

## Idiopathic Guttate Hypomelanosis: A Mini Review

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### Abstract

Idiopathic guttate hypomelanosis is a common, acquired and benign dermatosis characterized by multiple, round or oval, hypopigmented to depigmented macules which mainly appear in upper and lower extremities. The major histopathologic findings are the reduced number of melanocytes in combination with structural (limited melanosomes and dendrites) or functional alterations (decreased tyrosinase activity). Although the underlying pathways are still being elucidated, genetic and environmental factors have been incriminated in its pathogenesis. Although accumulating number of studies supports the central role of sun exposure, a definite causal relationship cannot still be established. Despite the lack of symptoms idiopathic guttate hypomelanosis is a main aesthetic problem. Intense research has oriented towards the development of treatment modalities ranging from topical agents to invasive procedures. Until now the results are encouraging but they still need to be verified by future clinical and epidemiological studies.

**Keywords:** Melanocytes; Pigmentation; Sun exposure

### Introduction

Idiopathic guttate hypomelanosis (IGH) represents a benign dermatosis which was first described in 1951 by Costa as «symmetric progressive leukopathy of the extremities» [1]. Fifteen years later Cummings and Cottel confirmed its incidence in a large number of patients and they introduced the term IGH in clinical practice [2]. IGH is characterized by multiple, round or oval, hypopigmented to depigmented macules ranging in size from 0.2 to 2 cm [3,4]. The macules appear in descending order of frequency in upper and lower extremities, trunk and face. Usually the total number increases with time, whereas the size remains unchanged [5]. Most patients are asymptomatic even though some individuals mention mild itching [3].

### Prevalence

The incidence of IGH is associated with advancing age. Although it affects nearly 87% of the population aged more than 40 years, it may also be present in young adults into the 20s and 30s [3,4]. Notably, a patient appeared IGH at the age of 3 years [4]. Epidemiological studies show that IGH occurs more commonly in females [4,6], whereas other investigators suggest that this slightly higher frequency concerns only young women because they consider IGH as a major aesthetic problem [4]. IGH appears in all types of skin but it is more distinct in dark skinned individuals [6,7].

### Pathogenesis

It is widely accepted that there is not enough information available in the published literature regarding the etiology and the mechanisms of the initiation and propagation of IGH. Despite the fact that the underlying pathways are still being elucidated, the pathogenesis of IGH seems to be complex and multifactorial. Its high incidence in

adult population suggests that not only genetic but also environmental factors are the most plausible causes [6,8].

The central role of hereditary factors in the pathogenesis of IGH was pointed out in a relatively recent study in which IGH occurrence in renal transplant patients was positively associated with HLA-DQ3 and negatively associated with HLA-DR8 [9]. In addition prior investigators had reported that IGH appears more frequently in patients with positive family history [6].

Sunlight has been long incriminated in the pathogenesis of IGH because lesions are mainly located at sun exposed body areas [3]. Interestingly when IGH appears in face, the distribution of the macules presents many similarities to that of Squamous Cell Carcinoma, which is correlated to sun exposure. The aforementioned clinical observations are further supported by histopathological findings like solar elastosis and epidermal atrophy, which are indicative of actinic damage [3]. Moreover the formation of IGH-like macules in patients during psoralen plus ultraviolet A light therapy (PUVA) or narrowband ultraviolet B phototherapy (NB-UVB) strengthens the widely held belief that IGH correlates directly with ultraviolet (UV) radiation [10]. Indisputably, sunlight plays a pivotal role in the pathogenesis of IGH but yet a definite causal relationship cannot be established. Although face and neck are constantly exposed to the sun, only a small percentage of patients have IGH lesions on these areas [4,6]. Furthermore the appearance of macules in body zones that are scarcely sun exposed raises important questions concerning the contribution of UV radiation to IGH pathogenesis. The answer is undoubtedly complex but the investigators of a study noticed that 90% of the patients, diagnosed prior to 10 years old, had lesions only on sun exposed areas such as face and arms, indicating that the role of sunlight in the development of IGH may differentiate depending on the age [4].

Repeated trauma is also included in the precipitating factors of IGH. High incidence of lesions on the anterior surface of tibias, where subcutaneous tissue is less, and in persons using body scrubs clearly

shows that the successional irritation of vulnerable body parts may essentially contribute to the formation of IGH lesions [3].

An increasing body of histopathological studies supports that the main trigger mechanism which leads to IGH is the reduction of melanocytes in combination with structural or functional alterations [4,6]. That decrease was not observed in another study which examined the punch biopsy specimens of four patients but the investigators attributed this finding to the recent onset of IGH suggesting that the last may possess different features depending on its duration [11]. Another researching team postulated that melanocytes of the IGH lesions had less or no dendrites and limited number of melanosomes [7]. The presence of defective melanocytes is supported by an ultrastructural study which revealed dilatation of the endoplasmic reticulum and swelling of the mitochondria [4]. Particularly important are the results of a study which demonstrated, by DOPA histochemistry, the decreased tyrosinase activity of the melanocytes [5]. Wallace et al. investigated if the previously mentioned features of the IGH lesions are ascribed to the perturbation of the melanocytes differentiation process, but the scarce appearance of undifferentiated melanocytes implies their minor contribution to the pathogenesis of IGH [12]. Several lines of evidence have emerged suggesting that the depigmented macules are formed because of the inability of keratinocytes to insert the melanosomes by phagocytosis. The normal number of melanocytes and the significantly reduced number of melanosomes in the cytoplasm of keratinocytes corroborate the aforementioned point of view [11].

The potent role of local factors in the development of IGH was documented by investigators who observed repigmentation of human IGH lesions and increased number of melanocytes, twenty days after their transplantation to nude mice models [13]. Falabella et al. transplanted skin from IGH lesions to individuals with normal skin and vice versa. After eighteen months they observed that IGH lesions not only were present but also they were slightly enlarged. Simultaneously the minigrafts of normal skin became depigmented clearly showing that IGH is promoted by an active process [6].

## Histopathology

The main histopathological findings observed in IGH lesions are basket weave hyperkeratosis and decreased number of melanocytes [3,6]. As stated previously, melanocytes may have less melanosomes, dilated endoplasmic reticulum, swelled mitochondria and attenuated dendrites [4]. Melanosomes contained in the adjacent keratinocytes may be reduced or even absent [11]. Additionally, researchers have noticed the appearance of atrophic epidermis and flattened rete ridges [6]. In the dermis fibroblasts, elastic and collagen fibres appear to have normal configuration [11]. Areas of elastosis are often observed in the papillary dermis because of the correlation of IGH with sun exposure [3]. Although IGH is a non inflammatory skin disorder, the examination of facial IGH lesions revealed that 85% of them had mild infiltration by mononuclear inflammatory cells which were gathered in the perivascular region of the upper dermis [3].

## Dermoscopy

The dermoscopic study of IGH lesions reveals the existence of normally pigmented specks scattered within the macules and perimetric pigmented extensions. IGH may be developed according to four patterns, which are nebuloid, petaloid, amoeboid and feathery. The first three patterns concern hypopigmented to depigmented

macules with smudged borders, polycyclic margins and pseudopod-like extensions respectively. In the fourth pattern macules are irregularly pigmented, the margins are feathery and also the presence of whitish areas in the centre of the lesions has been mentioned [14,15]. In addition researchers have reported the correlation of the patterns with the duration of IGH. Petaloid, amoeboid and feathery patterns are usually observed in long-standing lesions, whereas the nebuloid pattern is detected in recently formed macules [15].

## Differential Diagnosis

The differential diagnosis of IGH includes vitiligo, pityriasis versicolor, pityriasis alba, tuberous sclerosis, lichen sclerosis and atrophicus, guttate morphea, hypopigmented flat warts and post-inflammation hypomelanosis [3,8]. IGH is frequently confused with vitiligo of early stage. Their differentiation is necessary, especially in societies that consider vitiligo as social stigma, in order feelings like depression, reduced self - estimation and social withdrawal to be avoided. Present melanocytes, even reduced or defective, is the main feature for the discrimination of the above skin disorders. IGH is distinguished from the rest dermatoses based on the different size and distribution of the lesions, the age of onset and the absence of fine scale and clinical signs of prior dermatitis or virus infection [3,8].

## Treatment

Since beauty standards present the flawless body as absolutely desirable, IGH is considered one of main aesthetic concerns, leading to the development of various treatment options.

In recent years, lasers represent the most promising solution for many skin disorders. Fractional lasers are used in order to induce repigmentation with satisfactory results. It is speculated that the thermal damage, caused by lasers, is the key determinant for the removal of dysfunctional melanocytes and the induction of a healing process which stimulates the secretion of cytokines and growth factors and enhances the recruitment and proliferation of the surrounding melanocytes. The effect of fractional CO<sub>2</sub> laser therapy on IGH was explored in two clinical studies. In both studies, two months after a single use, a significant percentage of patients ranging from 41.6% to 90% exhibited more than 50% improvement according to the assessments performed by dermatologists and simultaneously more than 82% of the patients expressed their satisfaction. Despite the encouraging results, few patients exhibited erythema and post-inflammation hyperpigmentation which are common side effects of the fractional CO<sub>2</sub> laser therapy, and especially in dark skinned individuals because of its deep penetration into the dermis [16,17]. The choice of non-ablating fractional laser is suggested based on the evidence derived from a clinical study conducted by Rerknimitr et al. The investigators used fractional Ytterbium/Erbium fibre laser once a week, for 4 weeks, for the treatment of two lesions from one side of the body, whereas two lesions from the other side served as control. At the end of the study the improvement score evaluated by dermatologists and the patients' overall satisfaction were significantly higher in the treatment group compared to the control group. None of the patients exhibited post-inflammation hyperpigmentation. Side effects included oedema and erythema lasting from 24 to 72 hours and bronzing which abated in the next 4-6 weeks [18].

Cryotherapy is an alternative treatment for IGH. The mechanisms by which repigmentation is achieved are probably related to the inactivation of inhibitory enzyme or other chemokines participating in

melanogenesis and the removal of the defective keratinocytes [19]. Thorough examination of the lesions treated with cryotherapy substantiated the induced increase of the melanogenic activity as well as melanin pigment. Nevertheless, the total number of melanocytes remained low in comparison to normal skin [12]. According to another point of view cryotherapy may activate inflammatory pathways enhancing post-inflammation hyperpigmentation [19]. Data about the efficacy of the method are limited as only two studies have been mentioned in the medical literature. In the first study 90.8% of the treated lesions were repigmented 6-8 weeks after being gently frozen with liquid nitrogen, which was applied with a cryoprobe for 10 seconds. Despite the satisfactory results, it seemed that the formation of vesicles was required in order repigmentation response to be achieved [20]. Similar degree of repigmentation, without the risk of blistering and scarring, was documented by other investigators by using a liquid nitrogen spray gun for 3-5 seconds [19].

Dermabrasion has become very popular among dermatologists as a preferable treatment for many skin disorders. Hexsel et al. examined the effect of superficial dermabrasion on the IGH lesions of twenty patients. Although repigmentation was achieved in 80% of the patients, the initial enthusiasm was limited because of the subsequent erythema which insisted for 6 months [21]. Another researching team chose spot peel with 88% phenol, which is cheap, simple and safe, for the treatment of IGH. Repigmentation was observed in 64% of the treated lesions [22]. The inflammation induced by both dermabrasion and local application of phenol may result to the secretion of chemokines that stimulate the surrounding melanocytes to migrate and proliferate [23].

Another interesting study identified the topical application of retinoids as a potent therapeutic choice. Treatment of IGH macules with progressively increased tretinoin for four months was able to induce clinical improvement and essential histopathological improvement like redevelopment of rete ridges and augmentation of melanin density throughout the whole epidermis [24].

The repigmentation response after either intralesional injection of triamcinolone or implantation of normal skin into the centre of IGH lesions or their combination was evaluated by Falabella et al. Repigmentation was satisfactory only when triamcinolone was injected either alone or in combination with the implantation, probably due to its immunosuppressive action, whereas only one of the fifteen patients in whom minigrafts were implanted exhibited good repigmentation [6].

In recent years research has oriented towards calcineurin inhibitors which are immunosuppressive agents able to promote the recruitment and proliferation of melanocytes and to increase not only the activity of tyrosinase but also its expression in human melanocytes [25,26]. The topical application of either 1% pimecrolimus cream or 0.1% tacrolimus ointment on IGH lesions enhance their repigmentation after 2 and 6 months respectively. Despite the satisfactory results, the time required for their achievement and the high cost are important limiting factors [27,28].

## Conclusions

Disorders of pigmentation affect a large proportion of the population and according to current epidemiological evidence their prevalence shows essential rise, causing great concern not only for human health, but also for the induced social implications [29]. IGH is a common, acquired disorder of pigmentation which has become the

focus of scientific research in order new treatment options to be developed. The present article is a systematic review of the available information derived from experimental and clinical studies about the pathogenesis, histopathological and dermoscopic features and the therapeutic approaches of IGH.

Undoubtedly researches of the past years have significantly contributed on acquiring improved knowledge, but still the pathways underlying the pathogenesis of IGH remain obscure. Although IGH is characterized by lack of symptoms, it represents a major aesthetic problem, affecting both men and women. Various treatments have been proposed with promising results, but the small number of studies substantiating the benefits of those methods is a major limiting factor.

In conclusion the conduction of large scale clinical and epidemiological studies in the future is necessary in order to obtain in depth knowledge of IGH and to develop successful treatment modalities, compatible to the needs of each patient.

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