of TG Ab and TPO Ab. This study included thirty SV patients, thirty NSV patients and thirty age and sex matched individuals free from vitiligo as a comparative group. Estimation of serum anti-TPO, anti-TG, serum TSH and serum FT3 andFT4were done by using the ELISA kits.

Subjects and Methods: in our study, most of the patients were of Fitzpatrick skin type IV. Two cases only had poliosis in NSV and five in SV patients. Koebner phenomenon was absent in SV patients while, there was 40% of NSV group of patients. **Results:** mean TSH levels were normal in all the studied subjects. FT3 showed a statistically significant difference between NSV patients and the comparative groups. There was a statistically significant increase in the prevalence of anti TPO antibody in NSV patients compared to the SV group and vitiligo free group. No statistically significant increase in the prevalence of anti TG among the comparative groups. The levels of anti TG and anti TPO levels show significant increase with duration of the disease, VASI score and female gender in NSV group.

Conclusion: the presence of higher mean levels of anti-TPO in the NSV group compared to the SV group and vitiligo free group was in favor of the autoimmune pathogenesis hypothesis as they point to a disturbance in the autoimmune system of the NSV patients and this supporting the view that the pathogenesis of SV and NSV is different.

Keywords: thyroperoxidase, thyroglobulin.

INTRODUCTION

Vitiligo is a pigmentary disorder characterized by the appearance of a chromic macules due to the disappearance of functional melanocytes from the epidermis [(1)].

Vitiligo has been recently classified, according to the clinical presentation of macules, into three major forms, namely non-segmental vitiligo, segmental vitiligo, and undetermined/unclassified vitiligo [(2)].

Although the pathophysiology of all forms of vitiligo likely involves autoimmune or inflammatory mechanisms**,** non-segmental and segmental vitiligo differ, in addition to their clinical presentation, for the pathophysiology, clinical course, prognosis, response to treatment, and associated comorbidities [(3)].Namely, non-segmental vitiligo patients have increased frequencies of associated autoimmune disorders [(4)].

Among them, autoimmune thyroid disorders **(ATD)** are the most frequently found co morbidities [(5)].International guidelines on vitiligo management recommend periodic screening of thyroid function [(6)] because a recent meta-analysis has reported the presence of antithyroglobulin **(Tg)** or antithyroperoxidase **(TPO)** in 20.8 % of vitiligo patients [(7)].Among the various thyroid autoantibodies, some are selectively directed toward thyroid hormones **(TH)** thyroxine **(T3)** and triiodothyronine **(T4) (T3- and T4-Ab),** which are the less frequently detected class of thyroid antibodies in human serum [(8)] with a prevalence of 0.07 % in the general population. Their pathogenetic role is still unknown, but they have been found to be increased in individuals with ATD and extrathyroid autoimmune diseases [(9)].Regarding the triggering factors of ATD, it has been shown that alcohol, smoking, iodine, iodine-containing compounds and other chemical agents, grouped into the category of the thyroid disruptors [(10)]that can elicit the appearance of ATD [(11)].

AIM of the WORK

This study aimed to evaluate the thyroid dysfunction in vitilligo patients by assessment of serum levels of TSH, T3, T4, Anti Thyroid Anti Bodies.

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SUBJECTS AND METHODS

A hospital-based study was conducted at the outpatient dermatology clinic of Al-Azhar University in New Damietta. The study include two groups; the first group includes 60 vitiligo patients (30 segmental vitiligo patients and 30 non-segmental vitiligo patients) and the other group includes 30 healthy individuals as a control group.

Inclusion criteria for vitiligo patients: segmental and non segmental vitiligo, any age group, both males and females were included.

Patients who had the following criteria were excluded*:* patients with concomitant autoimmune diseases associated with vitiligo such as Addison's disease, alopecia areata**,** autoimmune pernicious anemia, adult onset type 1 diabetes mellitus, rheumatoid arthritis, psoriasis, morphea, pemphigus (vulgaris, erythematous us and foliaceus), Halo nevus, adrenocortical insufficiency, celiac disease, myasthenia gravis, systemic or discoid lupus erythematous, Sjogren syndrome or others and patients with melanoma.

Selection of the vitiligo free group: they were recruited from those accompanying patients other than their relatives and also they were recruited from individuals accompanying attendants of other outpatient clinics of Al-Azhar University in New Damietta.

Inclusion criteria of vitiligo free group: apparently healthy, free from any type of vitiligo or auto immune diseases, age and sex matched with vitiligo patient groups.

Exclusion criteria of vitiligo free group: individuals with**:** history of any systemic or skin diseases, history of anti-thyroid drugs intake, relatives of enrolled patients in this study to avoid genetic susceptibility of skin or thyroid disease.

Data collection: after explaining the purpose of the study to the study subjects, a written consent was taken from each one. The study subjects were subjected to a personal interview, dermatological examination and laboratory investigations to fulfill a specially designed questionnaire. The questionnaire included items about:

1- Sociodemographic data: data of subjects regarding age, gender, origin, residence, marital status, education, occupation**.**

2-Medical history: all individuals in this study were subjected to the following*:* Full history taking including; thyroid, systemic, autoimmune and other skin diseases. History of vitiligo regarding age at onset, duration of disease, also medication taken, type, duration of use, systemic or local.

3- Family history: history of autoimmune skin diseases among family members of vitiligo patients.

4- Medical and dermatological examination: general examination was performed for all subjects with emphasis on the signs of hyperthyroidism (fine hair, thin skin, muscle weakness, tachycardia, tremors, stare and lid lag), signs of hypothyroidism (dry coarse skin and bradycardia).

Local examination of the thyroid gland: dermatological examination including a detailed coetaneous examination to determine the skin photo type, associated skin diseases, clinical type of vitiligo, site of involvement.

METHODS

VASI calculation: the percentage of body surface area involved by vitiligo using Vitiligo Area Score Index (VASI) according to **Hamzavi *et al.*** [(12)] was calculated in terms of hand units. One hand unit (which encompasses the palm plus the volar surface of all digits) was approximately equivalent to 1% of the total body surface area.

The degree of pigmentation was estimated to the nearest of one of the following percentages: 100% - no pigment was present, complete depigmentation, 90% - specks of pigment present; 75% - depigmented area exceeds the pigmented area; 50% - pigmented and depigmented areas were equal, 25%- pigmented area exceeds depigmented area, 10% - only specks of depigmentation were present. The VASI for each body region was determined by the product of the area of vitiligo in hand units and the extent of depigmentation within each hand unit measured patch. Total body VASI = all body sites [hand units]x[residual depigmentation]. A note was made of hair involvement and mucosal involvement.

Statistical Design: data collected were reviewed and coded. The numerical codes were fed in the computer where statistical analysis was done using the statistical package of social science version 17 (SPSS 17.0).

RESULTS

Table 1: comparison between the different studied groups according to demographic data

	Group I (n= 30)		**Group II (n= 30)**		**Group III (n= 30)**		**Test of sig.**	**P**
	No.	**%**	**No.**	**%**	**No.**	**%**		
Gender								
Male	10	33.3	6	20.0	12	40.0	χ^2=2.903	0.234
Female	20	66.7	24	80.0	18	60.0		
Sig.bet.Grps	p_1=0.243,p_2=0.592,p_3=0.091							
Age								
Min. – Max.	11.0 – 30.0		11.0 – 40.0		11.0 – 30.0		F=6.054*	0.003*
Mean ± SD.	15.20 ± 4.85		21.30 ± 8.88		17.47 ± 6.25			
Median	14.0		18.50		16.50			
Sig.bet.Grps	p_1=0.003*,p_2=0.441,p_3=0.083							
Marital status								
Single	24	80.0	17	56.7	19	63.3	χ^2=3.900	0.142
Married	6	20.0	13	43.3	11	36.7		
Sig.bet.Grps	p_1=0.052,p_2=0.152,p_3=0.598							
Occupation								
Professional person	4	13.3	10	33.3	5	16.7	χ^2=8.377	^{MC}p= 0.072
House wife	3	10.0	7	23.3	3	10.0		
Student	23	76.7	13	43.3	22	73.3		
Sig.bet.Grps	p_1=0.031*,$^{MC}p_2$=1.000,p_3=0.061							
Occupation setting								
Outdoor	4	13.3	10	33.3	5	16.7	χ^2=4.136	0.126
Indoor	26	86.7	20	66.7	25	83.3		
Sig.bet.Grps	p_1=0.067,$^{FE}p_2$=1.000,p_3=0.136							

p: p value for comparing between the three groups
p_1: p value for comparing group I and group II
p_2: p value for comparing group I and group III
p_3: p value for comparing between group II and group III
*: Statistically significant at $p \leq 0.05$
Group I: Segmental vitiligo
Group II: Non segmental vitilligo
Group III: vitiligo free group

Regarding to the age of onset and duration of the disease there was a statiscally significant difference between SV group and NSV group **(P = 0.045, P =0.016 respectively)(Table 2).** Also, we found significant difference between SV and NSV group as regarding to presence of koebner phenomenon **(P <0.001))(Table 2).**

Table 2: comparison between the two studied groups according to clinical characteristics

	Group I(n= 30)		Group II (n= 30)		Test of sig.	P
	No.	%	No.	%		
Koebner phenomenon						
Absent	30	100.0	18	60.0	χ^2=	
Present	0	0.0	12	40.0	15.000*	<0.001*
Poliosis						
Absent	25	83.3	28	93.3	χ^2=	^{FE}p=
Present	5	16.7	2	6.7	1.456	0.424
Age of onset (years)						
Min. – Max.	8.0 – 29.0		8.0 – 36.0		U=	
Mean ± SD.	13.13 ± 4.17		18.47 ± 8.56		315.50*	0.045*
Median	12.0		15.50			
Duration of vitiligo (years)						
Min. – Max.	0.08 – 7.0		0.33 – 17.0		U=	
Mean ± SD.	1.68 ± 1.70		3.23 ± 3.38		287.50*	0.016*
Median	1.0		3.0			
Fitzpatrick skin type						
III	9	30.0	7	23.3		
IV	14	46.7	9	30.0	χ^2=3.670	0.160
V	7	23.3	14	46.7		
VASI						
Min. – Max.	0.50 – 3.50		0.25 – 11.0		U=	
Mean ± SD.	1.74 ± 0.81		3.13 ± 3.24		398.0	0.439
Median	2.0		1.85			

p: p value for comparing between the two groups
Group I: segmental vitiligo
Group II: non segmental vitiligo

Results of the frequency of the normal, elevated thyroid functions tests and thyroid autoantibodies levels in the studied groups:

According to the results no one of the studied groups had low levels of thyroid hormones. There was a statiscally significant difference between the three groups regarding to FT3 **(P<0.001, p1<0.001, p3<0.001).** Also, there was asignificant difference regarding to FT4 between the studied groups **(P=0.001, p1=0.007, p3=0.002)(Table 3).**

Table 3: comparison between thyroid function tests and thyroid autoantibodies among the studied groups

	Group I (n= 30)		Group II (n= 30)		Group III (n= 30)		□□	P
	No.	%	No.	%	No.	%		
FT3 (pg/ml)								
Normal	29	96.7	14	46.7	29	96.7	31.250*	<0.001*
Elevated	1	3.3	16	53.3	1	3.3		
Sig.bet.Grps	p_1<0.001*, FEp_2=1.000, FEp_3<0.001*							
FT4 (ng/dl)								
Normal	27	90.0	18	60.0	28	93.3	13.199*	0.001*
Elevated	3	10.0	12	40.0	2	6.7		
Sig.bet.Grps	p_1=0.007*, FEp_2=1.000,p_3=0.002*							
TSH (µiu /ml)								
Normal	30	100.0	30	100.0	30	100.0	-	-
Elevated	0	0.0	0	0.0	0	0.0		
TG ab (IU/ml)								
Normal	29	96.7	25	83.3	30	100.0	6.137	FEp= 0.057
Elevated	1	3.3	5	16.7	0	0.0		
Sig.bet.Grps	FEp_1=0.195, FEp_2=1.000, FEp_3=0.052							
Tpoab (IU/ml)								
Normal	30	100.0	22	73.3	29	96.7	14.074*	FEp=0.002*
Elevated	0	0.0	8	26.7	1	3.3		
Sig.bet.Grps	FEp_1=0.005*, FEp_2=1.000, FEp_3=0.026*							

p: p value for comparing between the three groups
p_1: p value for comparing group I and group II
p_2: p value for comparing group I and group III
p_3: p value for comparing between group II and group III
*: Statistically significant at $p \leq 0.05$
Group I: segmental vitiligo
Group II: non segmental vitilligo
Group III: vitiligo free group

Results of the mean thyroid functions tests and thyroid autoantibodies levels among the studied groups:

Mean FT3 level in NSV patients group was significantly higher in comparison with the other groups **(P<0.001).** Although the mean thyroglobulin antibody (TG Ab) level was higher in NSV patients group compared with the SV group and vitiligo free group but statistically no significant difference between the three groups **(P= 0.184).** Mean thyroid peroxidase antibody (TPO Ab) level was significantly higher in NSV group compared to the other groups **(P =0.001)(Table 4).**

Table 4: comparison of the mean levels of thyroid functions tests and thyroid autoantibodies among the studied groups

	Group I (n= 30)	Group II (n= 30)	Group III (n= 30)	H	P
FT3 (Ppg/ml)					
Mean ± SD.	3.37 ± 0.97	6.46 ± 1.11	3.43 ± 0.74		
Median	3.25	6.13	3.30		
Sig.bet.Grps	$p_1<0.001^*, p_2=0.744, p_3<0.001^*$				
FT4 (ng/dl)					
Mean ± SD.	1.44 ± 0.07	4.22 ± 0.08	1.87 ± 0.68		
Median	1.28	1.48	1.21		
Sig.bet.Grps	$p_1=0.008^*, p_2=0.339, p_3=0.087$				
TSH (MiU/ml)					
Mean ± SD.	2.24 ± 0.10	2.02 ± 0.16	1.85 ± 0.14		
Median	2.23	2.11	1.97		
TG ab (Iu/ml)					
Mean ± SD.	33.20 ± 4.27	67.48 ± 6.96	16.21 ± 5.81		
Median	19.45	16.35	15.65		
Tpoab					
Mean ± SD.	17.61 ± 8.11	68.56 ± 3.53	19.63 ± 4.32		
Median	15.65	21.40	12.60		
Sig.bet.Grps	$p_1=0.033^*, p_2=0.125, p_3<0.001^*$				

p: p value for comparing between the three groups
p_1: p value for comparing group I and group II
p_2: p value for comparing group I and group III
p_3: p value for comparing between group II and group III
*: Statistically significant at $p \leq 0.05$
Group I: segmental vitiligo
Group II: non segmental vitilligo
Group III: vitiligo free group

Correlation between thyroid function tests and basic characteristics among the NSV group:

There was a correlation between FT3,FT4 among NSV group (groupII) and duration of the disease with a significant P value **(P =0.003, P <0.001 respectively) (Table 5).**

There was a correlation between FT3 and female gender with a significant P value **(P =0.049*)* (Table6).**

Correlation between thyroid autoantibodies and basic characteristics in NSV patients group:

Based on our study there was a correlation between anti TG and the duration of the disease, VASI, female gender with a significant P value **(P =0.029, P =0.024, P =0.017 respectively**) **(Tables 5,6).**

Regarding TPO Ab there was a correlation with the duration of the disease, VASI and female gender with a significant P value **(P =0.031, P =0.035, P =0.001 respectively**) **(Tables 5,6).**

Table 5: correlation between thyroid function tests (FT3, FT4 and TSH) and thyroid autoantibodies (TG Ab and TPO Ab with basic characteristics in NSV group patients(Group II)

	FT3 (Ppg/ml)		FT4 (ng/dl)		TSH (MiU/ml)		TG ab (Iu/ml)		Tpoab	
	r_s	P	r_s	p	r_s	P	r_s	p	r_s	p
Age	0.019	0.919	0.220	0.243	-0.173	0.360	0.121	0.524	0.159	0.402
Age of onset (years)	-0.058	0.761	0.038	0.840	-0.181	0.339	0.044	0.815	0.091	0.632
Duration of vitiligo (years)	0.530	0.003*	0.690	<0.001*	0.072	0.705	0.399	0.029*	0.395	0.031*
VASI	-0.004	0.982	0.186	0.325	-0.190	0.315	0.412	0.024*	0.387	0.035*

*: Statistically significant at $p \leq 0.05$
Group II: on segmental vitilligo

Table 6: relation between gander, poliosis with thyroid function tests (FT3, FT4 and TSH) and thyroid autoantibodies (TG Ab and TPO Ab) in NSV group patients (group II).

	Gender		**Poliosis**	
	Male (n= 6)	**Female (n = 24)**	**Absent (n= 28)**	**Present (n= 2)**
FT3 (Ppg/ml)				
Mean ± SD.	4.36 ± 2.11	6.98 ± 3.13	6.34 ± 3.16	8.08 ± 2.23
Median	4.03	6.97	5.07	8.08
U(p)	34.0*(0.049*)		18.0(0.406)	
FT4 (ng/dl)				
Mean ± SD.	3.96 ± 0.38	4.28 ± 0.12	3.82 ± 0.91	9.76 ± 1.66
Median	1.28	1.54	1.43	9.76
U(p)	60.0(0.533)		8.0(0.096)	
TSH (MiU/ml)				
Mean ± SD.	1.13 ± 0.01	2.24 ± 0.11	2.04 ± 0.20	1.76 ± 0.06
Median	0.81	2.16	2.11	1.76
U(p)	38.0(0.063)		28.0(1.000)	
TG ab (Iu/ml)				
Mean ± SD.	11.95 ± 1.02	81.38 ± 13.96	53.66 ± 10.01	260.95 ± 32.31
Median	11.70	19.50	15.40	260.95
U(p)	26.0(0.017*)		12.0(0.183)	
Tpo ab (Iu/ml)				
Mean ± SD.	11.12 ± 2.25	82.93 ± 9.75	65.59 ± 3.07	110.20 ± 17.0
Median	11.15	30.70	21.40	110.20
U(p)	10.0*(0.001*)		19.0(0.454)	

p: p value for association between gander, poliosis with different parameters

*: Statistically significant at $p \leq 0.05$

Group II: non segmental vitilligo

Fig. 1: a patient with generalized vitiligo

Fig. 2: a patient with acrofacial vitiligo

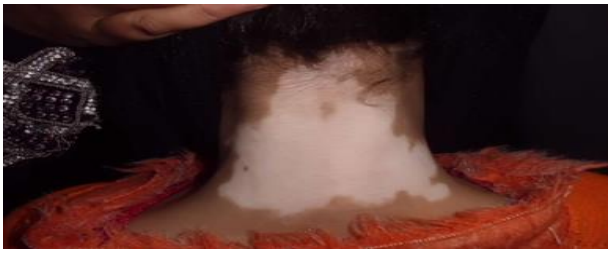

Fig. 3: a patient with localized vitiligo

DISCUSSION

Vitiligo is one of the disorders of melanin pigmentation that affect approximately 0.5-2% of the population [13]. Although the pathogenesis of this disease is not fully understood, the autoimmune hypothesis is the most commonly accepted theory. This theory is supported by the clinical association of non-segmental vitiligo (NSV) with various autoimmune disorders [14].Various thyroid autoantibodies including thyroid stimulating antibody, anti-thyroglobulin antibody and thyroid peroxidase antibody were detectable in autoimmune thyroid diseases. The latter is the most sensitive tool for the detection of early subclinical autoimmune thyroid diseases, follow up of the response to immunotherapy and identification of at risk cases for autoimmune thyroid diseases [15].

Autoimmune thyroid disease is more frequently seen in association with vitiligo than in the normal population in several previous studies [16]. There are possible connections between thyroid proteins and melanocytes and might imply a potential cross-reactivity. Cysteine rich units of thyroglobulin share some structural similarities with the epidermal growth factor homologous repeats that can be found also in tyrosinase and tyrosinase-related protein TRP-1 and TRP-2, So TG Ab might cross-react with tyrosinase, TRP-1 or TRP-2 leading to a possible inactivation of this melanocytic enzyme leading depigmentation. Moreover, the 570 residues at the carboxylic acid terminus of thyroglobulin are evolutionarily connected to acetylcholinesterase (AChE) and serum butyrylcholinesterase (BChE). The carboxylic acid terminus of TG might have a role on vitiligo pathogenesis. It has been demonstrated indeed that both AChE and BChE are present in vitiligo epidermis where their activity is reduced by the high amount of hydrogen peroxide typical of vitiligo skin. Therefore, thyroglobulin might react also with epidermal AChE and BChE leading to the inactivation of these enzymes and to a consequent increase in local acetylcholine concentration. As acetylcholine has an inhibiting effect on 3,4-dihydroxyphenylalanine oxidase, this event might result in a blockade of melanogenesis and therefore in depigmentation [17]. Based on our study we confirmed that AITD is one of strongest associated comorbidities with vitililgo especially NSV and this result is in line with many studies worldwide. In this study we will discuss the association between vitiligo and AITD from different aspects in comparison with other studies.In our study, we found that the incidence of thyroid parameter alternations in vitiligo patients were significantly greater than that in healthy population, and varied between the different types of vitiligo. There were many cases of thyroid malfunction in the NSV group than SV group and normal population. These findings are consistent with those of **Gey *et al.*** [18] and **Lim *et al.*** [19] who supported the view that the pathogenesis of SV and NSV was different. NSV had a high incidence of increase organ-specific auto-antibodies, thus it may be related to autoimmune abnormalities, but SV had fewer correlation with autoimmune diseases. This implies that neuromediated aberration may play role in SV disease as suggested. On the other hand, recent evidence supports a continuum between SV and NSV and an autoimmune background for SV. **Van Geel *et al.*** [20] reported a case of SV presenting with alopecia areata, psoriasis and halo naevi, suggesting an autoimmune mediated antimelanogenic response. Based on our results, none of our vitiligo patients had hypothyroidism. **Osman and Mirghani** [21] found that all the detected hormonal abnormalities in vitiligo patients were of hyperthyroidism and not of hypothyroidism. On the other hand, **Naveen** [22] found that thyroid abnormalities among vitiligo patients were of hypothyroidism type.

All our studied subjects were clinically free of both symptoms and signs of thyroid dysfunction. Vitiligo has been reported to precede the onset of overt thyroid dysfunction by up to 7 years [7] and routine screening has been recommended by **Kumar *et al.*** [15] for all NSV patients. Our results confirmed that the predominant age incidence of vitiligo before 20 years, where around 65% of the enrolled patients aged < 20. This is consistent with the study of **Iacovelli *et al.*** [23].This study confirmed that segmental vitiligo usually begins in childhood with early age of onset which is matched with the study of **Taïeb and Picardo** [24]. Our study noted the presence of poliosis in segmental vitiligo rather than non-

segmental type which is consistent with the study of **Sleiman *et al.* [25].** The present study demonstrated that FT3, FT4 and TPO Ab were significantly higher in patients with non-segmental vitiligo compared with other groups. This supports the results of the study done by **Colucci *et al.* [17].** Although,the frequencies of the elevated levels of both thyroid autoantibodies were significantly higher in non-segmental vitiligo patients compared to the segmental vitiligo group and vitiligo free group; the mean thyroglobulin antibody level was statistically non-significant between the three comparative groups and the mean thyroid peroxidase antibody (TPO Ab) level was significantly higher in NSV patients compared to the other groups. Anti-TPO antibodies are considered to be the most sensitive to diagnose AITD as reported by **Gey *et al.* [18]** who considered the diagnosis of AITD in patients with positive anti-TPO antibodies and not in those with exclusively anti-TG antibodies. **Lim *et al.* [19]** found that TPO Ab was significantly higher in NSV group than SV group but TG Ab did not show this significance and this significance in TPO Ab was not present between vitiligo patients and normal population. The role of anti-thyroid hormones autoantibodies to cause the depigmentation is still obscure. These included the cross-reaction of anti-thyroid hormone autoantibodies with melanogenic enzymes or enzymes involved in regulating oxidative stress, leading to the inhibition of their activity and subsequent impairment of melanogenesis **[26].**There was a positive correlation between levels of anti TPO and the disease duration among vitiligo patients. This is supporting the findings of **Gey and his colleagues [18]** who stated that the risk of patients with vitiligo developing AITD is doubled every 5 years, meaning that patients should be regularly screened for ant-thyroid antibodies. Also, we found that there was a positive correlation between levels of anti-thyroid anti bodies and female gender with NSV, they are more prone to develop AITD than men and these findings are in line with the study of **Gey *et al.* [18]** who stated that AITD shows a strong female predominance explaining that by hormonal theory. Oestrogens are thought to be potent stimulators of autoimmunity whereas androgens seemed to be protective in this respect **[27].** Unfortunately we cannot confirm this association because most of our patient's candidates were females. **Vasanop *et al.* [28]** reported additional association between poliosis and AITD explaining this by the presence of poliosis reflects long standing disease allowing sufficient time to develop autoimmune phenomenon. Our study did not demonstrate this association. Although some other studies denies presence of relation between VASI score and positivity of autothyroid antibodies but our study demonstrated the association between them which is supported by the results of **Gey *et al.* [18]** who reported that AITD was more likely to develop in NSV patients with larger body surface area than the patients with less body surface area.

CONCLUSION

In conclusion, patients with NSV displayed an increased presence of elevated anti-TPO antibodies which is the most sensitive test for the diagnosis and follow-up of the autoimmune thyroid diseases. In addition to that the autoimmune co-morbidities are more common in patients with NSV than SV. These findings are supporting the theory of the pathogenesis of SV and NSV is different.

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