INTRODUCTION

Vitiligo is one of the most common skin disorders with a prevalence of 1-2% in different populations. The condition occurs when pigmented cells are destroyed, causing patches of skin to lose their normal color and appear whiter ***(Alkhateeb et al., 2003; Iacovelli et al., 2005)***.

The etiology of this disorder is not clear but different theories suggest that autoimmune, genetic disorders, toxic metabolites, oxidative stimuli are the main factors. The nervous system and or the absence of the melanocyte growth factor may be included ***(Ongenae et al., 2003)***. From these factors, autoimmune disorder is the most common cause and some of the patients have antibodies to melanocytes or melanocytic proteins. Although it is not confirmed that these antibodies cause disease or lead to melanocyte destruction, there is some evidence that cell-mediated immunity plays a role in melanocyte destruction ***(Yu et al., 1993; Vanden et al., 2000; Kurtev and Dourmishev, 2004)***.

Autoimmune thyroid diseases with prevalence of up to 30% accompany vitiligo, from which hypo-thyroidism is one of the most common disorders ***(Iacovelli et al., 2005)***. In one study of 121 children with vitiligo, 16% showed some abnormalities in the thyroid function tests. The antithyroid peroxidase

antibody (Anti-TPO) was the most common disorder ***(Iacovelli et al., 2005)***.

Similar studies showed that vitiligo is commonly associated with thyroid disorders and positive thyroid antibodies (anti-TPo & anti-TG) ***(Manighalam et al., 2002; Dave et al., 2003; Alkhateeb et al., 2003 and Daneshpazhooh et al., 2006).***

AIM OF THE WORK

The aim of this study is to investigate the thyroid dysfunction and antithyroid antibodies (anti thyroid peroxidase and anti thyroglobulin) in patients with vitiligo.

MELANOGENESIS

Melanocytes:

Melanocytes are cells capable of synthesizing tyrosinase, which when incorporated within specialized organelles, the melanosomes, initiates events leading to the synthesis and deposition of melanin ***(Prota, 2000).***

In addition to the dermal epidermal junction, hair follicles and dermis, melanocytes in human are also found in mucous membranes, nervous system (pia-arachnoid), eye (uveal tract and pigment epithelium), inner ear, cochlea (wall of the modiolus, spiral lamina, reissner's membrane and stria vascularis), and vestibular system (saccule, uteride, and ampullae) ***(Witkop, 1983)***.

Melanocytes are derived from melanoblasts that migrate from the neural crest and the outer layer of the optic cup during the first 2 months of fetal development ***(Fitzpatrick and Szabo, 1959; Kovacs, 1998).***

Melanocytes in the skin, oral mucosa and uvea are derived from the spinal protein of the neural crest, although those in the leptomeninges evolve from the cephalic portion ***(Goldgeier et al., 1984; Kovacs, 1998)***.

Within melanocytes, melanin is formed after the occurrence of tyrosine reactions in the melanosomes (a derivative of the essential amino acids phenylalanine) ***(Kovacs, 1998)***.

The melanocyte cells transform the peptide tyrosinase into two different forms of melanin: eume-lanin and pheomelanin. Eumelanin is metabolized from 5,6-Dihydroindole-2-carboxylic acid (DHICA) and produces a brown color in hair in its intact form; pheomelanin is metabolized from 5, 6 indole quinone, which produces a red color in hair in its intact form ***(Prota, 2000)***.

Epidermal Melanin Unit:

The epidermal - melanin unit, a functional unit that produces and distributes melanin, is composed of one melanocyte, and approximately 36 neighbouring keratinocytes ***(Ortonne, 1995; Jimbow, 1995; Seiberg, 2001).***

Pigmentation of the skin, also referred to as complexion coloration, results from a complex process of melanin synthesis within melanocytes of the interfollicular epidermis, and the subsequent transfer, translocation and degradation of this melanin to, in and by the recipient keratinocytes respectively**.** Therefore, skin pigmentation is a combination of type and amount of melanin synthesized by the melanocyte

factory and the handling of the melanin product by the keratinocyte consumer ***(Boissy, 2003).***

Melanin pigmentation of the human skin is conveniently divided into two components. Constitu-tive skin colour and facultative skin colour. Constitu-tive pigmentation is the amount of cutaneous melanin pigmentation generated according to cellular genetic programs without any direct effect by radiations of solar origin. It is the level of pigmentation acquired in those parts of the body habitually shielded from the light ***(Pawelek et al., 1998; Boissy, 2003)***.

The synthesis of constitutive pigmentation by the melanocyte is controlled, primarily by the tyrosinase gene family of proteins tyrosinase, TYRP1 and TYRP2 which regulate the type of melanin synthesized ***(Pawelek et al., 1998; Jimbow et al., 2001).***

Boissy, (2003) had identified additional proteins that also regulate the synthesis of melanin in the melanosome (i.e., pmel 17, p protein, OAI protein).

Constitutive pigmentation can be modulated by various environmental factors such as ultraviolet light ***(Gilchrest et al., 1998),*** and numerous physiological factors ***(Norris and Morelli, 1998).*** Various auto-crine and paracrine hormones/cytokines produced both in the skin and

extracutaneously modulate this constitutive pigmentation, a process termed facultative pigmentation ***(Boissy, 2003).***

Early light and electron microscopy studies documented the membrane layering and organization during melanosome transfer, suggesting numerous possible mechanisms for melanosome transfer:

a. The release of the melanosomes by the melanocytes and the subsequent endocytosis of the released granules by the keratinocyte *(**Jimbow and Sugiyama, 1998; Boissy, 2003)***.
b. The keratinocyte engulfing the dendritic tips of the melanocytes by active phagocytosis and incorpo-rating portions of the melanocytes within them (i.e. cytophagocytosis) ***(Okazaki et al., 1976; Seiberg, 2001; Boissy, 2003)***.
c. The active transfer or injection of melanosomes directly into the keratinocyte by the melanocytes ***(Seiberg, 2001; Boissy, 2003).***
d. Continuous pore developing between the plasma membrane of the melanocytes and the keratinocytes, through which the melanosomes are passed ***(Boissy, 2003).***

Molecules recently identified that participate in "this process consist of Rab27a **(Menasche et al., 2000)** myosin-Va

and melanophilin ***(Province, et al., 2002; Fukuda, et al., 2002).***

The protease-activated receptor-2 (PAR-2) and unidentified surface lectins and glycoproteirs facilitate this transfer process ***(Dery et al., 1998; Boissy, 2003).***

Ultraviolet irradiation (UVR) can modulate the process of melanosome transfer from the melanocytes to the keratinocytes UVR can upregulate expression of PAR-2 and lectin- binding receptors ***(Boissy, 2003).***

Virador et al., (2002) demonstrated that UVR and MSH increase phagocytic activity of cultured keratinocytes.

The distribution of recipient melanosomes within the keratinocytes varies according to comp-lexion coloration as demonstrated over a quarter of a century ago. In dark-skinned individuals, melano-somes are approximately 0.8μm in diameter and are maintained as individual organelles throughout the cytosol of the keratinocyte. In contrast, in light skinned individuals, melanosomes are smaller than 0.8 um and are aggregated into membrane-bound clusters ***(Konrad and Wolf, 1973)***.

VITILIGO

The word Vitiligo may have evolved from the Latin word vitilium, meaning a defect ***(Carter, 1992)***, or vitelius signifying a calf's white patches ***(Fitzpatrick, 1964).***

Documentation of the use of the word vitiligo occurred in the first century AD when the Roman physician A.cornelius Celsus wrote his classic text De Medicina ***(Nair, 1978)***.

Vitiligo is cited in many ancient writings. Indian literature dating to 1500 to 1000 BC refers to the word Kilas ("Kil" means white, "as" means to cast or throw away) and palita ("pal" implies gray, old, and aged), referring to white patches on the skin ***(Singh et al., 1974)***.

In the Holy Koran, the word baras, meaning white skin, is used to describe a condition that Jesus cured ***(Sharque, 1984).***

Vitiligo is a depigmentation disorder affecting between 1% and 2% of the general population without any racial, sexual or regional differences in preva-lence. Vitiliginous patches contain either reduced melanin or no pigment at all. Initially small, they may enlarge and coalesce into larger patches ***(Huggins et al., 2005)***.

In vitiligo the selective destruction of the skin melanocytes results in the development of unsightly depigmented patches. The disease can have devas-tating consequences on an individual's relationships with others and internal feelings of self-worth. Fifty percent of vitiligo patients experience disease onset before the age of 18 when they are most concerned about their appearance, and self-image is the most fragile ***(Ortonne et al., 2003; Schwartz, 2005)***. Additionally, in regions where leprosy is endemic, individuals with vitiligo are stigmatized due to similarities in appearance between the two diseases. Fortunately, advances in our understanding and management of vitiligo are reducing its effect on the millions of individuals afflicted ***(Huggins et al., 2005)***.

Vitiligo suggests a systemic disease that can extend beyond the skin. It may be linked with Hashimoto's thyroiditis, diabetes mellitus, Addison's disease, and other autoimmune processes. It may be associated with ocular abnormalities, exclusively, or as part of a constellation of symptoms, as it is in Alezzandrini syndrome or Vogt-Koyanagi-Harada (VKH) syndrome ***(Huggins et al., 2006)***.

It is of interest to note, too, that more medical interest is being given to vitiligo because of its association not only with the previous conditions but also because of its occurrence surrounding metastatic lesions of melanoma. This may be best

termed vitiligo-like hypopigmentation rather than true vitiligo ***(Bystryn et al., 1987; Nordlund, 1987)***.

Genetics

The earliest evidence suggesting a genetic basis for vitiligo was its association with a number of other autoimmune disorders known to have heritable predispositions, such as diabetes mellitus. Genetic diseases are substantially more prevalent in children of parents who are close relatives. A study conducted in Bangalore, India, a community where consan-guineous marriages are common, reported that as many as 20% of the population developed depig-mented lesions ***(Ramaiah et al., 1988)***.

Additionally, in patients with nonsegmental vitiligo, a significantly earlier onset has been observed when there is a family history of vitiligo (on average, 24.8 versus 42.2 years) ***(Hann and Lee, 1996)***.

25% to 30% of patients with vitiligo have positive family history ***(Mandry et al., 1996).*** There is clearly a multifactorial genetic component of vitiligo that appears to predispose individuals to the disease. This multifactorial genetic component may be responsible for the complex nature of the presentation of vitiligo by patients ***(Nath et al., 1994; Sun et al., 2006).***

A more recent study suggests that there may in fact be two coexisting modes of inheritance for vitiligo depending on age of onset ***(Arcos-Burgos et al., 2002)***. In patients with early onset vitiligo (before the age of 30), vitiligo inheritance most closely followed a dominant mode of inheritance with incomplete penetration. However, a predisposition to vitiligo resulting from a recessive genotype and exposure to certain environmental triggers appeared to explain the inheritance pattern of late onset vitiligo (after 30 years of age) ***(Huggins et al., 2005).***

Several HLA studies have been performed which showed sporadic association between vitiligo and certain HLA groups. However, there is no clear or regular association with any class 1 or 2 alleles. The gene or genes directly implicated in this dermatosis remain to be identified. Linkage and association studies have provided strong support for vitiligo susceptibility genes on chromosomes 4q13-q21, 1p31, 7q22, 8p12 and 17p13, while loci of interest at 6p, 6q, 14q, 9q, 13q, 19p and 22q require further follow-up ***(Zhang et al., 2005).***

Gene polymorphisms in the MHC Class II region of the HLA locus have been previously found to be associated with other autoimmune diseases, such as type 1 diabetes mellitus and juvenile-onset rheuma-toid arthritis ***(Deng et al., 1995; Prahalad et al., 2001)***.

Another study suggested that the catalase gene (CAT) is associated with vitiligo ***(Bradley et al., 2002).***

Catechol-O-methyl transferase (COMT) is an enzyme that plays a major role in the metabolism of toxic or biologically active drugs, neurotransmitters and metabolites. One such metabolite, O-quinones, can be formed during melanin synthesis in the absence of adequate COMT activity. A COMT polymorphism has been found to be significantly associated with acrofacial vitiligo ***(Tursen et al., 2002)***.

Chromosome 1p31 has been found to be associated to a highly significant degree with generalized vitiligo in North American and United Kingdom whites. It is termed the autoimmune susceptibility locus (AISL), and it is responsible for susceptibility to autoimmunity, particularly vitiligo, whereas the presence of other genes (e.g., the major histocompatibility locus on chromosome 6), combined with exposure to extrinsic or intrinsic factors, may mediate the occurrence of Hashimoto's thyroiditis in individuals who are AISL susceptible. This is the reason for the increased prevalence of Hashimoto's thyroiditis for patients with vitiligo, and it seems to be genetically determined ***(Alkhateeb et al., 2002; Fain et al., 2003).***

Recently, the cytotoxic lymphocyte antigen 4 (CTLA-4) gene encodes a protein involved in the inhibition of improperly-activated T-cells. CTLA-4 variants have been linked to numerous autoimmune diseases. Recently, a study comparing 100 United Kingdom patients with vitiligo to controls found an association between the CTLA-4 polymorphism and vitiligo when it occurred with other autoimmune diseases, though not isolated vitiligo ***(Blomhoff et al., 2005).***

Epidemiology:

Vitiligo affect 1-2% of the word population ***(Shajil and Begum, 2006)***, approximately one half of those with vitiligo acquire the disease before the age of 20 years and the incidence decreases with increasing age ***(Ortonne et al., 2003).***

All races are affected. Vitiligo may develop at any age; onset has been reported from birth to 81 years of age. Both sexes are affected equally; the female prevalence in some studies probably can be attributed to greater concern (and greater willingness to express concern) about a cosmetic defect. Fifty percent of vitiligo patients experience disease onset before the age of 18 when they are most concerned about their appearance, and their self-image is the most fragile ***(Schwartz, 2005).***

Congenital vitiligo is very rare, however. The peak age of onset in all series was between 10 and 30 years; in 50 percent of cases, the age of onset fell within the first two decades of life ***(Ortonne et al., 2003).***

Precipitating Factors:

Vitiligo patients often can attribute the onset of their disease to a specific life event, crisis, or illness. Many can relate it to loss of a job, death of a close family member, an accident, or a severe systemic disease ***(Picardi et al., 2003).***

In darker-skinned individuals who have lost their previous summer tans, a single sun exposure may darken normally pigmented skin to reveal amelanotic macules not previously apparent ***(Ortonne, 2003).***

In some, the onset follows a physical injury such as a cut or abrasion, or sun exposure; this development of vitiligo congruent with a site of injury is referred to as the Isomorphic Koebner phenomenon (IKP) ***(Ortonne et al., 2003)***.

At least two studies have concluded that the IKP is significantly more common in patients with progressive vitiligo and it is characteristic of at least a third of patients with non-segmental vitiligo but, it is rarely seen in segmental vitiligo ***(Gauthier, 1995).***