INTRODUCTION

Vitiligo is an acquired pigmentary disorder of skin, mucous membranes, or both, characterized by loss of epidermal melanocytes ***(Pajvani et al., 2006)***. Vitiligo occurs worldwide with an estimated prevalence of 0.5-1% in most populations ***(Ezzedin et al., 2012a)***. It may present anytime in life, including the neonatal period and childhood. The onset of vitiligo has been reported to occur before the age of 10 years in 25% of cases ***(Lacovelli et al., 2005; Palit & Inamadar, 2012)***.

It seems that vitiligo has a multifactorial etiology, where genetic factors, various kinds of stress (emotional stress, oxidative stress with the accumulation of free radicals), accumulation of toxic melanin precursors in melanocyte (e.g., DOPA dopachrome, 5, 6-dihydroxyindole), disturbance of melanocyte homeostasis (e.g., impaired intracellular and extracellular calcium), and autoimmunity can all contribute to the development of the disorder ***(Njoo & Westerhof, 2001; Dell'anna & Picardo, 2006)***.

Vitiligo is divided clinically into two main forms, segmental vitiligo (SV) and non-segmental vitiligo (NSV) respectively. The latter also includes three major subsets, namely

generalized vitiligo, acrofacial vitiligo, and universal vitiligo ***(Ezzedin et al., 2012a)***. Recently, mixed vitiligo (MV) has been described as an initial SV, which later (usually several months) spreads into bilateral NSV patches ***(Ezzedin et al., 2011a)***. However, because the progress of vitiligo is unpredictable, it is not uncommon for NSV to evolve over time, modifying its extension and distribution ***(Faria et al., 2014)***.

The diagnosis of vitiligo depends on history and physical examination which reveal depigmented skin patches or lesions. In some challenging cases, such as vitiligo in lightly pigmented patients, a Wood`s lamp can be useful for highlighting areas of pigment loss ***(Kostovic and Pasic, 2005)***.

Vitiligo, although not a life-threatening disease for the child, can be a life-altering disease ***(Halder et al., 1996).*** Difficulties in coping with impaired appearance are most pronounced during childhood and are particularly important in children's future social and psychological development. Children with vitiligo are affected differently, depending on the location and extent of their disease, their age, individual capacities, and social environment ***(Hill-Beuf & Porter, 1984)***.

Many methods are available for evaluation of vitiligo severity: Vitiligo European task force (VETF) which is a system that incorporates three components of vitiligo: extent, stage and progression of disease spreading ***(Hamzavi et al., 2004)***, Vitiligo area severity index (VASI) Its name is an adoption from PASI score in psoriasis ***(Bhor and pande; 2006)***, Vitiligo disease activity score (VIDA) which is a six-point scale for evaluating vitiligo activity and Individuals own opinion is the base in this score ***(Feily; 2014)***, Potential repigmentation index (PRI) for prediction of potential repigmentation in non-segmental vitiligo ***(Benzekari et al., 2013)***, Vitiligo extent tensity index (VETI) that proposes to measure the extent of vitiligo by a numerical score and combines analysis of extensity and severity of vitiligo and produce a constant and reproducible number like PASI ***(Feily; 2014)*** and Vitiligo extent score (VES) that is used in our study which uses clinical pictures improving the accessibility of using the tool ***(Van Geel et al., 2016)***.

Successful treatment of vitiligo is often difficult, and treatment modalities have traditionally centered on a combination of camouflage products, topical corticosteroids, topical immuno-

modulators, psoralen plus ultraviolet A light therapy (PUVA), and ultraviolet B (UVB) light therapy ***(Al-Otaibi et al., 2009).***

AIM OF THE WORK

The aim of the current study is to study the pattern and distribution of vitiligo in children attending Vitiligo outpatient clinic of Al-Demerdash hospital and Kobri El-Qubba Armed Forces Medical Complex.

Chapter 1
VITILIGO

➢ Definition:

Vitiligo is the most frequent pigmentary disorder ***(Bagherani et al., 2011).*** It is an idiopathic disorder of pigmentation characterized by the presence of de-pigmented skin macules due to the chronic and progressive loss of melanocytes from the cutaneous epidermis ***(Taieb & Picardo, 2010).*** **(Figure 1)**

Vitiligo is not only a disease of melanocytes of the skin, human melanocytes are derived from the neural crest and are located on various parts of the body, the involvement of skin melanocytes is the most visible one, but a systemic involvement of melanocytes can be observed, some types of vitiligo (nonsegmental vitiligo) may also be associated with various diseases, mainly with autoimmune pathogenesis ***(Lotti & D`erme, 2014)***.

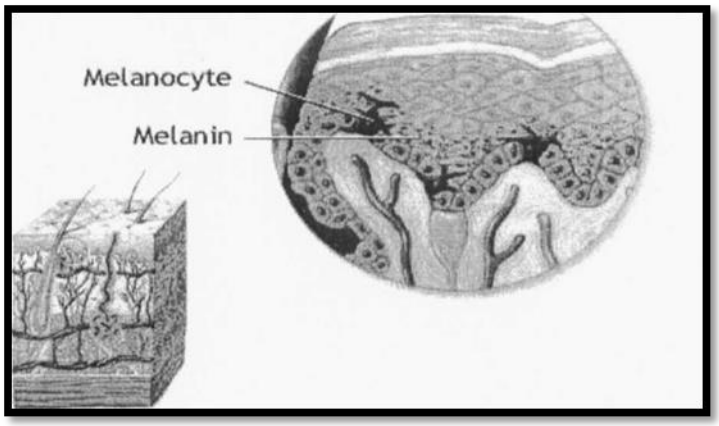

Figure (1): Melanocytes in the basal layer of the epidermis ***(Sravani et al., 2009).***

➢ Epidemiology:

Vitiligo is the most prevalent pigmentary disorder that occurs worldwide with an incident rate between 0.1% and 2% irrespective to age, race ethnic origin or skin color ***(Whitton et al., 2008).*** The prevalence has been reported as high as 4% in some south Asian, Mexican and United States populations ***(Sehgel and Srivastava, 2007).*** Childhood vitiligo differs from adult-onset vitiligo for several features, but is basically the same disease, with a potentially better regenerative capacity of the melanocytic lineage ***(Taieb et al., 2017)***.

Vitiligo can develop at any age, but about 50% of cases appear before the age of 20 and nearly 70-80% before the age of 30 years ***(Halder and Nootheti, 2008)***. ***Barona et al. (1995)*** found that in patients with unilateral vitiligo; mean age of onset was 16.3 years, compared to 24.8 years in patients with bilateral vitiligo.

Both sexes are equally affected although the greater number of reports among females is probably due to the greater social consequences to women and girls affected by this condition ***(Handa and Dogra, 2003)***.

➢ Precipitating Factors:

i.Psychological:

Psychological trauma such as crisis, illness, loss of job, death of a close family member, an accident, or a severe

systemic disease may increase individual's susceptibility to vitiligo ***(Guerra et al., 2010).***

ii.Physical injury:

In some patients the onset of vitiligo follows a physical injury such as a cut or abrasion, or sun exposure; this development of focal vitiligo congruent with a site of injury is referred to as the isomorphic köebner phenomenon ***(Ortonne et al., 2003; Batalla and Feal, 2010).***

iii.Nutrition:

There is a potential link between nutrition and pathophysiology of vitiligo due to the important contribution of ROS (reactive oxygen species), estrogen, tannin, and phenol-containing chemicals which can compete with tyrosine to produce reactive quinones ***(Namazi and Chee Leok, 2009).***

Mango, cashew, pistaschio, oak, cassava, areca nut, red chillies, cherry, raspberry, cranberry, blackberry and tea contain naturally occurring plant phenol and polyphenolic compounds (tannins), which may aggravate vitiligo ***(Birol et al., 2006).***

iv.Drugs:

Vitiligo can be induced by anticonvulsants (carbamazepine, valproic acid), antimalarial drugs (chloroquine), biological drugs (infliximab) and other drugs (clofazimine,

dopamine) in some reported cases. Pathomechanisms of reported cases can be classified into 3 groups: 1.drug-induced activation of cytotoxic T cells directed against melanocyte antigens (MART-1/MelanA, gp100, TRP-1, TRP-2), 2.drug-induced damage to sympathetic nerves that are connected by chemical synapses to melanocytes, which indirectly leads to their functional disturbances, 3.direct, cytotoxic effects of drugs on melanocytes (apoptosis) ***(Curzytek et al., 2007)***.

- **Etiopathogenesis:**

Although the etiology of vitiligo remains unclear, several theories have been developed. However, the autoimmune hypothesis remains the leading one.

i.Autoimmune theory:

It is widely known that vitiligo can be associated with several autoimmune diseases, including autoimmune thyroid diseases, alopecia areata, halo nevi, and Addison's disease ***(Lepool & Lutin, 2008)***.

Vitiligo could be present in all the autoimmune polyglandular syndromes (APS) ***(Amerio et al., 2006)***. Furthermore, it was reported that Addison's disease, systemic lupus erythematosus, and inflammatory bowel diseases were all associated with vitiligo, although these were an uncommon event ***(Alkhateeb et al., 2003)***.

Although the role of anti melanocyte antibodies in vitiligo is still not well known, high levels of circulating auto antibodies have been found in about 10% of patients, especially against tyrosinase one and two (TRP-1andTRP-2) ***(kemp et al., 2011)***. However, their detection could be linked to the damage of keratinocytes and melanocytes ***(Le Poole & Lutin, 2008)***. In addition, other antigenic proteins have been detected in vitiligo, including glycoprotein 100 (gp100) and melanoma antigen recognized by Tcells1 (MART-1) ***(Naughton et al., 1983; Lannela et al., 2016)***.

Several studies showed CD4+ and CD8+ lymphocytes in the dermal-epidermal junction of areas of skin near a vitiligo lesion, highlighting the activation of cell mediated immunity ***(Oyarbid et al., 2006 and Zhou et al., 2012)***.

An invitro study identified the presence of cytotoxic T-lymphocytes, that kill melanocytes in peri lesional skin ***(Vanden et al., 2009)***. The frequency of these lymphocytes correlates with both the extent and activity of the disease ***(Lang et al., 2001)***.

More specifically, it was demonstrated that reduction of regulatory T cells (Tregs) in the peripheral blood and their dysfunctional activity raised the damage of melanocytes in vitiligo patients ***(Ben Ahmed et al., 2012; Lili et al., 2012 and Dwivedi et al., 2015)***.

There are many unclear essential points about the breakdown of self-tolerance in pathogenesis of vitiligo as already reported in other autoimmune diseases ***(Greco et al., 2013a; Greco et al., 2015; Granata et al., 2015)***. B lymphocyte activating factor of the tumour necrosis factor family (BAFF) is considered one of the elements mediating this breakdown as it can regulate the activation of both B and T cells. Excessive expression of BAFF may result in breakdown of the self-tolerance and subsequent autoimmune reactions involved in pathogenesis of vitiligo via several possible mechanisms ***(Xiran et al., 2011)***.

Cytokines also have been studied in vitiligo, which is considered a Th1-related disease. Indeed, it has been reported that there is a significant increase in tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), and IL-10 ***(Taher et al., 2009 and Speeckaert et al., 2015)***. IL-17 also has been found at higher levels in the blood and tissues of patients. Its activity influences the production of TNF-α, which is also elevated in vitiligo. Inaddition, it has been shown that the persistence of vitiligo is related to IL-17 levels ***(Bassiouny and Shaker, 2011)***.

ii. Adhesion defect theory:

Gauthier et al. (2003b) postulated that non-segmental vitiligo (NSV) could be caused by chronic detachment of melanocytes provoked by trauma, mainly mechanical rubbing

of healthy skin. This concept is now known as "melanocytorrhagy theory". Indeed, it was reported that vitiligo patients showed Köebner phenomenon in up to 31% of the Caucasian population ***(Njoo et al., 1999)***. Koebnerization in vitiligo is now considered as a migration of melanocytes through the epidermal basal skin layer ***(Gauthier et al., 2003a)***.

Furthermore, an autoimmune activation could be provoked by dendritic cells or memory T cells detecting auto-antigens during melanocytorrhagy through the epidermis basal layer ***(Gauthier et al., 2003a)***.

Some adhesion proteins have been studied to explain the loss of melanocytes. Tenascin, an extracellular matrix molecule thought to inhibit adhesion of melanocytes to fibronectin, was increased in vitiligo patients, thus reducing melanocyte adhesion ***(Le Poole et al., 1997)***. In addition, discoidin domain receptor-1 (DDR1), a domain implicated in adhesion of melanocytes to the basal skin, has been demonstrated to be reduced in vitiligo lesioned skin ***(Ricard et al., 2012)***.

iii. Biochemical theory:

It has been speculated that an alteration of redox balance in vitiliginous skin could lead to melanocyte damage and cause hypopigmented macules ***(Khan et al., 2009; Bassiouny and Shaker, 2011 and Speeckaert et al., 2015)***.

It was also demonstrated that patients with vitiligo had a raised level of H2O2 ***(Schallreuter et al., 1999)***. Indeed, an increment in superoxide dismutase (SOD) activity was reported by several authors ***(Dammak et al., 2009; Sravani et al., 2009)***. However, there may be several reasons why H2O2 level can be raised in several ways in vitiliginous skin. Firstly, an increase of nitric oxide synthase (NOS) and nicotinamide adenine dinucleotide phosphate oxidase (NADPH) activities ***(Hann et al., 2000);*** secondly, an increase in monoamine oxidase A (MAO-A), that causes a direct and an indirect cytotoxic action by increasing catecholamine production ***(Morrone et al., 1992)***. This could explain why mental stress facilitates the appearance of vitiligo macules by activation of the hypothalamic-pituitary-adrenal axis ***(Schallreuter et al., 1994)***. Thirdly, a rise in (6R)-L-erythro 5,6,7,8-tetrahydrobiopterin (6-BH4) levels, that leads to inhibition of the phenylalanine hydroxylase enzyme and causes a marked reduction in L-tyrosine synthesis resulting in impairment of melanin production ***(Schallreuter et al., 1994)***.

➢ Classification of vitiligo:

Vitiligo is divided clinically into two main forms, segmental vitiligo (SV) and non-segmental vitiligo respectively ***(Taieb and Picardo, 2009)*** **(Table 1)**. The latter also includes three major subsets, namely generalized vitiligo, acrofacial vitiligo, and universal vitiligo ***(Ezzedine et al., 2012a)***.

Recently, mixed vitiligo (MV) has been described as an initial SV, which later (usually several months) spreads to form bilateral NSV patches ***(Ezzedine et al., 2011a)***.

However, because the progress of vitiligo is unpredictable, it is not uncommon for NSV to evolve over time, modifying its extension and distribution. Despite this clear classification, two unclassified forms were reported, namely focal vitiligo and mucosal vitiligo ***(Faria et al., 2014)***.

Focal vitiligo is characterized by few, small, and isolated white macules without a segmental distribution that fails to progress to NSV after a couple of years from onset. Mucosal vitiligo is identified by the presence of only oral or genital mucosa involvement. However, when vitiligo affects a mucosa in the context of NSV, it is considered a true NSV ***(Lannela et al., 2016).***

Table (1): Typical Features of Segmental and Nonsegmental Vitiligo ***(Taieb and Picardo, 2009).***

	Nonsegmental Vitiligo	**Segmental Vitiligo**
Prevalence	72-95%	5-28%
Onset	Any age	Early (childhood)
Course	Progressive, with flare-ups	Rapid onset and stabilizes within 2 years
Etiology (most plausible)	Autoimmune	Neurochemical
Distribution	Symmetrical, non-dermatomal	Unilateral, dermatomal
Common site of affection	Commonly occurs at sites sensitive to pressure and friction and prone to trauma	Face
Koebnerization	Frequent	Rare
Autoimmune association	Strong	Rare
Hair involvement	In later stages	Soon after onset (>0.5 of patients have poliosis)
Response to autologous grafting	responsive with stable repigmentation	Frequently relapses insitu after autologous grafting