



A Study to Determine Prevalance of Thyroid Disorders in Children and Adolescents with Vitiligo

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ABSTRACT

Background- Vitiligo is a common skin depigmenting disease, which is thought to have, at least partly, an autoimmune aetiology. The link between vitiligo and thyroid disease has been proved in adult patients. This association has scarcely been studied in children.

Objectives- The purpose of this study was to assess the incidence of thyroid dysfunctions and autoimmune thyroiditis in children with vitiligo. The early diagnosis of clinical and subclinical forms of thyroid disease in these children and to facilitate early treatment and avoidance of the phenotypic manifestations of hypothyroidism.

Methods- 110 children and adolescents (50 boys, 60 girls) with known vitiligo were enrolled. Serum free triiodothyronine, free thyroxine, thyroid-stimulating hormone, and antibodies to thyroperoxidase were measured. Thyroid gland efficiency was evaluated.

Results- Twenty three (20.9%) out of 110 patients had abnormalities of thyroid function tests or thyroid autoantibodies or alterations in USG for thyroid. Previously reported prevalence of thyroid disease in children with vitiligo ranged from 10.7 to 24.1%, and the prevalence of 20.9% determined in our study was comparable with the literature.

Conclusion- In paediatric patients with vitiligo, a significant incidence of thyroid dysfunction was found. Since vitiligo usually appears before the development of the thyroid disease, it may be useful to screen thyroid autoantibodies in all paediatric patients with vitiligo to assist in the early diagnosis and therapy of autoimmune thyroiditis. Also, the high rate of subclinical hypothyroidism determined in these patients attracted attention to the probable development of overt hypothyroidism in a long term.

Keyword: Autoimmunity, child, thyroid function tests, vitiligo.

INTRODUCTION

Vitiligo is an acquired primary, usually progressive melanocytopenia, affects 1% of the

world's population without any racial predilection.¹ Its exact etiology remains obscure and perhaps multifactorial. A positive family

history in 30-40% of patients suggests a genetic predisposition.¹ Vitiligo in children and adolescents represents an important entity since in 50% of patients the onset is before the age of 20 years and in 25% before the age of 10 years. Of the total population of patients with vitiligo, 23% are reported to be children younger than 12 years of age.² Vitiligo has a negative psychological and social influence, especially in children and adolescents, and this may persist into adulthood.

The etiology of this disorder is not clear but different theories are proposed. An autoimmune etiology is widely considered, and some genetic factors seem to play an important role in the pathogenesis of vitiligo.² The autoimmune hypothesis is supported by the observation that several autoimmune disorders e.g. thyroid diseases, Sutton nevi, juvenile diabetes mellitus, alopecia areata, pernicious anemia and Addison's disease are associated with vitiligo. Among thyroid disorders, hypothyroidism is one of the most common disorder.^{3,4}

Vitiligo frequently precedes the thyroid involvement; thus screening vitiligo patients for thyroid function and thyroid antibody seems plausible.⁴ Anti-thyroid peroxidase antibody, is a sensitive tool for the detection of early subclinical autoimmune thyroid disease.

The association of vitiligo with autoimmune thyroiditis has been described in adult patients, but it has scarcely been studied in children. To date, there have been only a few studies on the correlation between childhood vitiligo and autoimmune thyroid disease. This study aimed to elucidate the relationship between childhood vitiligo and associated diseases, especially autoimmune thyroiditis, by analysing abnormal parameters for thyroid functions and aberrant levels of autoantibodies, which may indicate potential thyroid abnormalities. A study have stressed upon routine thyroid screening in pediatric patients with vitiligo, as diagnosis of autoimmune thyroiditis is particularly important in this age group to avoid the negative impact of hypothyroidism on growth and health status.²

The aim of our study is to assess the prevalence of thyroid dysfunction in children and adolescents in vitiligo patients, and to establish whether routine screening for thyroid dysfunction is necessary or not, in children and adolescents who are suffering from vitiligo.

METHODS

The study was approved by the institutional protocol review board and Ethical Committee and informed written consent was taken from the parents of patients.

Patients

The study population was enrolled randomly from the dermatology outpatient department, Indira Gandhi Medical College and Hospital, between July 2014 and June 2015. Patients who had age above 18 years, had segmental vitiligo, received thyroid surgery or taken medication for thyroid disease were excluded. Diagnosis and classification were based on the defined publications. Patients were grouped into progressive or stable and segmental or non-segmental vitiligo. Detailed histories were taken and physical examinations carried out according to the questionnaire designed. The questionnaire included patients' demographic data, clinical features such as onset of the disease, involved sites, types and stages of vitiligo, associated diseases and family histories.

Laboratory Evaluation

For each patient, the following laboratory parameters were examined: FT4 (free thyroxine; normal range: 9.3–17 pg/ml), FT3 (free triiodothyronine; normal range: 1.8–4.6 pg/ml), TSH (thyroid-stimulating hormone; normal range: 0.2–5 IU/ml), Antibodies against thyroperoxidase (anti-TPO Ab). Both hormones and antibodies were measured by immunoassay in electro chemiluminescence. Hormone levels exceeding the established range were considered pathological. Anti-TPO Ab titre exceeding 100 units/ml or 1:100 were considered elevated. A thyroid echography was performed on children

with altered hormone levels and/or elevated antibody titre.

RESULTS

Clinical characteristics

Some of the demographic and clinical findings of vitiligo patients are presented in (Table 1).

Among 110 children and adolescents with vitiligo, 60 (54.54%) were females and 50 (45.45%) were males. The mean age of patients was 10.85 ± 3.9 years (range, 1.5–18 years), and the mean age of onset was 8.45 ± 3.42 years (range, 0.5–18 years). Nine (8.18%) patients had onset between the age of 0 and 3 years, 81 (73.86%) between 4 and 11 years, 20 (18.17%) between 12 and 18 years. The duration of vitiligo when thyroid function tests were performed was 2.37 ± 2.65 years (range, 0–14 years). Vitiligo vulgaris was the most common type (61.8%). The most commonly involved site was the face (59.08%). Leukotrichia was present in 22 (20%) patients while 20 (18.18%) patients showed koebnerization. Family history of vitiligo was found in 36 (32.7%) patients that included 12 (10.9%) first degree relatives, 16 (14.5%) second degree relatives and 8 (7.2%) third degree relatives.

Associated Diseases

Clinically, associated autoimmune disorders were present in 30 (27.27%) patients which included halo naevus in 17 (15.45%), alopecia areata in 3 (2.72%). History of atopy was recorded in 9 (8.18%) patients. History of anemia and pallor was seen in 5 (4.54%) patients.

Thyroid disorders

Out of 110 patients of non-segmental vitiligo, thyroid dysfunctions were found in a total of 23 (20.9%) patients; 9 males (39.1%) and 14 females (60.9%) either they had abnormalities of thyroid function tests or thyroid autoantibodies or in USG alteration of thyroid. Twelve (10.9%) patients showed deranged TSH levels.

Elevated anti-TPO antibodies were found in 16 (14.54%) patients. Five of them had anti-TPO

antibody and evidence of thyroid dysfunction i.e subclinical hypothyroidism (elevated TSH with normal FT3 and FT4). In these, 3 out of 5 patients on ultrasonographic evaluation of thyroid showed typical hypoechoic pattern of autoimmune thyroiditis. The remaining 11 patients had only an elevated anti-TPO antibody titre without hormonal or echographic alterations. Five patients showed only an altered TSH value with normal values of auto-antibodies, FT3 and FT4 as well as normal ultrasonography. Among these 5 patients, 4 showed subclinical hypothyroidism (elevated TSH with normal FT3 and FT4) and only 1 subclinical hyperthyroidism (decreased TSH with normal FT3 and FT4). Two patients had hypothyroidism (elevated TSH with low FT3 and FT4) and 1 of them had typical hypoechoic pattern of autoimmune thyroiditis on ultrasonography. (Table 2)

Table 1: Clinicodemographic features of vitiligo patients

Features	Number of patients (n=110) (%)
Sex Distribution	
Male	50 (45.45%)
Female	60 (54.54%)
Age groups	
0-3 years	05 (4.54%)
4-7 years	19 (17.27%)
8-11 years	38 (34.54%)
12-15 years	31 (28.18%)
16-18 years	17 (15.45%)
Duration Of Vitiligo	
Less than 1 month	02 (1.81%)
1month - 6month	24 (21.81%)
6 month – 1year	26 (23.63%)
1year – 5 year	47 (42.72%)
5year - 10 year	06 (5.45%)
More than 10 year	05 (4.54%)
Site on onset	
Eyelid	42 (38.18%)
Scalp; Face and neck	23 (20.90%)
Lower Limb	24 (21.81%)
Trunk	17 (15.45%)
Upper Limb	02 (1.81%)
Lips / Mucosal	02 (1.81%)
Family History Of Vitiligo	
FIRST DEGREE	12 (10.90%)
RELATIVE	04 (3.63%)
Mother	02 (1.81%)
Father	03 (2.72%)
Brother	03 (2.72%)
Sister	16 (14.54%)
SECOND DEGREE	06 (5.45%)
RELATIVE	03 (2.72%)
Grandmother	04 (3.63%)
Grandfather	03 (2.72%)
Aunt	08 (7.27%)
Uncle	06 (5.45%)
THIRD DEGREE	02 (1.81%)
RELATIVE	Nil (Nil)
Cousin	36 (32.72%)
Great Grandmother	
Great Grandfather	
TOTAL	
Pattern Of Vitiligo	
Vitiligo Vulgaris	68 (61.81%)
Localised/ Focal	27 (24.54%)
Acrofacial	06 (5.45%)
Acral	08 (7.27%)
Mucosal	01 (0.90%)
Associated Disorders	
Halo Nevus	17 (15.45%)
Alopecia Areata	03 (2.72%)
Anemia	05 (4.54%)
Atopy	09 (8.18%)
Diabetes Mellitus	Nil

Table 2: Thyroid Profile Of Patients (N=110)

Type Of Abnormality	Number Of Patients (n=110)
HORMONAL	
Deranged TSH	12 (10.9%)
Deranged T3	07 (6.36%)
Deranged T4	05 (4.54%)
IMMUNOLOGICAL	
Anti TPO	16 (14.54%)
RADIOLOGICAL	
USG neck (for thyroid) suggestive of thyroiditis	04 (3.63%)
TOTAL (Thyroid disorder)	23 (20.9%)

Laboratory findings and clinical diagnoses of pediatric vitiligo patients in whom abnormal thyroid function tests and/or thyroid antibodies were detected						
No. of patients	F T3	F T4	TSH	Anti TPO	USG for thyroid	Clinical Diagnosis
11	N	N	N	↑	N	Euthyroidism + Autoimmune thyroiditis
5	N	N	↑	↑	+ (in 3 pt)	Subclinical hypothyroidism + Autoimmune thyroiditis
1	↑	N	↑	N	+	Hypothyroidism + Autoimmune thyroiditis
4	N	N	↑	N	N	Subclinical hypothyroidism
1	↓	↓	↑	N	N	Hypothyroidism
1	N	N	↓	N	N	Subclinical hyperthyroidism

↑ = Increased; ↓ = Decreased ; N = Normal

DISCUSSION

Vitiligo is an acquired depigmentary disorder affecting around 1% of the world's population. It is more predominant in younger ages and approximately 50% of the cases have the onset of their disease prior to the age of 14 years.⁵ Autoimmune diathesis has been demonstrated to play a key role in non-segmental vitiligo, associated with genetic factors. On the other hand, segmental vitiligo is explained by the neural theory, which proposes that some chemical released from the peripheral nerve endings causes a decreased production of melanin.⁶ In various

studies performed, there were more cases of thyroid dysfunction in the non segmental vitiligo group than in the segmental vitiligo group.^{2,7}

Thus, in our study we excluded cases of segmental vitiligo and planned to evaluate the prevalence of thyroid dysfunction in children and adolescent with non segmental vitiligo.

Out of 110 patients, 50 (45%) patients were males and 60 (55%) patients were females. Similarly some studies reported female predominance.¹ In our study, alterations of thyroid parameters were more frequent in female patients (60.9%) than in males (39.1%); and it agrees with other studies

that showed a higher frequency of autoimmune thyroiditis (AT) in female than in males.⁷ The mean age of onset of vitiligo in our study is (8.45 ±3.42 yrs) which is in accordance with literature.^{8,9} Although its exact inheritance pattern remains complex which is probably polygenic with variable penetrance and nearly 11% to 46% of the patients have other affected family member.^{10,11} In our study family history of vitiligo was found in 36 (32.7%) patients.

Vitiligo is often associated with other autoimmune diseases such as thyroid disease, pernicious anaemia, type I diabetes mellitus, alopecia areata, halo nevus and systemic lupus erythematosus, and thyroid disorders being commonest of all.¹² Vitiligo-associated dermatosis, like halo nevi, have been reported commonly in children and incidence varies from 2.5% to 34% in various studies.^{10,11} This observation is in accordance to our finding, where we found halo nevi in 15.45% of patients. In the literature, 3.4–41% of patients had an evidence of atopic disorders^{2,13} and in our study too, atopy was seen in 8.18% of the patients. Similarly, the percentages of alopecia areata is 2.7% in our study, which also corresponds to the results found by other authors.¹³ The association with other disorders which are commonly found in adults seem to be less significant. Routine screening for these diseases might not be necessary and should be performed only in the presence of clinical symptoms.

Bjoro et al. have proposed that anti-TPO antibody may be a marker antibody, which often appears before thyroid dysfunction develops. The current view is that anti-TPO antibody is a trigger for the inflammatory response, because it can fix complement, induce cytotoxic damage and block enzymes.¹⁴ In contrast, anti-TG antibody plays only a minor role in the pathogenesis of AT, because it is unable to activate complement. In the literature the presence of anti-TPO antibodies is in correlation with Hashimoto's thyroiditis.¹⁴ Thus, in our patients only anti-TPO antibodies were done barring anti-thyroglobulin antibody due to cost effectiveness. Autoimmune (Hashimoto's)

thyroiditis is the most common cause of goitre and acquired hypothyroidism in children and adolescent in iodine-replete areas of the world. The diagnosis of the disease is based on positive serum anti-TPO antibodies or the characteristic echographic pattern of diffuse or irregular hypoechogenicity of the thyroid gland. According to international literature, the incidence of autoimmune thyroiditis in general pediatric and adolescent population is 1%-4%. However, it was found that autoimmune thyroiditis was more frequent in children and adolescents with vitiligo than in the general population without vitiligo.¹⁵

Few data have been reported about the association between vitiligo and autoimmune thyroiditis in pediatric populations and the risk for thyroid disease in childhood vitiligo is debatable. In our study thyroid dysfunction was seen in 23 (20.9%) patients and anti TPO positivity was in 16 (14.54%) patients .USG of thyroid suggestive of thyroiditis was seen in 4 (3.63%) patients. Subclinical hypothyroidism was in 9 (8.18%) patients, overt hypothyroidism was in 2 (1.81%) patients and subclinical hyperthyroidism in 1 (0.9%) patient. Our results are in accordance with literature as described. Lacovelli *et al.* and Kurtev *et al.* reported 13% and 40% of children with vitiligo showed auto immune thyroiditis respectively. However, these studies did not include control groups.^{2,16} Also, Kakourou *et al.* reported thyroid autoantibodies in 20.37% of children.³ These studies are in accordance with our study. In a study, conducted in China, 43 (11.8%) of 363 patients with childhood vitiligo had abnormal levels in the parameters studied for thyroid functions and antibodies, compared with 4 (4.3%) of the 93 controls; this difference was significant.⁸ The authors suggested that all patients with childhood vitiligo, especially those with non-segmental vitiligo, should be screened for thyroid function and antibody levels.

In our data, 9 (8.18%) patients had subclinical hypothyroidism. This may be an early change of AT. These children should be closely followed up as subclinical hypothyroidism is a laboratory

diagnosis characterized by an elevated serum TSH level associated with a normal total or free T4 and T3 values with no significant findings or symptoms associated with thyroid dysfunction in patients. Long-term follow up has demonstrated the development of overt hypothyroidism at a rate of 5-20% per year, especially in autoimmune thyroiditis.¹⁷ When we compare with literature where the prevalence of subclinical hypothyroidism is <2% in the pediatric age group, the rate of subclinical hypothyroidism found in our study in patients of vitiligo is higher. In our study, subclinical and overt hypothyroidism was seen in total 11(10%) patients as compared to subclinical hyperthyroidism which was seen in only 1 (0.9%) patient. Thus, we found that hypothyroidism was far more frequent than hyperthyroidism, thereby confirming the data in the literature.¹⁸ Also, Bettendorf reported that hyperthyroidism is rare in children and in adolescents compared to adults, and that the incidence of hyperthyroidism is only 1–5% of thyroid diseases before the age of 16 years.¹⁹

The early diagnosis of thyroid dysfunction is important to prevent any significant impact on growth, as thyroid hormones influences normal childhood development and play a crucial role as regulators of growth and puberty, dental and skeletal development, metabolism and organ functions.¹⁹

Based on our results, we believe that it is necessary to monitor levels of thyroid autoantibodies in children with vitiligo, especially non-segmental vitiligo. If autoantibody levels are increased, further examination of thyroid function is needed in the form of TSH, FT3, FT4 and ultrasonography.

We have demonstrated an increased incidence of autoimmune thyroid disorder in children and adolescents with vitiligo; therefore, we propose that patients with vitiligo should be annually screened for thyroid dysfunction, particularly autoimmune thyroiditis (with TSH, and anti-TPO) to achieve early diagnosis and management of subclinical disease. In particular, we propose that

in the presence of positive antithyroid antibodies (anti-Tg, anti-TPO, or both) with normal thyroid function (normal TSH, T4, and T3), additionally thyroid USG should be performed by an experienced radiologist. If the echographic findings are compatible with autoimmune thyroiditis, the patient should be referred to an endocrinologist for monitoring and possible replacement therapy. In the presence of positive antithyroid antibodies (anti-Tg or anti-TPO) and an elevated TSH level, after two tests 4 weeks apart, the patient should be referred promptly to an endocrinologist for monitoring and therapy. These patients have the highest rates of progression to overt hypothyroidism and L-thyroxine treatment should be started.²⁰

Limitations

Small sample size, absence of controls, and no follow-up for therapeutic outcome or development of disease in seropositive cases are some of the limitations in our study.

CONCLUSION

Vitiligo is often associated with other autoimmune diseases such as thyroid disease, pernicious anaemia, type I diabetes, alopecia areata, halo nevus and lupus erythematosus, but among these thyroid disorders being commonest of all. In our study, we have demonstrated an increased incidence of autoimmune thyroid disorder in children and adolescents with non segmental vitiligo. Therefore, we propose that children and adolescents with non segmental vitiligo should be annually screened for thyroid dysfunction, particularly for autoimmune thyroiditis with TFTs and anti-TPO and thyroid USG in cases of elevated thyroid autoantibody titer or TSH, to achieve early diagnosis and management of subclinical disease.

The early diagnosis of thyroid dysfunction is important to prevent any significant impact on growth and development, as thyroid hormones influences normal childhood development and play a crucial role as a regulators of growth and

puberty, dental and skeletal development, body metabolism and organ functions

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