Progressive macular hypomelanosis (PMH) treatable but often misdiagnosed
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1 GENERAL INTRODUCTION AND AIMS OF THE THESIS
Historical background and terminology

Until recently progressive macular hypomelanosis was an unknown disease entity. The term “progressive macular hypomelanosis” was coined by Guillet et al. (1985, 1988, 1992) in the 1980s to describe a pigment disorder in people of mixed racial (Negroid and Caucasoid) ancestry living in France, but originating from the French Caribbean islands. In the Netherlands patients with an identical clinical picture were identified by Menke et al. (1989, 1997, 2006) in the mid-1980s. They designated this condition “nummular and confluent hypomelanosis of the trunk”.

A similar entity was also reported by several other authors from different parts of the world, with many descriptive names being used to identify it. Borelli (1987) from Venezuela named the condition “cutis trunci variata”; Lesueur et al. (1994) from Martinique, West Indies, called it “creole dyschromia”; Fitzpatrick (1996) from the USA used the term “idiopathic multiple large macular hypomelanosis”. Recently Di Lernia and Ricci (2005) assumed that PMH and extensive pityriasis alba (EPA), as described by Zaynoun et al. (1983, 1986), are the same disease, based on the clinical and histological characteristics of both entities, however, although the clinical characteristics are similar, there are differences in the histological characteristics, with EPA showing histologically eczematous characteristics and PMH only diminished pigment in the epidermis.

Nowadays most authors choose for the term PMH, and until the aetiology of the condition is fully established this can be considered a plausible choice.

Epidemiology

Although the true prevalence of PMH is unknown, it seems to be a common disorder. In 2005 at The Netherlands Institute for Pigment Disorders (SNIP) 48 patients were diagnosed with PMH, compared to 23 patients with pityriasis versicolor and 17 patients with pityriasis alba. The number of PMH patients seen each year at the SNIP has been growing since. Lesueur et al. (1994) identified 121 patients with PMH during a systematic screening of 511 patients for leprosy in Martinique. In 2006 Kumarasinghe et al. (2006) mentioned that PMH was a common skin disorder in Singapore, although the exact number of patients was not given. PMH is probably more often diagnosed in countries with a population with darker skin types for the obvious reason that white spots are more easily recognized in pigmented skin. Contact with colleagues from Ivory Coast, Colombia, Brazil, the West Indies, India,
Sri Lanka, Singapore, Indonesia and The Philippines indicates that this disorder is most likely prevalent in many parts of the world. At the SNIP women seem to be predominantly affected with PMH. Guillet et al. (1985, 1988, 1992) observed PMH mainly in women, but Borelli (1987) mentioned an equal distribution in both sexes. PMH is mostly observed in adolescents and young adults (Menke et al. 1997, Lesueur et al. 1994, Fitzpatrick 1996). Guillet et al. (1992), Borelli (1987) and Fitzpatrick (1996) recognized PMH only in racially mixed people, but at the SNIP we have seen the disorder in a variety of patients of mixed and “unmixed” ethnicities. Kumarasinghe et al. (2006) observed PMH in Chinese, Mongoloid and Indian people.

**Histology and electron microscopy**

Guillet et al. (1992) as well as Kumarasinghe et al. (2006) performed histological examinations on the skin of PMH patients. Hematoxylin-eosin staining of the skin of hypopigmented spots showed only a subtle decrease in melanin content in the epidermis compared with that in normal adjacent skin. There was no significant inflammatory infiltrate or epidermotropism of leukocytes. Fontana-Masson-staining showed overall reduction in melanisation of the basal cell layer of lesional skin. Melanocytes stained negative for HMB 45 and Melan A stains. S100 staining did not detect any differences in the number of melanocytes, Langerhans cells, or other dermal dendritic cells. Occasional melanophages were noted in the dermis of both lesional and normal skin on hematoxylin-eosin and CD68 staining.

**Etiology and Pathogenesis**

Borelli (1987) considered PMH to be a genodermatosis, based on the fact that he observed the disorder in family members. According to Guillet et al. (1992) correlation of clinical and electron microscopic findings led to the hypothesis that the gene pair partly determining the Negroid type of melanin production in mixed races could be inactivated, at least temporarily, under several unknown conditions, thereby producing a switch from Negroid to Caucasoid melanogenesis. Fitzpatrick (1996) suggested that the hypopigmentation of PMH might originate from a fungal infection, with the pigment changes remaining long after the infection had disappeared.
In 2001 Westerhof observed a red follicular fluorescence in the hypopigmented spots that was not present in normal adjacent skin, while examining patients with PMH under strictly blinded conditions in a dark room using a Wood’s lamp. This gave rise to further investigations.

**Clinical characteristics**

PMH is a morphologic entity characterized by ill-defined nummular hypopigmented macules, symmetrically localized predominantly on the trunk, but sometimes progressing to the neck and the face and the proximal parts of the extremities. In the majority of patients, a rather well defined hypopigmented area that appears to originate from a confluence of macules can be recognized on the front and back of the trunk. The width of this confluent region varies from patient to patient. In the lateral regions of the trunk, more or less round solitary macules can be recognized (Figure 1). Kumarasinghe et al. (2006) also observed the macules on the buttocks and thighs. There seems to be no history of pruritus, pain, or a preceding inflammatory dermatosis.

The clinical descriptions provided by Guillet et al. (1992), Menke et al. (1997), Borelli (1987), Lesueur et al. (1994) and Kumarasinghe et al. (2006) correspond to a large
extent with our observations. However, Guillet et al. (1992) have stated that the macules were absent in the dorsolumbar line, something we could not confirm. Additional laboratory tests (ESR, complete blood count, blood glucose, liver enzymes and urea) and urine analysis were within normal limits and potassium-hydroxide tests of skin scrapings were negative (Menke et al. 1997), Kumarasinghe et al. 2006). Guillet et al. (1992) ruled out leprosy as a cause after performing physical examination and obtaining a skin biopsy. Furthermore Guillet et al. (1992) and Menke et al. (1997) reported negative serology tests for syphilis.

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Clinical implications for patients

In the Netherlands PMH is mainly a cosmetically disturbing disorder. However, especially in tropical countries were leprosy is endemic, patients may worry about the probability of having leprosy when they see the hypopigmented spots on their skin.

Differential Diagnosis

PMH should be distinguished from other disorders with acquired hypopigmentation appearing only or mainly on the trunk. Such disorders can be divided into four groups:

1. Hypomelanosis caused by non-bacterial / non-fungal inflammatory skin disorders, i.e. pityriasis alba and post inflammatory hypopigmentation (e.g. after atopic dermatitis, contact dermatitis and psoriasis).
2. Hypomelanosis caused by leprosy, i.e. hypopigmented macules in borderline tuberculoid leprosy or borderline lepromatous leprosy.
3. Hypomelanosis caused by fungi and yeasts, i.e. pityriasis versicolor and seborrhoic dermatitis.
4. Hypomelanosis caused by proliferative neoplastic disorders, i.e. hypopigmentation in cutaneous T-cell lymphoma (mycosis fungoides).

Table I summarizes the important differences between these skin disorders.

Treatment

Most authors who described PMH did not mention any effective treatment. Menke et al. (1997) attempted several treatment modalities, including topical and systemic antifungal agents and topical corticosteroids, but none of these treatments were successful. They observed disappearance of the hypopigmented spots with
psoralen plus UVA (PUVA) therapy; however, after cessation of this treatment, the induced pigmentation disappeared which resulted in exactly the same pattern of hypopigmentation as before.

**Prognosis**

Guillet *et al.* (1992) suggested that PMH disappeared spontaneously within 3-5 years. Menke *et al.* (1997) could not confirm this spontaneous regression; on the contrary, the disorder appeared to be stable during a follow-up period of 10 years, and spontaneous repigmentation was never seen. Lesueur *et al.* (1994) found the disorder to be persistent for more than 25 years. The fact that it has never been observed in elderly people indicates a spontaneous disappearance after young adulthood.
Aims of the thesis

PMH is a common skin disorder occurring worldwide. In our experience it has frequently been disregarded or misdiagnosed and consequently mistreated. It is often considered a postinflammatory hypopigmentation after either pityriasis versicolor or an inflammatory dermatosis such as atopic dermatitis. There is still much confusion whether PMH is a separate entity or part of (or a remainder of) an existing (hypopigmented) skin disorder. To gain a better insight in this skin disorder we conducted the following studies.

We noticed that in patients with PMH a red, follicular fluorescence can be observed in lesional skin, which is absent in the adjacent normal skin, when the skin is illuminated.

Table I Differential diagnosis of progressive macular hypomelanosis

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Clinical features</th>
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<tbody>
<tr>
<td>Progressive macular hypomelanosis</td>
<td>Symmetric, hypopigmented, ill defined spots mainly on the trunk, sometimes on the proximal extremities; non scaling, non itchy</td>
</tr>
<tr>
<td>Pityriasis versicolor</td>
<td>Irregular hypopigmented, sharply defined, often asymmetric spots; mottled distribution; scaling; mostly on neck and trunk, sometimes elsewhere</td>
</tr>
<tr>
<td>Pityriasis alba</td>
<td>Oval or irregular hypopigmented plaques; well defined border; fine lamellar scaling; initially erythematous; predilection for face, sometimes neck upper trunk and proximal extremities; usually disappearing in a few months or changing place; may be pruritic</td>
</tr>
<tr>
<td>Borderline tuberculoid leprosy, Borderline lepromatous leprosy</td>
<td>Hypopigmented macules with varying symmetry; remaining in exactly the same place; few to multiple lesions; marked to mild loss of sensation to fine touch</td>
</tr>
<tr>
<td>Mycosis fungoides</td>
<td>Circular or oval areas of hypopigmentation with well or ill defined borders on trunk and extremities, rarely the face; often symmetric; pruritus is variable</td>
</tr>
<tr>
<td>Post inflammatory hypopigmentation</td>
<td>positive history of former skin disorders; restricted to sites of primary lesion;</td>
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with a Wood’s lamp in a dark room. This ignited the idea that this could possibly be the result of porphyrin producing microorganisms like Propionibacterium acnes (P. acnes), which are known to show red follicular fluorescence under UV irradiation (or Wood’s light) (Johnsson et al. 1987). The observation of this fluorescence in lesional skin of PMH patients gave rise to the question if there might be a relation between bacteria producing this fluorescence and the hypopigmented macules.

Chapter two describes a study which compares conventional culture results from biopsy swabs taken from lesional follicular and inter-follicular skin in PMH patients as well as biopsy swabs taken from normal follicular and inter-follicular skin in the same patients.
The red follicular fluorescence that is observed in lesional skin of PMH patients is comparable with the red fluorescence seen in acne. In acne it is caused by \textit{P. acnes} bacteria residing in the pilosebaceous ducts of the skin. These bacteria are known for their contribution to the development of acne. Since previous studies confirmed the presence of \textit{P. acnes} solely in lesional skin of PMH it made us wonder why acne is hardly ever observed in PMH patients. Therefore we conducted a study to further identify and compare the precise microbial species related to acne and PMH.

**Chapter three** describes a study in which DNA fingerprinting by Amplified Fragment Length Polymorphism (AFLP), 16S rRNA gene sequencing and biochemical identification were performed to identify the exact bacterial species that is related to PMH but most probably can not be discriminated by conventional culture methods from the bacterial species causing acne. In short AFLP is a genetic mapping technique that uses specific amplification of a subset of restriction enzyme digested DNA fragments to generate a unique fingerprint for a particular genome. The AFLP has been widely applied in the identification and genotyping of various organisms because of its high discriminatory power and reproducibility, including \textit{Propionibacteria} (Vos et al. 1995, Savelkoul et al. 1999, Mohammadi et al. 2005). 16S DNA sequencing is the golden standard for taxonomic species identification; the comparison of the 16S rRNA gene sequences allows differentiation between organisms at the genus level in addition to classifying strains at multiple levels, including the species and subspecies level (Clarridge 2004).

Various descriptions have been given of PMH the last twenty years. All were more or less comparable, but none were systematically obtained and there was no consensus with regard to the clinical characteristics and natural course of the disorder. In order to gain a clear view, we developed a questionnaire for a survey among PMH patients at our institute.

**Chapter four** presents the results of this questionnaire. To provide a thorough and convenient arrangement of the natural course and clinical characteristics of PMH we additionally compared our results with previous descriptions from the literature.

Previous studies provided us with little information concerning the pathogenesis of PMH. We do know that there is a decrease in epidermal melanin in lesional skin of PMH and that electron microscopy studies thus far showed less mature melanosomes in lesional skin. But the question remains why these changes occur and what actually happens in the melanocytes and keratinocytes.
Chapter five further explores this question. To gain more insight into the mechanisms involved in the alterations in pigmentation in PMH an electron microscopic study was conducted in which biopsies taken from lesional skin were compared with biopsies taken from adjacent non-lesional skin of PMH patients. Electron microscopy provides us with a much higher magnification than light microscopy, making it possible to assess the skin at melanosomal level and therefore making it possible to view melanocytes with their melanosomal precursors, transfer of melanosomes to keratinocytes and melanosomes in the keratinocytes.

The following (logical) question that arose was that if P. acnes bacteria are indeed the causative agents in PMH, would antibacterial therapy be effective in the treatment of PMH and is there any difference in treatment results between an antibacterial approach and an anti-inflammatory approach?

The last study in Chapter six describes the results of a within-patient, left-right comparison of 5% benzoyl peroxide hydrogel/1% clindamycin lotion in combination with UVA irradiation (antibacterial treatment plus stimulation of pigmentation) versus 0.05% fluticasone propionate cream in combination with UVA irradiation (a typical and effective modality of anti-inflammatory treatment) in patients with PMH.

Chapter seven has been included in the thesis to provide an example of the existing confusion, when diagnosing skin diseases that resemble PMH.