“A CROSS SECTIONAL STUDY ON THYROID FUNCTION TEST AND ANTITHYROID PEROXIDASE ANTIBODIES IN CHILDREN UPTO 18 YEARS WITH VITILGO ”

Submitted by

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Under the guidance of

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LIST OF ABBREVATIONS

AITD	Autoimmune Thyroid Disease
Anti-Tg	Anti-thyroglobulin
Anti-TPO	Anti-thyroperoxidase
APECED	Autoimmune- Polyendocrinopathy—Candidiasis—Ectodermal Dysplasia syndrome
APS1	Autoimmune Polyendocrine Syndrome Type 1
CV	Childhood vitiligo
DLQI	Dermatology Life Quality Index
HLA	Human Leukocyte Antigen
KP	Koebner's Phenomenon
MHC	Major Histocompatibility Complex
NSV	Non-Segmental Vitiligo
T3	Triiodothyronine
T4	Thyroxine
TSH	Thyroid stimulating hormone
SV	Segmental Vitiligo
VGICC	Vitiligo Global Issues Consensus Conference

ABSTRACT

Background: Vitiligo is a an acquired pigmentary mucocutaneous disorder of unknown etiology that is clinically characterized by circumscribed depigmented macules and patches secondary to selective destruction of melanocytes. The exact etiology of vitiligo is not known, however, it is postulated to be probably due to autoimmune damage to melanocytes. Vitiligo affects approximately 1% of the world's population, of which 25% present with vitiligo before the age of 20 years. Many studies conducted to find the association between vitiligo and autoimmune thyroid diseases (AITD) has found that vitiligo patients are more likely to develop AITD than those individuals without vitiligo. The exact etiology of vitiligo is not clearly understood but it is hypothesized that an autoimmune role is at play and therefore this later affects the thyroid gland, probably due to a shared antigen between thyroid and melanocytes, by forming antibodies against thyroperoxidase (TPO) and thyroglobulin (TGO), which are important enzymes and protein containing transporters of thyroid hormones respectively. This results in the hypothyroidism manifestations of autoimmune thyroid disease, affecting approximately 20% of children with vitiligo.

Objectives: To investigate the association between vitiligo and autoimmune thyroid disease in individuals up to 18 years of age with the following objectives:

1. Assessment of thyroid function
2. Analyzing the relationship between vitiligo and thyroid autoimmune disease

Methodology: This was a hospital based cross-sectional study. Patients with vitiligo up to the age of 18 years attending the outpatient department of Dermatology, Venereology and Leprosy of a tertiary care hospital were enrolled in this study. A

detailed history and clinical assessment of type of vitiligo, duration, activity of disease, presence of family members with vitiligo or other auto-immune diseases, clinical evaluation of thyroid status including clinical examination of thyroid gland, thyroid functions and presence of antibodies to thyroperoxidase was done. Data was analyzed using odds ratio, 95% confidence interval and standard deviation.

Results: A total of 45 patients up to 18 years with vitiligo were included in this study. Both male and female patients were equally affected with a male to female ratio of 1:1. However, female preponderance was seen in patients with childhood vitiligo. The most common type of vitiligo observed was focal (37.5%) and vulgaris (35.6%). Focal vitiligo was the most common type of vitiligo observed in 9 (39.1%) of 23 patients with childhood vitiligo and vitiligo vulgaris was the most common type of vitiligo observed in 16 (35.6%) of 22 patients with later onset vitiligo. Family history of vitiligo was observed in 14 (31.1%) of 45 patients with vitiligo, commonly observed with patients of vitiligo vulgaris (50%). Twelve (26.6%) patients showed repigmentation of which 9 patients were of vulgaris type. All patient in this study observed to have a normal thyroid profile and thyroperoxidase antibodies were negative.

Conclusion: This study has found no association between patients up to 18 years with vitiligo and aberrant thyroid functions. It was also found thyroperoxidase antibodies were negative in all the patients.

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INTRODUCTION

Vitiligo is a an acquired pigmentary mucocutaneous disorder of unknown etiology that is clinically characterized by circumscribed depigmented macules and patches secondary to selective destruction of melanocytes. [1] The exact etiology of vitiligo is not known. In the past it was thought of as an infectious disease comparable to that of leprosy. [2]Even today, the knowledge about vitiligo among lay people living in developing countries still hold the view that the disease is contagious, resulting in these individuals being cast out of society. [2] The etiology of vitiligo is hypothesized to be probably due to autoimmune damage to melanocytes, has helped greatly in management of the disease and understanding why these patients are more prone to other autoimmune diseases compared to normal population. [2]

Many studies conducted to find the association between vitiligo and autoimmune thyroid diseases (AITD) has found that vitiligo patients are more likely to develop AITD than that of individuals without vitiligo and is the most common autoimmune disease seen in patients with vitiligo. [2] The autoimmune mechanism leading to destruction of melanocytes, later affects the thyroid gland, probably due to shared antigen between thyroid gland and melanocytes, by forming antibodies against thyroperoxidase (TPO) and thyroglobulin (TGO), which are important enzymes and protein containing transporters of thyroid hormones respectively. This results in the hypothyroidism manifestations of autoimmune thyroid disease. [2] Most of the studies have found the association of vitiligo with autoimmune thyroid disease in adult patients presenting with vitiligo. Few studies have been conducted on evaluating patients up to 18 years with vitiligo and its association with autoimmune thyroid disease. [34-40] These studies have found that up to 20% of children with childhood vitiligo develop autoimmune thyroid disease. [5]

In this study, all patients up to 18 years who presented with vitiligo were clinical assessed for type of vitiligo, its disease activity, underwent treatment, as well as a complete clinical examination of thyroid gland including thyroid function test and presence of antibodies to thyroperoxidase.

OBJECTIVE OF STUDY

To investigate the association between vitiligo and autoimmune thyroid disease in individuals up to 18 years of age with the following objectives:

1. Assessment of thyroid function
2. Analyzing the relationship between vitiligo and thyroid autoimmune disease

REVIEW OF LITERATURE

DEFINITION

Vitiligo is defined as an acquired pigmentary mucocutaneous disorder of unknown etiology that is clinically characterized by circumscribed depigmented macules and patches secondary to selective destruction of melanocytes. [1]

EPIDEMIOLOGY

Vitiligo affects about 0.5 to 1% of the world's population with half developing the disease before the age of 20, involves both sexes and there is no difference in terms of age, skin type or race. [1-3] The earliest known age at which it occurs is 6 weeks after birth. [3]

The prevalence of vitiligo in India is about 0.05%with Gujarat having the highest prevalence rate of vitiligo in the world (8.8%). [3,4] With regards to the peak incidence in either sex, it is seen in women before the age of 30 and men during the fifth decade of life with 64.4% cases diagnosed during the spring and summer. [1]

ETIOLOGY

The exact etiology as to what causes the damage to the melanocytes and its subsequent disappearance from the skin is unclear. The current hypothesis is that it represents a group of heterogenous pathophysiologic disorders with a similar phenotype, which states that stress, accumulation of toxic compounds, infection, autoimmunity, mutations, altered cell environment and impaired melanocyte migration all contribute to pathogenesis. [2]

The most prominent pathophysiological theories are autoimmune, neuro-humoral and autocytotoxic. None of these are mutually exclusive and likely each partly contribute. It has been postulated that autoimmune mechanisms likely underlie the generalized vitiligo while a non-humoral hypothesis may be responsible for focal or segmental type of vitiligo. [2]

- **Genetics**

  Most cases of vitiligo are sporadic, however 20% of vitiligo patients report an affected relative. [5] The frequency of vitiligo among first-degree relatives in Indo-Pakistani, white and Hispanic population is reported to be 6.1%, 7.1% and 4.8% respectively compared to the worldwide frequency of 0.14 to 2%. [5,6] It has also been shown through various epidemiological studies that vitiligo is inherited in a non-Mendelian, multifactorial and polygenic pattern with incomplete penetrance.[7]

  Familial clustering of generalized vitiligo with other autoimmune diseases has brought compelling evidence to an autoimmune diathesis (common underlying genetic susceptibility to an immunologic aberrancy). Various studies have shown

that 20% of vitiligo patients report autoimmune thyroid disease, which is a 8-fold increase over the general population. [5]

- **Genetic association studies**

Human leukocyte antigen (HLA) may contribute to vitiligo susceptibility. Of these, HLAs -A2, -DR4, DR7 and DQB1*0303 are most frequent. [8]

The strongest associations of vitiligo with particular HLA haplotype appears to be in patients and families with various vitiligo-associated autoimmune /autoinflammatory syndromes, further supporting an autoimmune diathesis. [9]

A recent meta-analysis revealed that specific small nucleotide polymorphisms in cytotoxic T lymphocyte antigen 4, a critical negative feedback regulator of T-cell activation and proliferation, were associated with vitiligo only in those with concomitant autoimmune disease. [10]

- **Genetic linkage studies**

The first genome-linkage analysis study uncovered a locus termed autoimmune susceptibility 1 (AIS1) located on chromosome 1p31.3-p32.2 that was associated with vitiligo in a large multigenerational family with vitiligo and other autoimmune diseases. [11] Within this AIS1 region is a promoter variant in FOXD3, which is a gene for an embryonic transcription factor that regulates melanoblast differentiation and development. [11]

Very recently linkage studies identified loci on chromosomes 7 and 9 that were significantly associated with vitiligo. [12]

- **Autoimmune hypothesis**

Substantial evidence has shown immune mediated damage of melanocytes. According to this hypothesis, vitiligo is mediated by both humoral and cell mediated immunity. [2]

1. Humoral Immunity

Antibodies in vitiligo patients are characterized as antibodies to a group of cell surface antigens known as common tissue antigens. These cell surface antigens include surface pigment cell antigens, intracellular pigment cell antigens and non-pigment cell antigens. [13]

The cell surface antigens that are involved in humoral immunity are of molecular weights 35, 40, 75, 90 and 150kDa (kilo-Daltons). The antigens most commonly involved are of 40, 75 and 90kDa, however, the 90kDa cell surface antigen is found exclusively on the pigment cell surface. [14] Although, the antibodies to these cell surface antigens are non-specific, the melanocytes are more sensitive to the antibodies' lethal, toxic or immune-mediated injury than the surrounding keratinocytes and fibroblasts. [13,14]

There is a direct correlation between antibody levels and disease activity. Studies have shown that the vitiligo patients serum are able to damage melanocytes in vitro both by complement activation and by antibody dependent cellular cytotoxicity and suggests this can also happen in vivo. [14] The presence of vitiligo in patients with metastatic melanoma is a good prognostic sign as the

pathological mechanisms resulting in destruction of melanocytes also destroys the melanoma cells. [15]

2. Cellular immunity

Altered cellular immunity is present in vitiligo in addition to and perhaps in combination with a humoral response. [16] Normal appearing skin has degenerative changes in the melanocytes, vacuolization of basal cells, lymphocytic infiltrates and melanophages in the upper dermis. Epidermotropic T-cells in perilesional skin have an increased CD8:CD4 ratio with many expressing the skin-homing cutaneous lymphocyte antigen and they frequently juxtapose the remaining melanocytes. [17] These T-cells also express activation of interleukin-2 (CD25), major histocompatibility complex II (specifically HLA-DR) and secrete interferon gamma, which promote T-cell migration to the skin by increasing intercellular adhesion molecule-1 expression. [17]

The peripheral blood of vitiligo patients show high frequencies of Melan A specific $CD8^+$ T cells with cutaneous lymphocyte antigens, and their number indicate severity of the disease. [18]

- **Neurohumoral hypothesis**

Dysregulation of the nervous system, either at a local or systemic level may damage melanocytes in vitiligo. Both the melanocytes and nervous system arise from the neural crest cells and therefore, some vitiligo is segmental (following a dermatome). [19]

There is evidence to suggest that neural dysregulation is systemic and that vitiligo often emerges during periods of increased stress. Morrone A *et al,* have reported increased levels of homovanillic acid and vanillmandellic acid from 24 hours urine samples in patients with recent onset or progressive vitiligo. [20,21]

- **Autocytotoxic hypothesis [22]**

Toxic metabolites, either from environmental exposure, such as phenols or quinones, or from intrinsic melanin synthesis pathways, may accumulate to damage melanocytes of genetically susceptible individuals. Chemical leukoderma is thought to occur through inhibition of enzymes in the melanin pathway. Tyrosine, a phenol, enters the pathways that eventually produce electrically unstable byproducts, with the potential to damage other substrates. Defects in the melatonin receptors may result in toxic byproducts without concomitant increase in melanin synthesis, leading to cellular damage. However, there is no scientific evidence to suggest the presence of functional melatonin receptors on melanocytes.

- **Oxidative stress hypothesis**

Studies have shown increased free radical levels and abnormally low levels of catalase from lesional and non-lesional skin from vitiligo patients. A single nucleotide polymorphism in the catalase gene may interfere with the enzyme's subunit assembly and function and is more frequent among vitiligo patients Hydrogen peroxide accumulation also degrades the active site of the catalase enzyme and its function. [23] Other plausible explanations include increases in norepinephrine and monoamine oxidase, hydrogen peroxide as a byproduct and

reduced glutathione peroxidase activity. [24] Defective calcium uptake could alter the thioredoxin reductase activities and alter the redox balance. [25]

- **Melanocytorrhagy hypothesis**

The Koebner's phenomenon seen in vitiligo is explained through this hypothesis, which proposes that the melanocytes are weakly anchored, therefore minor friction and/or other stress can induce upward migration and loss. [26] Tenascin, an extracellular matrix molecule that inhibits adhesion of melanocytes to fibronectin, is elevated in vitiliginous skin, and may contribute to loss of melanocytes. [26]

- **Decreased melanocytes survival hypothesis [27]**

Deficiency of survival signals leads to melanocyte apoptosis. Keratinocytes derived stem cell factor regulates melanocyte growth and survival by binding to membrane tyrosine kinase receptor, c-kit. The significantly decreased number of c-kit receptors in perilesional melanocytes and the lower expression of stem cell factor from surrounding keratinocytes may contribute to vitiligo pathogenesis.

CLASSIFICATION OF VTTILIGO

Lerner classified vitiligo into three main types, however according to the Vitiligo Global Issues Consensus Conference (VGICC) it has been reclassified into 3 main types with the following subtypes: [27,28]

a) **Localized**:

- **Focal:** Focal vitiligo refers to an acquired, small, isolated hypopigmented lesion that does not fit a typical segmental distribution, and which has not evolved into non-segmental vitiligo after a period of 1–2 yr. [27]

- **Segmental vitiligo (SV) (Dermatomal or Blaschko linear):** [14] One or more macules involving a unilateral segment of the body, lesions usually stop abruptly at the midline. Segmental vitiligo begins in childhood, in a unilateral or patterned distribution (most commonly in the trigeminal dermatome) which is described as 'Quasidermatomal" by some authors. The lesions develop over a short span of time, is associated with poliosis and tend to be stable.

- **Mucosal:** The involvement of the oral and/or genital mucosae. When mucosal vitiligo occurs in the context of NSV, it is classified as NSV. [30]

b) **Generalized vitiligo/Non-Segmental Vitiligo (NSV)**

The Vitiligo European Task Force defines non-segmental vitiligo as an acquired chronic pigmentation disorder characterized by white patches, often symmetrically distributed which usually increase in size corresponding to substantial loss of functioning dermal and sometimes hair follicle melanocytes. [30,31]

Generalized vitiligo is seen later in life, at sites sensitive to prefriction or trauma and typically progresses with flare-ups often associated with a family or personal history of autoimmune disorders. It is divided into 3 types:[28]

i) Vulgaris: scattered patches that are widely distributed.

ii) Acrofacial: involvement of distal extremities and face

iii) Mixed: various combinations of segmental, acrofacial and/or vulgaris

c) **Universal** [28]

Universal vitiligo corresponds to complete or nearly complete depigmentation of the skin involves more than 80% of the body surface area and has the worst Quality of Life and has comorbidities and a positive family history.

Table 1: Taleb and Picardo 2010 Vitiligo Classification [29]

Type of vitiligo	Subtypes	Remarks
Non-Segmental Vitiligo (NSV)	• Focal * • Mucosal • Acrofacial • Generalised • Universal	Subtyping may not reflect a distinct nature, but useful information for epidemiological studies
Segmental Vitiligo (SV)	• Focal • Mucosal • Unisegmental • Multisegmental	Further classification according to the distribution pattern possible, but not yet standardized
Mixed (NSV + SV)	According to severity of SV	Usually the SV component more severe in mixed type
Unclassified	Focal at onset, multifocal asymmetrical, non-segmental, mucosal (one site)	The category is meant to allow after a sufficient observation time (and if necessary investigations), to make a definitive classification

* Possible onset of non-segmental vitiligo

CLINICAL FEATURES:

Vitiligo is classically described as discrete, uniformly white macules or patches with convex borders surrounded by normal skin. [28]

Occurs at sites that are normally pigmented including the face (periorifacial), the dorsal surface of the hands, nipples, axillae, umbilicus, sacrum, inguinal and anogenital region. [31]

On extremities it favors the elbows, knees, digits and flexor wrists. [43] Leukotrichia is the significant greying of hair without underlying vitiliginous area before the age of 30 years. [28] Poliosis is defined as a localized patch of white hairs.[28]

Occupational vitiligo/Contact vitiligo: [29]

Vitiligo induced by exposure to certain chemicals containing aromatic or aliphatic derivatives of phenols and catechols. The cutaneous depigmentation may be limited to the areas exposed to chemicals, which later may extend progressively from the initial site of chemical contact to the whole body, leading to typical NSV. These chemical agents may serve as uncommon environmental triggers or haptens for the induction of vitiligo. According to the VGICC, a clearer definition is required by both case studies and epidemiological investigation in at-risk populations exposed to these causative chemicals, investigation of potential predisposing factors, time between exposure and onset of depigmentation of exposed areas, and time between first depigmentation and onset of generalized vitiligo at present. For now, contact vitligo should not be included in the classification of vitiligo as a separate entity.

OTHER CLINICAL VARIANTS [31]

a) Vitiligo ponctué:

Multiple small confetti-like, discrete amelanotic macules, superimposed upon a hyperpigmented macule.

b) Inflammatory vitiligo/Red vitiligo (Vitiligo with raised inflammatory borders):

Erythema observed at the margins of vitiligo lesions.

c) Figurate papulosquamous vitiligo:

Erythema observed at the margins of the lesions along with pink, scaly plaques along with fine scales.

d) Blue Vitiligo:

Vitiligo that develops in areas affected by post-inflammatory hyperpigmentation.

e) Trichrome Vitiligo:

A zone of varying width between the normal and depigmented skin. Histopathologically this zone has inflammatory cells, Langerhans cells and melanophages, with lesser number of melanocytes compared to normal skin but more than vitiliginous skin.

f) Quadrichrome vitiligo:

This variant has same features as trichrome along with an additional margin of perifollicular hyperpigmentation more commonly seen in darker skinned individuals and areas of repigmentation

CHILDHOOD VITILIGO (CV)

Childhood vitiligo is defined as onset of vitiligo before the age of 12 years. [2] It occurs more commonly in girls than boys and has a lower incidence of autoimmune and/or endocrine diseases in comparison to later onset vitiligo. [32] The exact prevalence of childhood vitiligo is not known, however epidemiological data indicate that 25% of patients developed vitiligo before 12 years of age. [33-34] A study by Nicolaideu *et al,* also observed that childhood vitiligo showed several differences compared to later onset vitiligo: (a) CV involved different sites at time of presentation (b) CV included more cases of segmental type (c) CV demonstrated a slower rate of progression (d) CV had a higher prevalence of allergic diseases and lower prevalence of thyroid disease. [37]

Childhood vitiligo is classified epidemiologically into two main types: non-segmental vitiligo (NSV) and segmental vitiligo (SV). [38] The prevalence of SV was found to be higher in childhood vitiligo as compared to that of later onset vitiligo. [39] With regards to ethnicity, a study by Cho et al, found that Korean children had a higher incidence of SV, reporting 32.5% childhood vitiligo patients with SV. [33]

Family members of children affected with vitiligo have a higher incidence of vitiligo and other autoimmune diseases compared to control, varying between 11% and 46%. [34,39,40] A study by Pajvani et al, has reported earlier onset of vitiligo in children in whom there was family history of vitiligo, leukotrichia or other autoimmune disorders. However, in focal and segmental vitiligo, there was no family history of vitiligo or other autoimmune disorders. [39]

Various clinical studies have observed that the most common type of childhood vitiligo observed was vitiligo vulgaris, followed by focal and SV. [39-43] Acrofacial and mucosal vitiligo have a lower incidence in childhood. [38] The exact

incidence of mucosal vitiligo is variable, however studies by Handa et al, and Halder et al, reported 0.6% and 13.8% respectively of all childhood vitiligo, have mucosal vitiligo. [32, 36] Universal vitiligo is a rare type of childhood vitiligo. [38]

The initial site of onset of both NSV and SV in childhood vitiligo is usually over the face and neck. [41] Individual vitiligo macules gradually enlarge attaining a geographic pattern or there may appearance of new lesions at other sites. [36] Although there is an extensive body surface area of involvement, most children with vitiligo have < 20% body surface area of involvement. [36] In NSV, initial lesions are periocular, perinasal or perioral and gradually spread to other body parts in a more symmetrical pattern. [42]

In SV, a study by Hann et al, found that the trigeminal segment was the most common dermatome clinically observed, followed by thoracic, cervical, lumbar and sacral. [41] Koebner phenomenon is observed in both SV and NSV, however it is more common in NSV. In SV it is mainly confined to the involved segment. [38] Prcic et al, observed poliosis in 55.5% of childhood vitiligo with poliosis and Hann et al, observed 48.6% of segmental childhood vitiligo patients with poliosis, the eyebrows being the most commonly involved site. [40,41]

STABILITY IN VITILIGO

Parameters to say that vitiligo is stable and that no new lesions develop there after, have been evolving since understanding the pathomechanism of the disease. Various authors such as Moellann et al, have defined vitiligo in 1982 as lesions that are enlarging in 6 weeks before examination. Cue et al, (1993) later defined active disease of vitiligo as development of new lesions or extension of old lesions in 3 months before examination. Presently, vitiligo is considered as stable as defined by Falabella et al, (1995) if the disease has not progressed for the last 2 years. [29]

Criteria for stable vitiligo. (Falabella et al,) [29]

i) Lack of progression of old lesions within the past 2 years.

ii) No new lesions developing within the same period.

iii) Absence of recent Koebner phenomenon either from history or experimentally induced.

iv) Spontaneous repigmentation or repigmentation of depigmented areas by medical treatment.

v) Positive mini-grafting test and lack of koebnerization at donor site.

KOEBNER PHENOMENON (KP)

Definition:

Koebner in 1876 defined the Isomorphic Phenomenon (Koebner Phenomenon) as the development of lesions at sites of specifically traumatized uninvolved skin of patients with cutaneous diseases. [29]

Incidence

Incidence of Koebner's phenomenon is between 21-62% in vitiligo patients. [38]Studies have shown that vitiligo patients with KP have a higher body surface area involvement, a higher mean age, mean age at onset and mean BSA involvement compared to KP negative patients.[44]

Evaluation of Koebner's Phenomenon in Vitiligo

The Vitiligo European Task Force (VETF) group developed an assessment criterion for Koebner's Phenomenon and classified KP due to vitiligo into three main types based on history, examination and if KP can be induced experimentally. [44, 45]

Table 2: Evaluation of Koebner's Phenomenon[44,45]

Koebner's Phenomenon	Assessment
Type 1 (History)	Depigmentation after trauma during last year Type of trauma a) Physical (wounds, cuts, scratching) b) Mechanical (friction) c) Chemical/thermal (burns) d) Allergic (contact dermatitis or irritant reactions) e) Chronic pressure f) Inflammatory dermatoses g) Therapeutic (radiotherapy, phototherapy, etc)
Type 2 (Clinically)	a) Depigmentation corresponding either to areas of repeated pressure or trauma or repeated chronic friction related to clothing b) Depigmentation clearly induced by trauma (linear, punctiform, crenate)
Type 3 (Experimentally induced)	a) Repeated pressure b) Superficial (epidermal), trauma c) Dermaoepidermal trauma

AUTOIMMUNE THYROID DISEASE (AITD) AND VITLIGO

Autoimmune thyroid disease (AITD) has been suggested to be associated with vitiligo. [46] Both clinical and subclinical AITD has been associated to be more common with vitiligo patients than normal patients. [47] AITD is associated with elevated serum levels of antibodies against thyroid specific antigens like thyroglobulin (Tg) and thyroperoxidase (TPO). [48] To date, the British guidelines for diagnosis and management of vitiligo in adults have recommended blood test to check for thyroid function. [51]

Patients with non-segmental vitiligo are reported to have increased frequencies of autoimmune thyroid disease, with the most common feature of autoantibodies directed against Tg and TPO. [48] Anti-TPO antibodies are considered the serological hallmark of AITD, which is found to be higher in vitiligo patients about 4.4-21%, compared to patients without vitiligo. [48]

Alkateeb et al, observed that women with NSV were more prone to develop AITD than men with NSV. [11] This could be explained based on the hormonal theory, which states that increased levels of oestrogen, which plays a pivotal role in the innate and adaptive immunity, is thought to be a potent stimulator of autoimmunity whereas androgens seen to be protective. [53]

Personal history of vitiligo with other autoimmune/auto-inflammatory diseases are also found to be strongly linked to the presence of AITD. [48] This association of multiple autoimmune diseases in patients with vitiligo is now largely supported by both association studies and genome-wide association studies suggesting shared susceptibility factors. [48]

The longer the duration and larger the body surface area (BSA) of involvement of NSV proportionately increases the risk of AITD. [48] The vitiligo disease duration and the BSA involvement may explain a possible shared antigen between thyroid and melanocytes. [48]

The association between vitiligo and autoimmune thyroid disease in children has been scarcely studied. In two studies involving patients with childhood vitiligo, patients with childhood vitiligo were mostly positive to serum thyroid autoantibodies, as compared to that of the control subjects. [32,51]

In a study where the patients where divided based on age and sex, a clear-cut preponderance of thyroiditis was found in adolescent girls, which also suggests that oestrogen plays a role in the in the pathogenesis of AITD. [54,49]

VITILIGO AND ASSOICATED DISEASES

Vitiligo may be associated with many primary autoimmune disorders and autoimmune thyroid disease is the most commonly observed autoimmune disorder. [2] It is seen in as much as 25% of the pediatric vitiligo group although the onset of autoimmune thyroid disorders develops more than a decade later with an observed higher incidence of thyroid microsomal antibody in vitiligo patients and their family members. [42]

Patients with generalized vitiligo especially when familial are more likely to have autoimmune disorders than those with segmental vitiligo. [55]

Hearing loss caused by functional loss of the intermediate cells (melanocytes) of the stria vascularis has been reported in up to 20% of patients with vitiligo. [56] Ocular anomalies occur in up to 40% of patients with vitiligo including choroidal anomalies, uveitis, iritis and some degree of fundal pigment disorder. [56]

In autoimmune-polyendocrinopathy-candidiasis-ectodermal dysplasia (APECED), an autoimmune polyendocrine syndrome type 1 (APS1), patients presents with a combination of Addison's disease, hypoparathyroidism, ectodermal dysplasia and/or chronic mucocutaneous candidiasis, but may also have vitiligo, alopecia areata, malabsorption syndrome, gonadal failure, corneal dystrophy, enamel dystrophy. [57] A study by Ahonen et al, of 68 patients with APECED, 13 patients had vitiligo. [57]

Schmidt syndrome (APS2), an autosomal dominant disorder with variable expressivity, presents with polyglandular failure (Addison's disease, hypothyroidism and type 1 diabetes mellitus) and occasionally with vitiligo and hypogonadism. [57]

Vogt-Koyanagi-Harada disease is a rare systemic T-cell mediated disorder

characterized by uveitis, aseptic meningitis, dysacusis, alopecia, poliosis, tinnitus and vitiligo. [58]

Kabuki syndrome is a rare multiple malformation disorder that is characterized by developmental delay, distinct facial anomalies, congenital heart defects, limb and skeletal anomalies and short stature. Associated autoimmune abnormalities include idiopathic thrombocytopenic purpura, hemolytic uremia, thyroiditis and vitiligo. [2]

Alezzandrini syndrome presents with unilateral facial vitiligo, poliosis, deafness and tapetoretinal degeneration. [2]

Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome, a mitochondrial disorder, presents with central nervous system abnormalities, neurosensory hearing loss, diabetes mellitus and cardiomyopathy and 11% of these patients had vitiligo as observed in one study. [59]

Table 3: Disorders and syndromes possibly associated with vitiligo [2]	
More common associations	**Less common associations**
▪ Addison disease ▪ Alopecia areata ▪ Atopic dermatitis ▪ Autoimmune thyroid disease ▪ Chronic urticaria ▪ Diabetes mellitus ▪ Halo nevi ▪ Hypoacusis ▪ Hypoparathyoidism ▪ Ichthyosis ▪ Ocular abnormalities ▪ Pernicious anemia ▪ Psoriasis ▪ Rheumatoid arthritis	▪ Acrokeratosis paraneoplastica Bazex ▪ Alezzandrini syndrome ▪ Autoimmune- Polyendocrinopathy—Candidiasis—Ectodermal Dysplasia syndrome (APECED syndrome) ▪ Asthma ▪ Ataxia-telangiectasia ▪ Deafness ▪ DOPA-responsive dystonia ▪ Dysgammaglobulinemia ▪ HIV ▪ Inflammatory bowel disease ▪ Kabuki syndrome ▪ Kaposi sarcoma ▪ Melanoma ▪ MELAS syndrome ▪ Morphea ▪ Multiple sclerosis ▪ Myasthenia gravis ▪ Nonmelanoma skin cancer ▪ Permphigus vulgaris ▪ Sarcoidosis ▪ Schimdt syndrome ▪ Systemic lupus erythematosus ▪ Turner syndrome ▪ Twenty nail dystrophy ▪ Vogt-Koyanagi-Harada syndrome

QUALITY OF LIFE

Vitiligo has a major psychosocial impact on an individual playing a major role on the individual's self-esteem and perception of self. In many societies, particularly in India, it is thought to be associated with leprosy or sexually transmitted disease.[60,61] In such societies women with vitiligo have difficulty in getting married and finding educational and vocational opportunities. [2] Many suffer embarrassment, depression and shame. Dermatological Life Quality Index (DLQI) done on all vitiligo patients have shown scores ranging from 4.82-14.72, which was found to be worse than the DLQI in psoriatic patients. [61]

Clinical variables such as duration of the disease, facial or chest involvement, darker skin type, patient assessed severity and extent of disease predicted a poorer QOL. [62]

HISTOPATHOLOGY:

The following features are seen on histopathology in vitiligo: [63]

1. Thinned epidermis
2. Absence of pigment and suprabasal vacuolization
3. Suprabasal clear cells in perilesional skin
4. Effacement of the dermo-epidermal junction
5. Perivascular inflammatory cell infiltrates
6. Perivascular mononuclear inflammatory cell infiltrates
7. Sweat gland degeneration
8. Sebaceous gland / hair follicle degeneration
9. Inflammatory changes, more often in those of short duration
10. Degenerative changes more prominent in long standing cases

Special stains used in vitiligo include DOPA which aides in detection of active melanocytes and HMB45, Mel-5 and NK1/beteb (anti-pMel-17), which detect both active and dormant melanocytes. [63]

DIAGNOSIS OF VITILIGO

Vitiligo is diagnosed clinically, however the British Association of Dermatologist has made the following recommendations: [64]

1. Vitiligo diagnosis is straightforward when presentation is classical.
2. When presentation is atypical, cases should be referred for expert assessment by a dermatologist.
3. In adults with vitiligo, a blood test to check thyroid function should be considered.
4. Wood's lamp may be of use in determining extent of activity of vitiligo, as well as monitoring response to therapy.
5. Response to treatment in vitiligo should be considered in context of the natural history, recognizing that spontaneous repigmentation may occur but is uncommon.
6. Clinicians should assess the psychological and quality of life effects of vitiligo patients.
7. In clinical trials of vitiligo, the patient's improvement and quality of life should be the most important outcome measure.

MANAGEMENT OF VITILIGO

The aim of vitiligo treatment is to bring about stabilization and repigmentation of the depigmented lesions. [28,65] The choice of therapy depends on the extent, location and activity of the disease along with patient's age, sex, skin type and motivation to undergo treatment. [65] A period of at least 2 – 3 months is required to assess if the lesions are responding to therapy. [65] The regions responding best to therapy are the face, neck, trunk and proximal extremities while the distal extremities and perioral regions are more resistant to therapy. [28, 65] Repigmentation can occur in 4 main patterns: perifollicular, diffuse, marginal and mixed. [28]

After initial clinical assessment based on the type of vitiligo, duration, stability and presence of Koebner's phenomenon, patients would fall in to one of the following categories: [65]

- Generalized, indolently progressive disease
- Localized vitiligo
- Disease warranting surgical management

Individuals in the first two groups are those with actively progressing disease and those with widespread lesions who are advised medical therapy. Systemic steroids in the form of betamethasone oral mini pulse therapy is given at a dose of 5mg twice weekly (2.5mg for children) for 4 months, following which the patients are assessed for stability of vitiligo and repigmentation of the lesions. Systemic steroids have a dual role to suppress the autoimmune damage and halt progression of vitiligo and thereafter induce repigmentation. [63] Other non-surgical options for repigmentation of vitiligo lesions once disease has stabilized are: (1) Psoralens with ultraviolet A (PUVA) (2) Narrow-band ultraviolet B (NBUVB) (3) Excimer laser or lamp. [28] For

focal vitiligo treatment options include the use of (1) topical superpotent and potent topical steroids (2) topical calcineurin inhibitors. [28,65]

Individuals with segmental type of vitiligo show poor response to medical intervention due to its non-autoimmune etiology and responds best to surgical procedures. [65] Mucosal vitiligo and acrofacial vitiligo also responds poorly to medical therapy due to lack of hair follicles acting as pigment reservoirs at these sites. Criteria for recruiting patients for surgical procedures include:

- Disease, which is stable for at least 2 years.
- Failure of appropriate and adequate medical therapy.
- Localized vitiligo.

Various vitiligo surgeries include (1) mini-punch grafting (2) blister grafting (3) autologous melanocyte cell transfer (4) dermabrasion followed by topical 5-fluorouracil and NBUVB. [65]

METHODOLOGY

SOURCE OF DATA:

A total of 45 patients with vitiligo up to the age of 18 years were considered from the outpatient department of Dermatology, Venereology and Leprosy in B.L.D.E.U Shri B.M. Patil Medical College Hospital and Research Centre, Vijayapura. The hospital based cross-sectional study was conducted between October 2013 to September 2015.

COLLECTION OF DATA:

INCLUSION CRITERIA:

- All patients up to the age of 18 years were considered for the study.

EXCLUSION CRITERIA:

- Previously treated cases of vitiligo with systemic steroids were excluded from the study

PROCEDURE:

In this study, a detailed history was taken from all patients up to the age of 18 years presenting vitiligo including history suggestive of any thyroid disease. A detailed history and clinical assessment of type of vitiligo, duration, activity of disease, presence of family members with vitiligo or other auto-immune diseases, clinical evaluation of thyroid status including clinical examination of thyroid gland, (thyroid stimulating hormone, triiodothyronine and thyroxine) and presence of antibodies to thyroperoxidase (anti-TPO) was done. To reduce the variability of test results, due to the diurnal variation of thyroid stimulating hormone (TSH), an early morning sample was preferred with overnight fast prior to the testing. The blood sample drawn was collected in a plain tube and sent for processing.

STATISTICAL ANALYSIS

The observations pertaining to the parameters undertaken for the study among the study subjects were expressed in percentage. The generated data (age and gender related) were represented diagrammatically. Mean values and standard deviations were calculated. Univariate analysis including odds ratio (OR) and 95% confidence interval was done.

ETHICAL CLEARANCE:

Institutional ethical committee clearance was undertaken for the study.

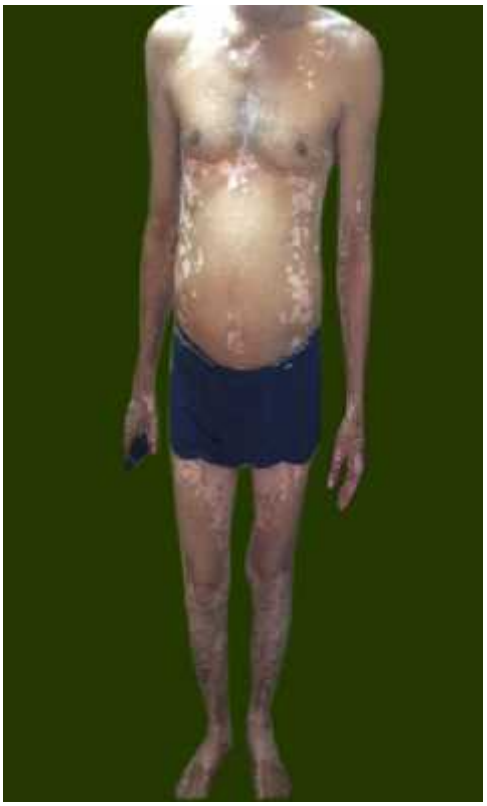


Figure 1: Vitiligo Vulgaris

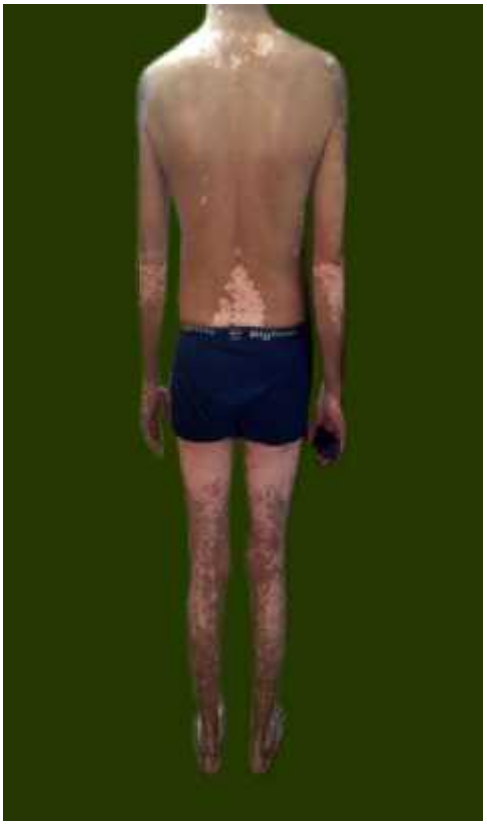


Figure 2: Vitiligo Vulgaris

Figure 3: Segmental Vitiligo

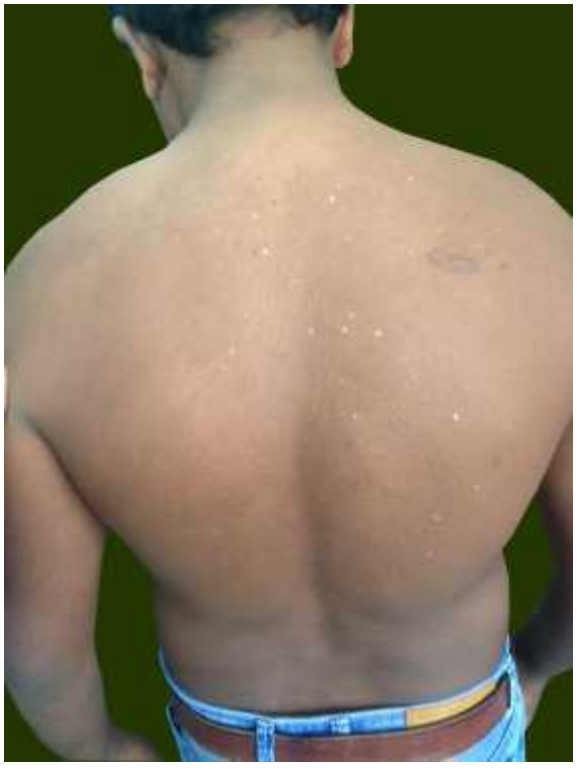


Figure 4: Vitiligo Ponctué

RESULTS

Table 4: Age distribution of vitiligo		
Age (Yrs)	**Number**	**Percentage**
<12 (Childhood vitiligo)	23	51.1
≥12 (Later onset vitiligo)	22	48.9

The study included a total of 45 patients with vitiligo before the age of 18 years. Of these 45 patients, 23 patients had childhood vitiligo and the remaining had later-onset vitiligo.

Table 5: Distribution of types of vitiligo

Type	Number	Percentage
Acrofacial	8	17.8
Focal	17	37.8
Segmental	4	8.9
Vulgaris	16	35.6
Total	45	100

Graph 1: Distribution of Types of Vitiligo

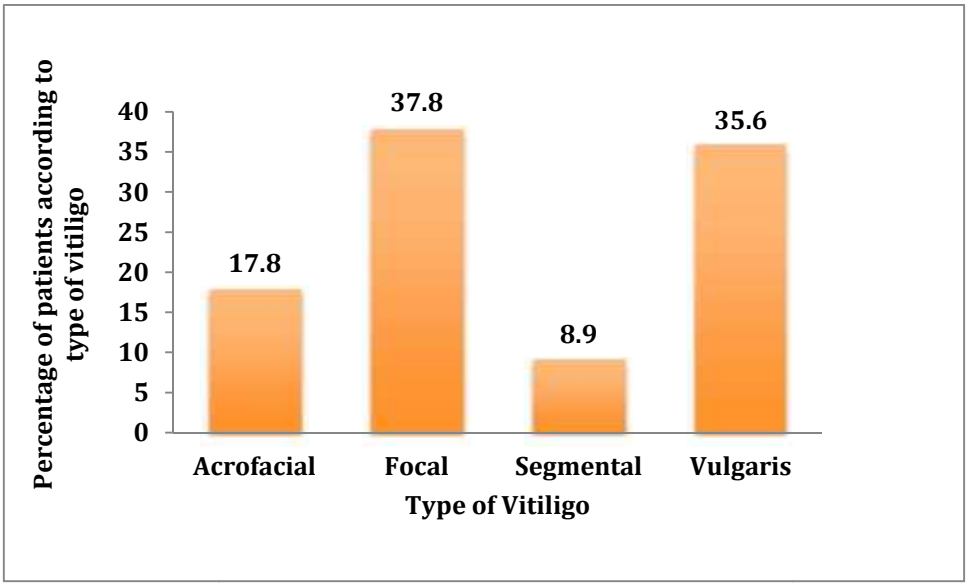
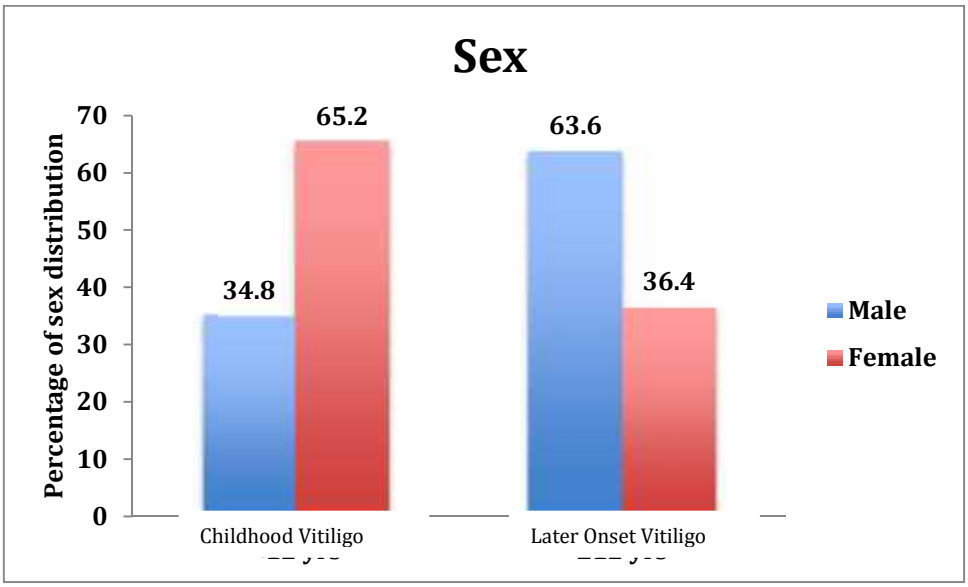


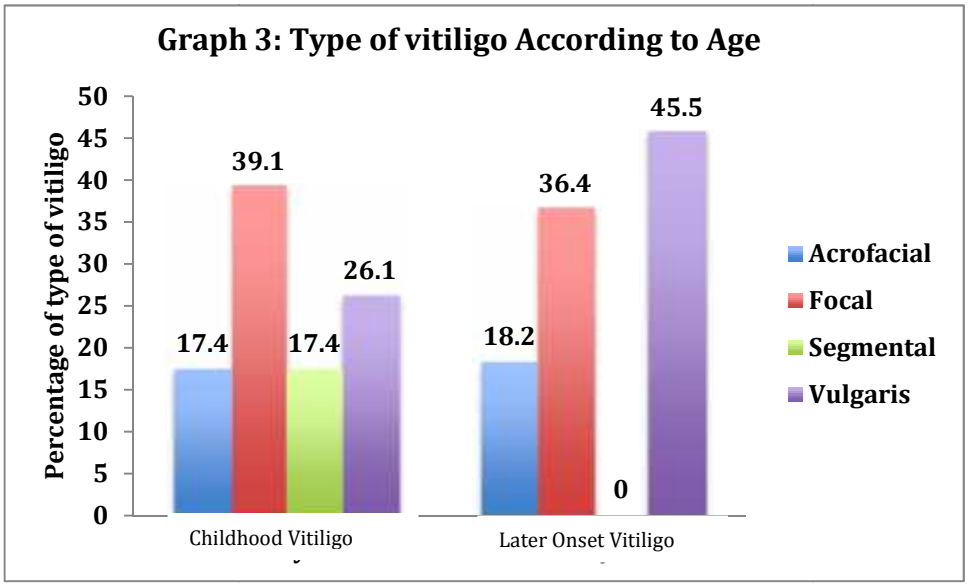
	Table 6: Sex Distribution of Vitiligo by Age						p value
	Childhood Vitiligo		Later Onset Vitiligo		Total		
Sex	**N**	**%**	**N**	**%**	**N**	**%**	
Male	8	34.8	14	63.6	22	48.9	0.053
Female	15	65.2	8	36.4	23	51.1	
	23	100.0	22	100.0	45	100.0	

Graph 2: Distribution of Childhood Vitiligo and Later Onset by Gender



The total number of female patients was 23, with a female to male ratio of almost 1:1. Female predominance was seen in childhood vitiligo compared to later onset vitiligo but this was not significant.

	Table 7: Type of Vitiligo and Age Distribution						p-value
	Childhood Vitiligo		Later Onset Vitiligo		Total		
Type of vitiligo	Number	Percentage	Number	Percentage	Number	Percentage	
Acrofacial	4	17.4	4	18.2	8	17.8	0.169
Focal	9	39.1	8	36.4	17	37.8	
Segmental	4	17.4	0	0.0	4	8.9	
Vulgaris	6	26.1	10	45.5	16	35.6	
	23	100.0	22	100.0	45	100.0	



The study also observed that focal vitiligo was the most common type of vitiligo in childhood vitiligo, while vulgaris was the most common type of vitiligo seen in later onset vitiligo. Segmental type of vitiligo was observed in childhood vitiligo.

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Table 8: Family History of Vitiligo

Family history	Number	Percentage
No	31	68.9
Yes	14	31.1
Total	45	100

Table 9: Distribution of Type of Vitiligo and Family History of Vitiligo

Type	Family History				Total	p-value
	No		Yes			
	Number	Percentage	Number	Percentage		
Acrofacial	7	87.5	1	12.5	8	0.214
Focal	13	76.5	4	23.5	17	
Segmental	3	75	1	25	4	
Vulgaris	8	50	8	50	16	

Family history of vitiligo was observed in 14 patients (31.1%), which was not significant and was predominantly seen in patients with vitiligo vulgaris (50%).

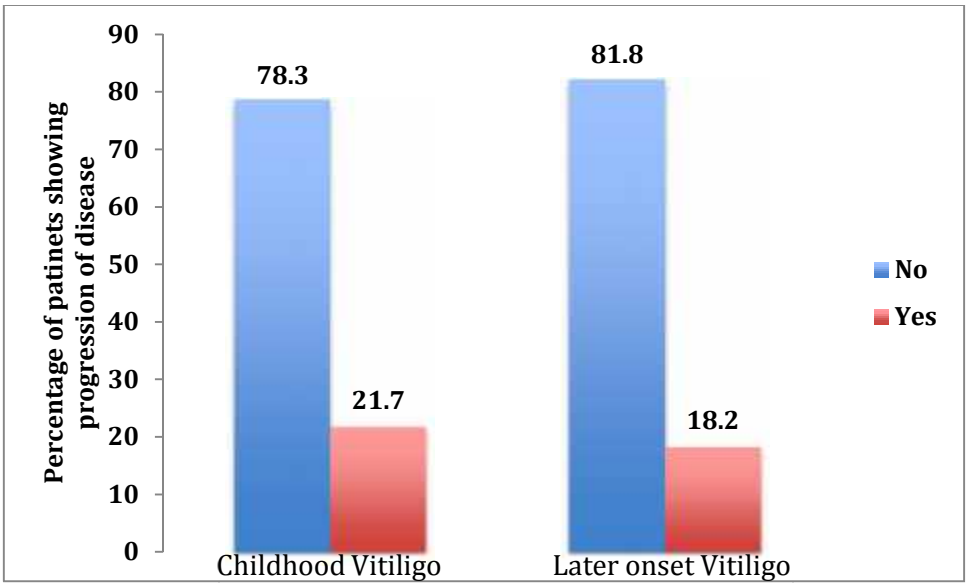
Table 10: Progression of Vitiligo According to Type of Vitiligo

Type	Progression				Total	p-value
	No		Yes			
	Number	Percentage	Number	Percentage		
Acrofacial	5	62.50%	3	37.50%	8	0.266
Focal	16	94.10%	1	5.90%	17	
Segmental	3	75.00%	1	25.00%	4	
Vulgaris	12	75.00%	4	25.00%	16	

Of the 45 patients considered in this study, 9 patients showed progression. It wsa observed in 3 (37.5%) patients with acrofacial and 4 (25%) patients with vuglaris types of vitiligo, which was not significant.

	Table 11: Progression of Vitiligo According to Age						p-value
	Childhood Vitiligo		Later onset Vitiligo		Total		
Progression	**N**	**%**	**N**	**%**	**N**	**%**	
No	18	78.3	18	81.8	36	80.0	0.766
Yes	5	21.7	4	18.2	9	20.0	
	23	100.0	22	100.0	45	100.0	

Graph 4: Progression of Vitiligo According to Type of Vitiligo Onset



In this study, all the patients reported a normal thyroid function and thyroperoxidase antibodies were negative.

DISCUSSION

The purpose of this study was to assess the presence of aberrant thyroid function and presence of thyroid antibodies in individuals with vitiligo up to 18 years of age.

Our study revealed fewdifferences between childhood vitiligo (CV) and later onset vitiligo. These findings were (1) CV involved different sites at time of presentation (2) CV included more of segmental type of vitiligo (3) females were predominately affected.

Childhood vitiligo (onset before 12 years of age) is relatively common occurring in almost 25% of vitiligo patients. [34,36]No clear sex predominance can be established in cases of childhood vitiligo, however some studies reported a female predominance.[34,51] In this study we have seen no difference in the female to male ratio of patients with vitiligo up to 18 years, however a female preponderance was seen in individuals with childhood vitiligo but was not significant.

In this study, 9 (20%) of the 45 patients from both the childhood vitiligo and later onset vitiligo reported a progression of their disease and it was observed with patients of vulgaris and focal type of vitiligo. Among the various types of vitiligo, it was found that the segmental type was seen in the childhood vitiligo.

As observed in this study as with other studies, children with vitiligo tend to have lower incidence of associated autoimmune thyroid disorders as compared with adults. [51,52]However it has been reported that the thyroid dysfunction can be subclinical, compared with that of normal children suggesting a propensity toward

autoimmune thyroid disease later in life in patients with childhood vitiligo. [55] A systematic review has reported that patients with non-segmental vitiligo have a higher prevalence of thyroid disease and autoimmune thyroid disease as compared to patients with segmental vitiligo. [53]The screening of thyroid antibodies in those with vitiligo serves as a useful tool as they can be present up to 7 years before the clinical diagnosis of autoimmune thyroid disease. [53]

Anti-TPO, historically referred to as antimicrosomal antibody, is a sensitive tool for the early detection of subclinical AITD as well as at-risk cases for AITDand tends to have better correlation with thyroid dysfunction as compared with anti-Tg antibodies.[53]Hence, anti-TPO rather than anti-Tg is recommended for screening in euthyroid patients with vitiligo.

In this study, all the patients up to 18 years with vitiligo were assessed for thyroid function and the presence of thyroid antibodies. It was found that all patients' thyroid function was normal and anti-TPO was negative.

Studies have reported a prevalence of family history of vitiligo in 35% of those with childhood vitiligo.[5,33]A study by Pajvani *et al,* reported that patients with vitiligo were 5 times more likely to have an immediate relative and almost 3 times more likely to have an extended relative with vitiligo compared to control and 4 times more likely to have an immediate relative with leukotrichia than patients in the control group. [39]A recent study by Laberge *etal,*found that vitiligo patients with multiple family members suffering from vitiligo developed the disease earlier compared to individuals with sporadic vitiligo.[66]In this study, 7 (30.4%) out of 23

patients with childhood vitiligo and 7 (31.1%) out of 22 patients with later onset vitiligo had history of family members with vitiligo but this was not significant.

The pathogenesis of vitiligo is poorly understood but the frequent occurrence of familial cases and associations with various genetic loci suggest that vitiligo may have a genetic origin. [6,8]A study by Zhang *et al,* involving a complex segregation analysis, found that focal, vulgaris, acrofacial and segmental types were explained by a polygenic additive model (influenced by a group of non-allelic genes that enhance the affect of the other genes in producing the phenotype) and in case of universal type by an environmental model.[67] Another study also found that the presence of humoral and cell-mediated immune aberrations and association with other autoimmune diseases point towards an autoimmune origin with also a genetic basis.[68]

In conclusion, this study has found no association of vitiligo with aberrant thyroid function and anti-TPO was negative in all patients in this study. The plausible reason for this was probably due to the limited sample size of 45 patients as compared to other larger sample size studies. In clinical practice however, we should always keep in mind that children with vitiligo can develop thyroid disease later in life if they have a positive family history of thyroid disease. Therefore, a thyroid profile including thyroid antibodies should be performed if the patient displays clinical features of autoimmune thyroid disease.

CONCLUSION

Vitiligo is an acquired pigmentary mucocutaneous disorder of unknown etiology that is clinically characterized by circumscribed depigmented macules and patches secondary to selective destruction of melanocytes. The association with thyroid autoimmune disease has been demonstrated in studies on both later onset and childhood vitiligo, suggesting that vitiligo has an autoimmune etiology. In our study, thyroid function tests were within normal limits and anti-thyroid peroxidase was negative in all patients up to 18 years.

Hence, it can be concluded that although tests for thyroid function and presence of anti-thyroid peroxidase can be a useful early diagnostic tool for both clinical and subclinical thyroid disease, it should be performed after a detailed history including progression, family history of vitiligo or thyroid disease and a thorough clinical examination in patients up to 18 years with vitiligo.

SUMMARY

This was a hospital based cross-sectional study on thyroid function test and antithyroid peroxidase test in children up to 18 years with vitiligo that was conducted during the period between between October 2013 to September 2015. Patients up to 18 years diagnosed with vitiligo were included in this study. Each patient a detailed history was taken and they were subjected to a complete systemic, cutaneous, thyroid examination along with a tests ff thyroid function and presence of anti-thryoperoxidase.

Following were the salient findings of this study:

- Both genders were equally involved, with female preponderance in patients with childhood vitiligo.
- Segmental type of vitiligo was seen in patients with childhood vitiligo.
- The most common type of vitiligo observed in later-onset vitiligo was vulgaris and the most common type of vitiligo observed in childhood vitiligo was focal type.
- Progression of disease was reported in patients with vulgaris and focal type of vitiligo.
- The thyroid function tests were normal and anti-thyroperoxidase antibody was negative in all patients in this study.

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APPENDIX – I

B.L.D.E UNIVERSITY'S
SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR-586 103
INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 13-11-2013 at 2:30 pm to scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected & revised version synopsis of the Thesis has been accorded Ethical Clearance.

Title "A cross sectional study on thyroid function test & anti-thyroid peroxidase antibodies in children upto 18 years of age with vitiligo"

Name of P.G. student Dr Joe Varghese Thomas

Department of Dermatology

Name of Guide/Co-investigator Dr Arun C Inamadar

Prof & H.O.D. of Dermatology

DR TEJASWINI VALLABHA
CHAIRMAN
INSTITUTIONAL ETHICAL COMMITTEE
BLDEU'S, SHRI.B.M.PATIL
MEDICAL COLLEGE, BIJAPUR.

Following documents were placed before E.C. for Scrutinization
1) Copy of Synopsis/Research project.
2) Copy of informed consent form
3) Any other relevant documents.

APPENDIX – II

SAMPLE INFORMED CONSENT FORM

BLDEU'S SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE,- VIJAYPUR-586 103

RESEARCH INFORMED CONSENT FORM

TITLE OF THE PROJECT: - A CROSS SECTIONAL STUDY ON THYROID FUNCTION TEST AND ANTITHYROID PEROXIASE ANTIBODIES IN CHILDREN UPTO 18 YEARS OF AGE WITH VITILIGO.

PG GUIDE :- DR.ARUN C. INAMADAR

PG STUDENT :- DR. JOE VERGHESE THOMAS

PURPOSE OF RESEARCH:-

I have been informed that this project will study the association of vitiligo with autoimmune thyroid disease in individuals up to 18 years of age.

BENEFITS

I understand that my child/ward's participation in this study will help the investigator to understand the disease better and will help in the management of the disease.

PROCEDURE

I understand that relevant history will be taken and my child/ward will undergo detailed clinical examination after which necessary investigation will be done whenever required.

RISK AND DISCOMFORTS

I understand there is no risk involved and my child/ward will experience minimal pain during the procedures performed.

CONFIDENTIALITY

I understand that medical information produced by this study will become a part of my child/ward's hospital records and will be subjected to the confidentiality and privacy regulation of the said hospital. Information of a sensitive personal nature will not be a part of the medical records, but will be stored in the investigator's research file.

If the data are used for publication in the medical literature or for teaching purposes no names will be used and other identifiers such as photographs and audio or videotapes will be used only with my special written permission. I understand I may see the photographs, videotapes and hear the audiotapes before giving this permission.

REQUEST FOR MORE INFORMATION

I understand that I may ask more questions about the study at any time concerned. The researcher is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of this study, which may influence my continued participation.

REFUSAL OR WITHDRAWAL OF PARTICIPATION

I understand that my child/ward's participation is voluntary and I may refuse to participate or may withdraw consent and discontinue participation in this study at any time without prejudice. I also understand that the researcher may terminate my child/ward's participation in this study at any time after he has explained the reasons

for doing so and has helped arrange for my child/ward's continued care by my own physician if this is appropriate.

INJURY STATEMENT

I understand that in the unlikely event of injury to my child/ward resulting directly from my child/ward's participation in this study and if such injury were reported promptly, then medical treatment will be available to me, but no further compensation will be provided. I understand that by my agreement for my child/ward's participation in this study, I am not waiving any of my legal rights.

I have explained to…….(patient/ parent/relevant guardian's name) the purpose of the research, the procedures required, and the possible risks and benefits to the best of my ability in patient's own language.

_____ _____

Investigator / P. G. Guide Date

I confirm that…….…….Name of the PG guide / chief researcher) has explained to me the research, the study procedures that my child/ward will undergo, and the possible risks and discomforts as well as benefits that my child/ward experience. I have read and I understand this consent form. Therefore, I agree to give my/my consent for my child's participation as a subject in this research project.

_____

Parent/Guardian Signature Date:

_____

Witness to signature Date:

APPENDIX – III

PROFORMA

B.L.D.E.U's SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL

AND RESEARCH CENTRE, VIJAYPUR.

DEPARTMENT OF DERMATOLOGY, VENEREOLOGY AND LEPROSY.

NAME:	SL NO.
GUARIDIAN NAME:	IP/OP NO
SEX:	OCCUPATION
ADDRESS:	

1. COMPLAINTS WITH
DURATION
-AGE OF ONSET
-SIZE AT ONSET
-DURRATION SINCE ONSET

2. FAMILY HISTORY OF VITILGO YES/NO

-
-
-
-

3.TREATMENT HISTORY

4. REPIGMENTATION

5. SPONTANEOUS/DRUG INDUCED

6. H/O HANDLING CHEMICALS

7. PROGRESSIVE/ NON-PROGRESSIVE

8. H/O KOEBNERIZATION YES/NO

9. H/O OTHER AUTOIMMUNE DISORDERS:

DIABETES MELLITUS/ PERNICIOUS ANEMIA/ ADDISON'S DISEASE

10. ATOPY YES/NO

11. THYROID HISTORY

- FATIGUE YES/NO
- ANXIETY YES/NO
- INTOLERANCE TO HEAT YES/NO
- INTOLERANCE TO COLD YES/NO
- PALPITATION YES/NO
- DISTURBED SLEEP YES/NO
- FEELING TIRED YES/NO
- MYXEDEMA YES/NO
- IMPAIRED CONCENTRATION YES/NO
- IMPAIRED CONCENTRATION YES/NO
- LETARGY YES/NO
- HOARSE VOICE YES/NO
- CONSTIPATION YES/NO
- DIARRHOEA YES/NO
- LOSS OF APPETITE YES/NO
- CONSTIPATION YES/NO
- TRAUMA YES/NO
- CHEILOSIS YES/NO

GENERAL PHYSICAL EXAMINATION

WEIGHT: BP:

PALLOR: ICTERUS: EDEMA:
CLUBBING: CYANOSIS: LYMPHADENOPATHY:

CUTANEIOUS EXAMINATION

BSA%:

CLINICAL TYPE:

FOCAL/SEGMENTAL/VULGARIS/UNIVERSAL/ACROFACIAL

- IF FOCAL
  - SIZE:
  - SITE:

KOEBERNIZATION

TRICHROME/QUADRICHROME

LEUKOTRICHIA LESIONAL/SCALP/EYEBROW/EYELASHES

THYROID EXAMINATION

INSPECTION

PALPATION

AUSULTATION

INVESTIGATIONS

T3

T4

TSH

Anti-TPO

INFERENCE:

KAY TO MASTER CHART

A	Acrofacial
F	Female
Fo	Focal
M	Male
S	Segmental
V	Vulgaris

APPENDIX – IV

MASTER CHART

S.No	OP No	Name	Age (years)	Sex	Duration (years)	Type	Family h	Progression	Thyroid h	Repigmentation	Treatment	Thyroid Profile including anti-TPO	Atopy
1	2013/24243	Sudha	14	F	10	V	No	No	Normal	No	Yes	Normal	Yes
2	2014/29609	Jyothi M	17	F	3 months	V	Yes	Yes	Normal	Yes	Yes	Normal	No
3	2014/57974	Keerti	10	F	1	V	Yes	No	Normal	Yes	Yes	Normal	No
4	2014/41321	Revatin B	10	F	1	S	No	No	Normal	No	Yes	Normal	No
5	2014/41505	Sabiya T	18	F	2	V	No	No	Normal	No	Yes	Normal	No
6	2014/61239	Geethu A	8	F	1	V	No	No	Normal	Yes	Yes	Normal	No
7	2014/72103	Abdul R	15	F	3	V	Yes	No	Normal	Yes	Yes	Normal	No
8	2014/354156	Renuka Patil	10	F	7	A	No	No	Normal	No	No	Normal	No
9	2014/411320	Aradhak R	12	F	7months	V	No	No	Normal	No	No	Normal	No
10	2014/433145	Anusha S	18	F	17	A	No	Yes	Normal	Yes	Yes	Normal	No
11	2015/22170	Varuna S	11	F	1	Fo	No	No	Normal	No	No	Normal	No
12	2015/22146	Gouramma P	14	F	2	Fo	No	No	Normal	No	No	Normal	No
13	2015/23145	Aarti M	12	F	6 months	Fo	Yes	No	Normal	No	No	Normal	No

14	2015/27156	Apsana S	3	F	1	Fo	No	No	Normal	No	No	Normal	No
15	2015/27710	Mohammed K	14	F	1	A	No	No	Normal	No	No	Normal	No
16	2015/29157	Ankita B	10	F	4	V	Yes	Yes	Normal	No	Yes	Normal	No
17	2015/33271	Prathiba P	12	F	4 months	Fo	Yes	No	Normal	No	No	Normal	No
18	2015/33417	Bhagyashree	15	F	5 months	Fo	No	No	Normal	No	No	Normal	No
19	2015/56201	Teju S Naik	8	F	8 months	Fo	No	No	Normal	No	No	Normal	No
20	2015/57984	Nasima H	15	F	3	V	No	No	Normal	Yes	No	Normal	No
21	2015/67023	Shanta Indi	15	F	1	Fo	No	No	Normal	No	No	Normal	No
22	2015/205185	Gettappa S	6	F	1	Fo	No	No	Normal	No	No	Normal	No
23	2015/239121	Ankita	15	F	4	V	No	No	Normal	Yes	Yes	Normal	No
24	2013/40124	Sunil	15	M	3	V	No	No	Normal	No	Yes	Normal	No
25	2013/29396	Ravikumar B	16	M	2 months	A	No	No	Normal	No	Yes	Normal	No
26	2014/41179	Gangadar	16	M	3	V	Yes	No	Normal	Yes	Yes	Normal	No
27	2014/41981	Math S	13	M	6 months	A	No	No	Normal	No	Yes	Normal	Yes
28	2014/42905	Kalleppa	10	M	1	A	Yes	No	Normal	Yes	Yes	Normal	No
29	2014/43988	Shamu	15	M	2	V	Yes	Yes	Normal	Yes	Yes	Normal	No

30	2014/89213	Mallikarjun	15	M	1	A	No	Yes	Normal	No	No	Normal	No
31	2014/83415	Seema	14	M	2	V	Yes	No	Normal	No	No	Normal	No
32	2014/314378	Soujanya	6	M	5 months	S	No	No	Normal	No	No	Normal	No
33	2014/419020	Rakesh R	1	M	1 month	Fo	No	Yes	Normal	No	No	Normal	No
34	2014/422902	Shamshad	15	M	13	S	Yes	Yes	Normal	Yes	Yes	Normal	No
35	2015/22156	Sachin M	18	M	1	Fo	Yes	No	Normal	No	No	Normal	No
36	2015/235156	Samarth P	7	M	5	Fo	Yes	No	Normal	No	No	Normal	No
37	2015/44238	Mubarak	15	M	5	A	No	Yes	Normal	No	Yes	Normal	No
38	2015/45229	Gajnan S	15	M	3	V	Yes	Yes	Normal	No	Yes	Normal	No
39	2015/46610	Gattappa S	6	M	6 months	Fo	No	No	Normal	No	No	Normal	No
40	2015/66241	Mohammed	13	M	7 months	Fo	No	No	Normal	No	No	Normal	No
41	2015/77584	Nikhilgouda	8 months	M	5 months	S	No	No	Normal	No	No	Normal	No42
42	2015/81210	Mohammed	13	M	1	V	No	No	Normal	Yes	Yes	Normal	No
43	2015/193836	Manjunath K	14	M	6 months	Fo	No	No	Normal	No	No	Normal	No
44	2015/202169	Mubarak Z	15	M	8 months	Fo	No	No	Normal	No	No	Normal	No
45	2015/238893	Shrishail K	18	M	3 months	Fo	No	No	Normal	No	No	Normal	No