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Macular Posterior Pigmentary Incontinence: Its Relation to Macular Amyloidosis and Notalgia Paresthetica

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Patients with clinical features of dorsal macular amyloidosis but without subepidermal amyloid deposits were followed for 2–11 years. The clinical appearance was fairly stable during this period of time, with little tendency of healing. Only 2 of the patients developed typical macular amyloidosis during the follow-up. It is concluded that a condition strongly resembling macular amyloidosis but without amyloid is an entity, and the designation "macular posterior pigmentary incontinence" is proposed. The relationship between macular posterior pigmentary incontinence and the two conditions macular amyloidosis and notalgia paresthetica is discussed. ***Key words: pigmentation; amyloid.***

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Macular amyloidosis (MA) is a fairly common and distinct entity with unknown etiology (1–3). Typically, the condition is characterized by one or several pigmented, usually itchy macules located in the interscapular area. At the light microscopic level small amyloid deposits, resembling Civatte bodies, are seen just below the epidermis together with melanophages (2, 4). A hyperpigmentation of the epidermal basal cell layer is also present. Over the last 10 years we have observed a number of patients sharing all the clinical and histological features of MA, except that they lack amyloid deposit in the skin. Since at the time of the start of this study the condition was not well described and it was not known if it represented a pre-stage of MA or was an entity of its own, we undertook a longitudinal and more thorough study in a group of patients with the clinico-histopathological picture of MA, but without amyloid, a condition we propose to be named "macular posterior pigmentary incontinence" (MPPI). The results suggest that MPPI, although occasionally progressing into MA, is usually a stable condition with no tendency towards amyloid formation in the skin.

PATIENTS AND METHODS

Patients

Over the period 1981–91 more than 20 patients with the clinico-histopathological picture of MPPI were diagnosed by us. Punch biopsies were usually taken because the caring clinicians suspected MA, diffuse seborrheic keratosis or other pigmented lesions. Eight patients were available for more elaborate investigations and/or follow-ups. At the first visit all patients had at least 1-year history of pigmentation of the back, and in all but one patient the lesion was itching. The patients were otherwise free of skin disease. Three of the patients were on systemic medication for other reasons when the skin symptoms commenced; one suffered from epilepsia and mild cardiac insufficiency and was taking fenantoin, barbiturate and furosemide, one had a mild hypertension and was taking prazosin and diazepam, and one was taking a low dose of prednisolone and analgetics (paracetamol and dextropropoxyfen) for arthralgia. The other patients were apparently in good health.

The clinical examination revealed a single, pigmented lesion about 5–10 cm in diameter in 6 of the patients. Two patients had multiple (3–8) lesions scattered over the back. Excoriations were rarely seen and the sensibility to needle pricking was normal in all but 2 patients. These patients also complained of paresthesia in the lesions.

After informed consent, skin biopsies were taken from both involved skin and uninvolved, adjacent skin. The following biopsies were taken after infiltrating the skin with 5 ml of 1% lidocain (Xylocain®, adrenaline): (i) 6-mm punch biopsy that was fixed in 10% buffered neutral formalin and embedded in paraffin for light microscopic examination, (ii) 6-mm punch biopsy, immediately frozen for immunofluorescence studies and (iii) 3-mm biopsies which were fixed in 2.5% glutaraldehyde in 0.1 M sodium cacodylate buffer, pH 7.2, containing 0.1 M sucrose, for transmission electron microscopy.

Methods

For light microscopy, the paraffin-embedded punch biopsies were cut into 5-μ sections, which were stained with van Gieson stain and alkaline Congo red. The Congo red-stained sections were examined under polarized light for the presence of amyloid.

For direct immunofluorescence, the biopsies were freeze cut and investigated for immunoglobulin and complement deposits, using commercially available antibodies and standard procedures.

For electron microscopy, the biopsies (without cutting) were post-fixed in osmium tetroxide and embedded in epoxy resin. Ultrathin

Table I. *Some characteristics of the patients at the first visit and results of the follow-up study*

Case No.	Age (years) Sex	Localisation	Symptoms			Duration (years)	Follow-up study	
			pigmentation	itch	paresthesia		(years)	PAD findings
1	70/F	Back, diffuse	++	++	–	6	2	Amyloid
2	42/M	Interscapular	+	+	+	18	10	No change
3	58/F	Interscapular	+	+	–	10	10	No change
4	61/M	Right scapular	+	++	–	6	6	No change
5	36/M	Back, diffuse	++	+++	+	18	11	Amyloid
6	46/M	Interscapular	+	++	+	11	7	No change
7	58/F	Interscapular	+	+	?	48	5	No change
8	42/F	Lumbar region	+	–	++	2	2	No change

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sections were contrasted with uranyl acetate and lead citrate and examined in a Jeol 100C electron microscope.

RESULTS

Characterization of MPPI when first diagnosed

Some characteristics of the patients are shown in Table I. Males and females were approximately equally affected. The first symptoms were noted in childhood by one patient (No. 7) and during late adolescence or adulthood by the others. Typical clinical pictures are shown in Fig. 1 A, B. Two patients had a somewhat different clinical appearance, with widespread pigmented areas all over the back (Fig. 1 C). The history of itch and/or pigmentation ranged from 2–48 years. The itch was graded as mild (3), moderate (2) or severe (2). In 3 patients, the itch started shortly after a severe sunburn reaction. Two patients had no itch whatsoever and paresthesia was either absent or mild in all cases. Histologically, a mild hyperkeratosis was sometimes seen. The basal layer was usually hyperpigmented. In the papillary dermis, melanin-filled macrophages occurred but no amyloid was identified. A typical histological picture of MPPI is shown in Fig. 2.

Seven patients (no. 1–7) were available for more elaborate investigations. Repeated skin biopsies confirmed the absence of amyloid both at the light and electron microscopic levels. Immunofluorescence investigations of immunoglobulin and complement deposits were non-contributory.

Electron microscopically, an increased number of melanosomes were seen in keratinocytes in both unaffected and affected skin (data not shown). The number of melanosomes varied more between individuals than between involved and non-involved skin in one person. In affected and to a lesser degree non-affected skin, macrophages containing conglomerates of phagocyted melanosomes were found in the upper dermis. Amyloid bodies were not identified in any of the studied biopsies.

Long-term follow-up of MPPI patients

The patients were repeatedly examined over a period of 2 to 11 years. The clinical picture was fairly constant over time, with only minor enlargements of the pigmented lesions. Two patients (No. 1 and 5) developed amyloid deposits in the subepidermal region during the follow-up study (see Table I); in case no. 1 the interval between diagnosing MPPI and MA was 2 years. This patient was not studied further. In case no. 5, the interval between diagnosing MPPI and MA was 5 years. Repeated investigations for up to 11 years after the first visit reproducibly showed amyloid deposits in this patient. The other patients remained negative for amyloid despite an observation period of maximally 10 years.

DISCUSSION

Pigmented, itchy areas on the back are a common symptom in middle-aged and elderly persons, which may pose diagnostic difficulties when presented to the doctor. A condition similar to the one we prefer to call MPPI has previously been described (5, 6). However, these authors did not perform any follow-up study on their patients but discussed the relation between notalgia paresthetica, MPPI and MA. In most instances, the distribution of notalgia paresthetica, MPPI and MA is identical. A relationship or even identity between MA and notalgia paresthetica has been proposed (5). It has also been suggested

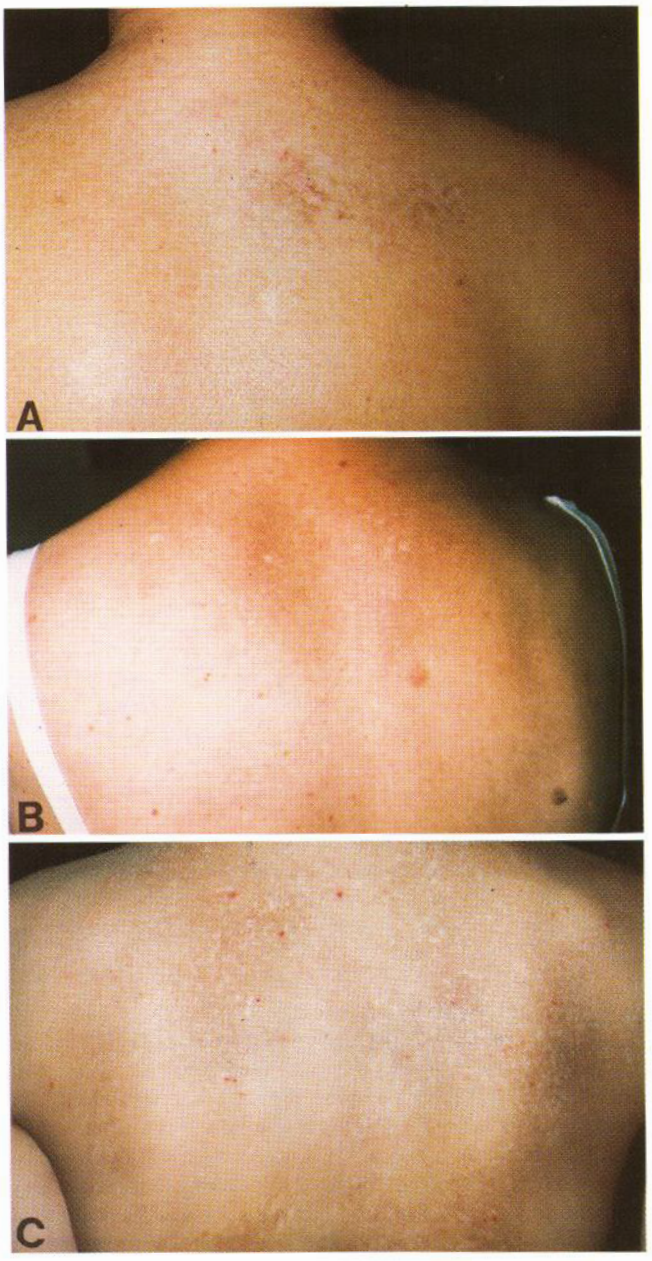

Fig. 1. Clinical appearance of patients no. 4 (A) and 7 (B), showing typical patches of brownish and slightly scarred skin surrounded by normal skin. Patient no. 5 (C) shows a more widespread pigmentation, excoriations and a few scars.

that notalgia paresthetica, MPPI and MA represent three stages of one disease (6). Therefore, a primary goal of our study was to follow patients with biopsy-verified amyloid-free MPPI over a long period of time, to see whether or not the lesions tend to heal or if they convert into MA. Our results clearly show that in a majority of individuals, the lesions persist virtually unchanged even for an observation time longer than 10 years. However, in 2 out of 8 MPPI patients, small amyloid deposits in the dermal papillae were found at follow-up, supporting the close relationship between MPPI and MA.

The etiology and pathogenesis of the three conditions notalgia paresthetica, MPPI and MA are unknown. A neurogenic etiology of notalgia paresthetica has been proposed, due to the

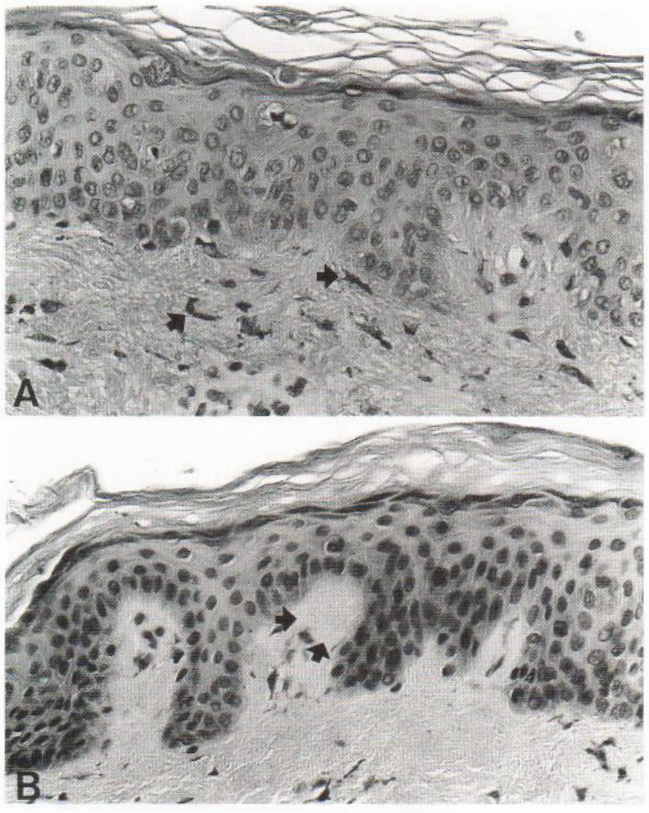

Fig. 2. Typical appearance of MPPI (A): slight hyperkeratosis but no acanthosis. Upper dermis contains many melanophages (*arrows*). The findings are similar to those in MA (B), but in the latter, small amyloid deposits (*arrows*) are found in dermal papillae. H&E × 300.

symptoms and to the dermatome-like distribution of the lesion. It has been pointed out that the thoracic nerves II-VI have an unusual anatomy which would make them sensitive to mechanical lesions (7). It has also been suggested that MPPI and MA are conditions secondary to a nerve lesion. An attractive line of events, coupling the conditions together, would therefore be a primary nerve lesion, followed by itching and secondary pigmentary incontinence. MA has been believed to occur as a result of keratinocyte death and conversion of keratin into amyloid fibrils (8). However, the nature of the amyloid in MA (or other related dermal amyloid forms) is not known, since no biochemical characterization has yet been reported.

There are several facts that should be taken into consideration when discussing the relationships between the three conditions. First, notalgia paresthetica is restricted to the upper back (7), while MA is not only seen in this area of the back but occurs also in other parts of the body (3, 9, 10). Second, MA sometimes occurs together with lichen amyloidosus (LA) (1, 4, 11), and these two skin amyloidoses cannot always be distinguished and are probably of identical chemical nature. No association of notalgia paresthetica and LA has been described to our knowledge. Third, in our patients there was no consistent association of MPPI with either paresthesia or sensory impairment, and MA sometimes appears without previous or concomitant itching (9). Therefore, we prefer to look at notalgia paresthetica, MPPI and MA as three related but frequently overlapping conditions (Fig. 3).

MA and MPPI may have an identical clinical appearance.

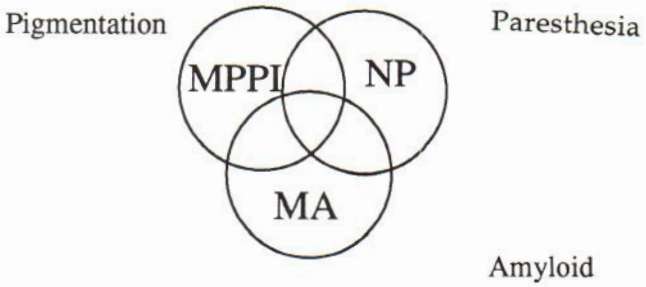

Fig. 3. Proposed interrelationship between macular amyloidosis (MA), notalgia paresthetica (NP) and macular posterior pigmentary incontinence (MPPI).

Microscopically, the only difference is lack of amyloid in MPPI. The amyloid in MA is always close to the epidermis and occurs mainly as small globules, resembling Civatte bodies. A central role of the epidermis in the pathogenesis of the amyloid in MA is obvious and most probably, the amyloid fibril protein is a keratinocyte product (8, 11, 12). A difference in production or metabolism of this as yet not identified (although possibly keratin-related) protein may explain whether or not amyloid is formed.

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