Progressive macular hypomelanosis (PMH) treatable but often misdiagnosed
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GENERAL DISCUSSION,
SUMMARY
AND
CONCLUSIONS
General discussion, summary and conclusions

In 1987 the first article appeared about a skin disorder that consisted of symmetrically localized, hypopigmented macules on the trunk that according to morphology, course and treatment results, differed from other skin disorders with hypopigmentation (Borelli 1987). In 1988 the name Progressive Macular Hypomelanosis (PMH) was given to this disorder (Guillet et al. 1988). In practice this condition was often misdiagnosed as other known skin disorders with hypopigmentation such as pityriasis versicolor.

Over the years more descriptions of similar skin diseases appeared which nowadays we consider to be PMH, however all with different names (“Creole dyschromia” Lesueur et al. 1994, “idiopathic multiple large macule hypomelanosis” Fitzpatrick 1996, “nummular and confluent hypomelanosis of the trunk” Menke et al. 1997) and systematic research was lacking. In this thesis we systematically studied the pathology, epidemiology, cause, clinical features and treatment of PMH in order to gain evidence that this disorder should be considered a separate entity.

Chapter 1 is an introduction in which we describe the historical background and terminology of PMH. This chapter is a summary of what was known on PMH at the time we started our research.

Chapter 2 provides a description of histological and microbiological findings in PMH. This study was based on clinical finding in patients with PMH of red, follicular fluorescence in lesional skin when examined with a Wood’s lamp in a dark room. This fluorescence was absent in the follicles of adjacent normal skin. We suspected the presence of porphyrin producing bacteria, such as Corynebacterium minutissimum or Propionibacterium species, since red fluorescence is one of the characteristics of these bacteria.

We biopsied skin from follicles of lesional and adjacent (normal) skin and of inter-follicular, lesional and adjacent (normal) skin in 8 PMH patients.

Histological investigation of the follicular, lesional skin showed Gram positive bacteria in the pilosebaceous ducts of all 8 patients. In the follicles of the normal skin and in the inter-follicular skin (lesional as well as normal) these microorganisms were not
observed. Conventional cultivation showed \textit{P. acnes} bacteria in 7 out of 8 biopsies of the follicles of lesional skin. From none of the other biopsies \textit{P. acnes} could be cultured.

We concluded that there seems to be a relation between the presence of \textit{P. acnes} and the hypopigmented macules. Furthermore we speculated that the bacteria might produce a depigmenting substance that interferes with pigment synthesis.

In \textbf{Chapter 3} we further investigated the type of \textit{Propioni} bacteria found in PMH. \textit{P. acnes} plays an important role in the cause of acne. However in a previous study (chapter 2) we showed that these bacteria probably also play a role in the pathogenesis of PMH. It is striking that in general most PMH patients do not have acne. This led to the hypothesis that a subtype of \textit{P. acnes} is involved in PMH.

Therefore we conducted a study in which we took biopsies of red follicular fluorescent lesional skin in 14 PMH patients and from a red follicular fluorescent follicle at the site of an acne lesion in 10 acne patients. The biopsies were then smeared on blood agar plates for provisional conventional identification. Next we further analyzed one isolate per plate by the DNA fingerprinting method: amplified fragment length polymorphism (AFLP). For confirmation of our AFLP results we additionally conducted 16S rRNA gene sequencing analysis on isolates from various DNA groups that resulted from the AFLP analysis. These isolates were compared with the reference \textit{P. acnes} strain ATCC 6919. To exclude the presence of a mixture of different species in one patient, we re-sampled 3 acne patients and newly sampled 3 PMH patients. This time a maximum of ten isolates per patient was submitted to DNA fingerprinting by AFLP.

All provisional conventional identified isolates were \textit{P. acnes} bacteria. This was determined by biochemical tests and the accompanying resistance pattern. The AFLP analysis resulted in 3 different DNA groups. Compared to the \textit{P. acnes} reference strain, isolates from group 1 (8 acne and 6 PMH patients) showed a similarity between 55 and 100% suggesting the same species, isolates from group 2 (2 acne patients) showed a similarity between 30 and 55% suggesting a variant of \textit{P. acnes} and group 3 isolates (8 PMH patients) formed a clear distinct DNA group with a similarity of less than 30%. This low level of homology suggested that these isolates belong to a different species. Isolates from group 3 comprised strains isolated solely from PMH patients \((n = 8)\). For these strains a similarity level of < 30% with the reference
P. acnes strain was observed. All clinical strains showed a similarity level of < 30% when compared with Propionibacterium avidum, Propionibacterium granulosum and Propionibacterium propionicus. This suggests another species based on the low level of homology. 16S rRNA gene sequencing analysis of 2 isolates from DNA group 1, 1 isolate from DNA group 2 and 3 isolates from DNA group 3 showed the following: isolates from group 1 showed no difference with the reference strain. The isolates from group 2 showed a single nucleotide difference on position 827 with the reference strain. Two isolates from group 3 showed a single nucleotide difference on position 1243 with the reference strain and 1 isolate from group 3 showed two nucleotide differences on position 712 and 1243. The results of the second AFLP analysis were comparable with our former findings and “mixture” of isolates could be excluded. Additional biochemical tests of bacteria from the different DNA groups confirmed our AFLP findings, however the resistance pattern of the bacteria in the three different groups was exactly the same.

Because of the small differences we found with 16S rRNA gene sequencing analysis and biochemical tests and the comparable resistance pattern between the different DNA groups, we concluded that we are probably dealing with an until now unidentified Propionibacterium species. The fact that bacteria from DNA group 3 were only found in PMH patients and not in acne patients, made us conclude that there is a relation between group 3 bacteria and PMH.

Chapter 4 provides a description of PMH within de patient population of the Netherlands Institute for Pigment Disorders.

To gain a better insight in the clinical characteristics and natural course of PMH we conducted a study in which a questionnaire was drawn up that consisted of questions about the skin type of the patient, the beginning of the disorder, the family history, signs and symptoms, the progression of the disorder and previous treatments. Additionally we asked about the medical history, to verify whether relations with other diseases were probable. The questionnaire was sent to 152 PMH patients of whom 101 patients returned a fully completed questionnaire. The results of the questionnaire were then compared with descriptions of the clinical characteristics in the literature to provide a complete overview.
PMH consists of symmetrically localized, hypopigmented, non-scaled macules on the trunk. Usually it starts on the trunk and progresses further on the trunk and in a limited number of patients to the face and the proximal part of the extremities. Often there is confluence of the macules on the trunk. Spontaneous remission probably begins after adolescence, since PMH is practically nonexistent in middle aged people and the elderly. If there is a remission, for instance after treatment, the macules reappear often at exactly the same sites. PMH is mainly seen in adolescents and young adults. The male : female ratio remains indistinct, however most authors observed the disorder especially in women, this corresponds with the distribution in our own patient population. Most of the patients have skin type III to VI and are of mixed (mainly caucasian-negroid) ancestry, although Asians and Mongolians were also mentioned. In most patients a previous diagnosis of pityriasis versicolor was made and patients were often treated with local anti-mycotics. However, in none of the patients these treatments were effective.

Based on the present available information on PMH we concluded that our study gives an as complete as possible description of the clinical characteristics and the course of PMH. Furthermore the results can serve as a guideline for physicians to diagnose PMH in patients with hypopigmentations.

In Chapter 5 the electron microscopic findings of PMH are described. In this study we searched for ultrastructural correlates of the hypopigmentations to gain more insight into the pathogenesis.

We took 2 mm biopsies from the hypopigmented and normal adjacent skin from 8 PMH patients with skin type III through VI. These biopsies were examined through electron microscopy and the findings were compared.

The results showed that in patients with skin type V and VI the melanosomes that are produced by the melanocytes in the lesional skin of PMH patients can be described as smaller, stage I to III, aggregated melanosomes, while the melanosomes in the normal, adjacent skin can be described as bigger, stage IV, single melanosomes. Stage I to III melanosomes are usually seen in light skin (skin type I through IV). Stage IV melanosomes are seen in colored skin and dark skin (skin type V and VI). The transfer of melanosomes from the melanocyte to the keratinocyte seemed undisturbed. There was no accumulation of melanosomes in the dendrites and the
function of the melanocytes seemed intact, since all precursors of the melanosomes were present in the melanocyte.

We earlier (Chapter 2) proposed the hypothesis that P. acnes produces a depigmenting factor. On theoretical grounds two different pathways may lead to the observed change in melanosome formation: a) by inhibiting tyrosinase activity and increasing L-cysteine concentration the hypothetical factor induces a switch from eumelanogenesis to pheomelanogenesis, resulting in smaller, aggregated melanosomes (stage I to III) and thus a lighter skin; so in this proposal the target of the hypothetical factor is the melanocyte; b) recent studies showed that factors within the keratinocytes determine whether aggregated, stage I to III melanosomes, or single, stage IV melanosomes are produced. The hypothetical factor produced by P. acnes might affect the regulatory factors within the keratinocyte, leading to the production of smaller aggregated melanosomes.

In Chapter 6 we conducted a study based on previous findings, in which we compared antibacterial therapy with anti-inflammatory therapy.

In this study we included 45 PMH patients. In these patients the front or back side of the trunk was divided in two halves. After randomization one side was treated with benzoyl peroxide 5% hydrogel in combination with clindamycin 1% lotion once daily and the other side was treated with fluticasone cream once daily. Both sides were treated with UVA phototherapy three times a week during 20 minutes. Patients were treated with these therapies for three months. Pictures were taken of all patients before, during and after treatment. The pictures were assessed by three independent dermatologists who were blinded for treatment sides. Furthermore before, during and after treatment objective skin color measurements were performed with a spectrocolorimeter.

At the end of the study a significant better treatment result was observed on the side that was treated with benzoyl peroxide in combination with clindamycin than the side treated with fluticasone. The same results were found after a therapy-free follow up period of 3 months.

We concluded that the results of this study support our hypothesis that PMH is caused by a *Propionibacterium*. 
Chapter 7 concerns a “letter to the editor”. This letter was written as a reaction to a case report published in the Journal of the European Academy of Dermatology and Venereology, in which the authors (Di Lernia and Ricci 2005) implied that PMH and extensive pityriasis alba (as described by Zaynoun et al. 1983) are the same disease. Because of the clinical and ultrastructural similarities between extensive pityriasis and PMH we believe they are similar and that extensive pityriasis alba is not a severe form of pityriasis alba, like most handbooks imply.

Conclusion and future perspectives

The results of the studies presented in this thesis confirm the opinion that PMH is a separate, treatable and relatively new entity, which if the right diagnostic tests are performed can easily be distinguished from other hypopigmented skin disorders. Although the precise pathogenesis is still unknown, we gained more insight and gave a more accurate description of PMH. The investigations demonstrating the relation between Propioni bacteria and PMH provide the strongest evidence in confirming the idea that it is a separate entity. We propose that the clinical characteristics of PMH in combination with red, follicular fluorescence in lesional skin and/or gram-positive bacteria with a rod-like structure in the pilosebaceous glands of lesional skin, should be considered as diagnostic criteria for PMH. It is obvious that further research is necessary, for instance to consolidate the diagnostic criteria, to develop additional treatment modalities and to identify the postulated factor that is produced by the bacteria, influencing melanogenesis.