INTRODUCTION

Disorders of melanin pigmentation can be divided morphologically into two types: hypermelanosis and hypomelanosis. Hypermelanosis is the term used to describe an increased amount of melanin in the skin, whereas hypomelanosis is described as a lack of pigment in the skin, which therefore appears white or lighter than the normal color. Amelanosis is the term applied when there is a total lack of melanin in the skin. The term depigmentation implies loss of preexisting melanin pigmentation ***(Gilchrest et al., 1977).***

Every disease has a number of factors that characterize it, such as aetiopathogenesis, clinical features, histopathology, special diagnostic investigations and modes of treatment. Despite all these unique differences, the diagnoses of certain pigmentary disorders still pose a challenge. On the other hand, a precise diagnosis is imperative to efficiently eliminate the disease ***(Fitzpatrick and Jimbow, 1981).***

Idiopathic guttate hypomelanosis (IGH) is a common acquired type of leukoderma of unknown cause ***(Polysangam et al., 1990)***. It is found especially on the sun exposed surfaces of the forearms and legs, that is why ultra-violet rays could be a predisposing factor ***(Kim et al., 2010)***. IGH is also considered a result of skin aging ***(Savall et al., 1980)***.

The condition is more frequently observed in persons of both sexes who are 30 years of age or older, the number of lesions tends to increase with age and with sun exposure ***(Polysangam et al., 1990)***. It is proven that positive family history plays a role with IGH ***(Savall et al., 1980)*** and autoimmunity also has been suggested as causative factor ***(Kim et al., 2010)***.

The clinical picture of IGH shows multiple discrete angular, round or oval macules, usually 2 to 8 mm in diameter. The macules are off-white or porcelain in color without scale or atrophy and are located predominantly on the exposed areas of the upper and lower extremities ***(Polysangam et al., 1990)***.

The histological findings associated with IGH are hyperkeratosis, atrophic epidermis and flattened rete ridges. In addition, a decreased melanin content and reduced numbers of melanocytes compared to the perilesional normal skin. Perhaps, moderate flattening of the rete ridge and epidermal atrophy could be ascribed to skin aging ***(Kim et al., 2010)***. The ultrastructural studies have indicated that melanocytes were infrequently observed and showed degenerative changes with a decreased number and size of melanosomes with less electron density compared to the perilesional melanocytes ***(El-Ghandour et al., 2012)***.

The treatment of IGH is still challenging. It has been proven that by destroying some or the entire epidermal melanin

unit, the surrounding keratinocytes and melanocytes migrate into the affected skin and produce repigmentation ***(Goldust et al., 2013)***. The treatment nowadays is by gently freezing the lesion with liquid nitrogen to destroy the epidermis partially or completely ***(Kumarasinghe, 2004)***. Using Erbium-Yag laser for epidermal destruction has not been previously tried.

AIM OF THE WORK

The aim of this study is to assess the efficiency of using the ablative Erbium-Yag laser 2940 in the treatment of idiopathic guttate hypomelanosis.

1. HYPOPIGMENTARY DISORDERS

Changes in pigmentation can arise in a number of ways and can be due to a variety of genetic and environmental factors. Abnormalities may involve the formation of melanosomes in melanocytes, melanization of melanosomes, secretion of melanosomes into keratinocytes or the transport of melanosomes in keratinocytes with or without degradation ***(Van den Wijngaard et al., 2001; Bleehan, 2004).***

Every hypopigmented disorder has its own aetiopathogenesis, clinical features, histopathology, special diagnostic investigations and modes of treatment. History, physical examination and histopathology can quickly establish the diagnosis or at least limit the differential diagnosis. Whether the lesions are acquired or congenital, generalized or localized, stable or progressive greatly differentiates disorders from each other ***(Bleehan, 2004).***

1.1. Idiopathic Guttate Hypomelanosis (IGH)

1.1.1 Definition & Aetiology :

Idiopathic guttate hypomelanosis (IGH) was first described under this name in ***1966*** by ***Cummings and Cottel***. It is a common acquired type of leukoderma of unknown cause ***(Polysangam et al., 1990)***. Ultra-violet rays could be a predisposing factor because it is found more on the sun exposed surfaces of the forearms and legs ***(Kim et al., 2010)***. Skin aging also is a main

cause of Idiopathic guttate hypomelanosis ***(Savall et al., 1980)***. The condition is more frequently observed in persons of both sexes, the number of lesions tends to increase with age and with sun exposure ***(Polysangam et al., 1990)***. Body scrubbing could also be a trigger ***(Min-Kung Shin et al., 2011)***. In addition, HLA-DQ3 was found to be significantly associated with IGH in a group of 22 colombian renal transplant patients ***(Arrunategui et al., 2002)***. It is proven that positive family history plays a role with IGH ***(Savall et al., 1980)*** and autoimmunity also have been suggested as causative factor ***(Kim et al., 2010)***.

1.1.2 Clinical picture:

The clinical picture of IGH shows multiple discrete angular, round or oval macules, usually 2 to 8 mm in diameter. The macules are off-white or porcelain in color without scale or atrophy and are located predominantly on the exposed areas of the upper and lower extremities ***(Polysangam et al., 1990)***.

There appears to be two general types of IGH. The first is the actinic type. The second is a non actinic familial type, which does not necessarily occur on sun-exposed areas and is found particularly on the trunk ***(Ortonne1990a; Grosshans, 1994)***. A genetic predisposition is possible ***(Arrunategui et al., 2002)***. On the other hand a study evaluated the role of sun exposure in the pathogenesis of idiopathic guttate hypomelanosis revealed that a relationship between chronic actinic exposure and this disorder could not be established ***(Kaya et al., 2005)***. However

an aggregation survey disclosed a higher prevalence of idiopathic guttate hypomelanosis in family members of patients with the disease than in a control group ***(Arrunategui et al., 2002).***

1.1.3 Histopathology:

The histological findings associated with IGH are hyperkeratosis, atrophic epidermis and flattened rete ridges. In addition, a decreased melanin pigments and reduced numbers of melanocytes compared to perilesional normal skin. Perhaps, moderate flattening of the rete ridge and epidermal atrophy could be ascribed to skin aging. The ultrastructural study has indicated that melanocytes were infrequently observed and showed degenerative changes with a decreased number and size of melanosomes. However, some specimens had normal melanocytes with a decreased number of melanosomes. Therefore, the decrease in the pigmentation found in IGH lesions might be due to a decrease in melanocytes or, in some cases, due to dysfunction of the melanocytes. The exact mechanism underlying IGH is still unclear ***(Kim et al., 2010; El-Ghandour et al., 2012)***.

Most of the melanocytes are rounded in form and either lacked dendrites or have fragmented ones. Ultrastructural study confirmed the progressive loss of epidermal melanocytes in skin affected by IGH and revealed two types of melanocytes, healthy

melanocytes with normal melanogenic activity and melanocytes containing few or no immature melanosomes but showing no melanogenic activity ***(Loquai et al., 2005)***. Another ultrastructural study revealed a decrease in the melanin content of affected epidermis and pigment granules were irregularly distributed. There was a decrease in the number of dopa-positive melanocytes in hypomelanotic macules ***(Wallace et al., 1998)***.

Depigmentation in IGH seems to occur in two stages, loss of melanogenic activity in certain melanocytes and elimination of inactive melanocytes. The basic defect in IGH melanocytes may reflect the aging process ***(Ortonne et al., 1990a; Ortonne et al., 1990b)***. Additional features included flattening of the dermal-epidermal junction, a moderate to marked reduction of the melanin granules in the basal and prickle cell layers, epidermal atrophy, and basket-weave hyperkeratosis ***(Wallace et al., 1998; Loquai et al., 2005)***.

1.1.4 Treatment:

Intralesionel injection of steroids was tried ***(Kim et al., 2010).*** Furthermore, minigrafts of normal skin implanted in IGH lesion was used but was not successful ***(Flabella et al., 1987)***. Localized superficial dermabrasion was suggested by ***Hexsel (1999)*** but was ineffective. A recent study reports limited success of the 1% pimecrolimus cream in inducing repigmentation in this hypomelanotic disorder ***(Asawanonda et al.,2010).*** Application of topical Tacrolimus was studied at a

regimen of twice daily for six months, yet the cost was very high and the improvement was not satisfactory. Some patients even showed mild burns after its use ***(Reknimitr et al., 2013).***

It has been proven that by destroying some or the entire epidermal melanin unit, the surrounding keratinocytes and melanocytes migrate into the affected skin and produce repigmentation. So another method was attempted by gently freezing the lesion with liquid nitrogen to destroy the epidermis ***(Polysangam et al., 1990). Kumarasinghe et al. (2004)*** also demonstrated that a 3-5 seconds liquid nitrogen freeze appears to be sufficient compared to the 10 seconds freeze previously reported for the treatment of IGH. This technique is safe, quick, low in cost and effective, and avoids at the same time the side effects associated with a longer freeze, like scarring. It also demonstrates that vesiculation is not necessary to achieve the repigmentation response.

A very recent study evaluated the effect of carbon dioxide laser therapy on IGH. The hypopigmented lesions were treated using a 10,600-nm carbon dioxide fractional laser (CO_2FL). Two months after a single treatment, physician's clinical assessments were performed and the patient's overall satisfaction was evaluated. The study was done on 40 patients, and the results showed more than 50% improvement in 36 patients (90%). Although a few patients complained of long-

standing erythema and post inflammatory hyperpigmentation, these problems spontaneously resolved within 2 months after assessment. No other noticeable side effects were observed ***(Shin et al., 2012). Goldust et al. (2013)*** applied 10,600 nm fractional carbon dioxide lasers on 240 patients, two months after a single treatment, 115 patients (47.9%) exhibited more than 75% clinical improvement, 100 patients (41.6%) achieved 51– 75% clinical improvement, whereas 25 patients (10.3%) showed 25–50% clinical improvement. In addition, 95 of the 240 patients (39.6%) were very satisfied with their clinical outcomes, 102 (42.5%) were satisfied and 43 patients (17.9%) were slightly satisfied. No patient was unsatisfied with the treatment Moreover; there were no noticeable adverse events, such as infection, scarring and aggravation. All patients experienced pain during the treatment, as well as a burning sensation and erythema after the treatment. However, they subsided within a day, and post-treatment crusting spontaneously disappeared within a week. Long standing erythema persisting for more than a month was observed in fifteen patients (6.2%), but it spontaneously resolved within the following 2 months. Thirty patients (12.5%) reported post inflammatory hyperpigmentation at the treated sites and also spontaneously regressed within 3 months ***(Goldust et al., 2013).***

1.2 Vitiligo

1.2.1 Definition :

Vitiligo is the most common of all pigmentary disorders, it is an acquired skin disorder caused by the disappearance of pigment cells from the epidermis that gives rise to well-defined white patches which can change in shape and size over time ***(Westerhof, 2000; Van den Wijngaard et al., 2001)***.

1.2.2 Aetiology :

The aetiology of vitiligo could be genetic predisposition ***(Casp et al., 2002),*** the nervous system ***(Bystryn, 2000)***, autoimmunity ***(Naughton et al., 1983; Cui et al., 1992)*** and oxidative stress ***(Passi et al., 1998)***. A convergence theory combining all these pathogenic hypotheses have also been suggested ***(Le Poole et al., 1993a)***. Between 30 and 40% of patients have a positive family history, and a genetic factor is undoubtedly involved. No age is immune to vitiligo, but in 50% of cases it develops before the age of 20 years. The condition is gradually progressive, sometimes extending rapidly over a period of several months and then remaining quiescent for many years ***(Majumder et al., 1993; Bradley, 2002)***. Very often vitiligo begins to appear after a psychological or a physical trauma, it is characteristic of at least a third of vitiligo patients ***(Van Geel et al., 2011)***. Many patients related onset to sun exposure; which is a factor that induces koebnerization in

predisposed individuals ***(Halder et al., 1987; Taieb, 2000)***. Radiotherapy could also induce koebnerization of vitiligo in cancer patients ***(Phiske, 2013)***.

A study has demonstrated an incidence of vitiligo as 0.5-4 percent **o**f population ***(Kovacs, 1998)***.Vitiligo can affect all races, dark skin types are more affected though. Both sexes are affected equally; but females tend to express a deeper concern and seek medical advice more often than do men, due to the cosmetic aspect of the disease ***(Hann and Nordlund, 2000).***

1.2.3 Clinical picture:

Hypomelanotic macules are usually first noted on the sun-exposed areas of skin, on the face or on the dorsum of hands. These macules later turn milky white. Some patients complain of itching at the site of vitiligo macules while others present with sunburn ***(Kemp et al., 2001; Nordlund et al., 2006).*** The sites of hypomelanotic macules may vary; usually the hyper-pigmented areas are more affected, such as the face, axillae, groins, areolae and genitalia. Areas subjected to repeated friction and trauma are also likely to be affected, for example the dorsum of hands, feet, elbows, knees and ankles. The distribution of the lesions is usually symmetrical, although sometimes it is unilateral and may have a dermatomal arrangement ***(Hann and Nordlund, 2000; Nordlund et al., 2006)***. Clinical picture of vitiligo could be segmental unilateral, focal, symmetrical bilateral, acrofacial, inflammatory and

trichrome. Some very few cases develop generalized vitiligo, although a few pigmented areas almost always remain. The pigment loss may be partial or complete, or both may occur in the same areas (trichrome vitiligo). Confetti macules**,** which are typical in color but only 1 to 2mm in diameter, may occur randomly or may be perifollicular. It could appear up to hundreds of macules, small or large, in a single patient ***(Bleehan, 2004)***. The macules increase irregularly in size and fuse with neighboring lesions to form complex patterns. The hairs in the patches frequently remain unchanged, but in older lesions the hairs too become amelanotic ***(Nordlund et al., 2006)***. The margins of the lesions may become hyperpigmented. The distribution, age of onset and hyperpigmented border will suggest the diagnosis. Spontaneous repigmentation could happen in about 10–20% of patients, most frequently in sun-exposed areas. It is usually seen in younger patients ***(Bradley, 2002 and Bleehan, 2004)***. Usually the diagnosis of vitiligo is by direct clinical inspection followed by examination of the depigmented area under wood's light.

1.2.4 Histopathology:

The histological features of vitiligo reveal basal hypopigmentation and dermal inflammatory infiltrates. Other features include hyperkeratosis, acanthosis, exocytosis, spongiosis, rete ridge elongation, telangiectasia ***(Kim et al., 2008)***. Perilesional skin specimens demonstrate melanocytes with dilated endoplasmic reticulum, granular deposits,

prominent golgi apparatus and vacuolization. There are no intact melanosomes in the melanocytes or in the keratinocytes. There is also increased cellularity of the dermis ***(Kim et al., 2006).*** Vitiligo persisting for long time with no treatment is characterized by a complete loss of melanin and absence of melanocytes from the epidermis. This has been proven via conducting an immunohistochemical study using a panel of 18 antibodies against melanocytes, none of which detected their presence ***(Le Poole et al., 1993a; Abdulla et al., 2003).***

The ultrastructure specimens of vitiligo show residual melanocytes with melanosomes. Intact melanosomes are rarely seen but there are a lot of poorly-melanized melanosome organelles. They also show dilated rough endoplasmic reticulum and vacuolization ***(Panuncio and Vignale, 2003).*** The architecture of the suprabasal keratinocytes is completely distorted. The presence of desmosomes is the key feature that identifies keratinocytes. Most cells have irregular nuclei. Some cases show dilated Golgi complex and fragmented tonofilaments may be seen. Despite the presence of desmosomes, the intercellular space appears increased and is filled by granular deposits with moderate electron density. Other keratinocytes show dilated endoplasmic reticulum and fragmented intermediated filaments, distributed homogeneously. Few secondary melanosomes can also be observed in keratinocytes ***(Panuncio and Vignale, 2003 and El-Ghandour, 2012).***

However, there are some sporadic reports that indicate that vitiligo lesions are not fully devoid of melanocytes. For example, it was demonstrated that melanocytes could be isolated and established in vitro from all samples of lesional and normal skin, independent of disease duration and treatment ***(Kim et al., 2008).*** It was also proven that there are in fact, dopa positive melanocytes in the epidermis of lesional vitiligo (***Husain et al., 1982)*** and that melanin pigmentation may remain for a period of time after the development of the disease ***(Tobin et al., 2000)***. Furthermore non negligible amounts of melanin were detected in basal keratinocytes in 1-3 year old vitiligo lesions. Also, melanocytes and melanin pigments may be observed in the border areas around lesions of vitiligo ***(Bartosik et al., 1998)***. Therefore, there is a suggestion that there is no relationship between the duration of vitiligo and the number of melanocytes, or amount of pigment, and the possibility of intact melanogenesis or melanin transfer in vitiligo is highly suggested ***(Kim et al., 2008)***.

1.2.5 Treatment:

There are multiple modalities for treatment of vitiligo. This includes photochemotherapy ***(El–Mofty et al., 2010)*** and surgical treatment ***(Van Geel et al., 2010).***Steroids can also be effective in recent onset vitiligo and in stopping the progression of vitiligo in general ***(Lee et al., 2010).*** Cosmetic camouflage could also be done as make up and tattoos ***(Van Gal et al., 2001).*** The content of cosmetic creams and the technique for