Symptoms of Nostalgia Paresthetica May Be Explained by Increased Dermal Innervation

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Nostalgia paresthetica is a sensory neuropathy characterized by infrascapular pruritus, burning pain, hyperalgesia, or tenderness. To assess whether the symptoms may be caused by alterations in the cutaneous innervation, skin from the affected area of patients (n = 5) was compared with controls (n = 10) comprising the contralateral unaffected area from the same patients and site-matched biopsies of normals, using immunohistochemistry. Frozen sections were immunostained with antisera to the neuropeptides substance P, calcitonin gene-related peptide, vasoactive intestinal polypeptide, and neuropeptide with tyrosine, and to the general neural marker PGP 9.5 and the glial marker S-100 to show the overall innervation and glial cells, respectively. No discernible change in the distribution of neuropeptide-immunoreactive axons was found, but all of the specimens from the affected areas had a significant increase in the number of intradermal PGP 9.5-immunoreactive nerve fibers compared with unaffected areas from the same patients and normal controls. Epidermal dendritic cells immunoreactive for S-100, possibly Langerhans cells, were substantially increased. It is concluded that there is an increase in the sensory epidermal innervation in the affected skin areas in nostalgia paresthetica, which could contribute to the symptoms, and that neural immunohistochemistry of skin biopsies could be helpful in the diagnosis of the disease. J Invest Dermatol 97:555–561, 1991

Nostalgia paresthetica is an infrequently reported condition characterized by sensory neuropathy, possibly having an hereditary component in some cases [1–9]. The lesion involves the posterior rami of the second through sixth dorsal nerves [1,4]. The most common symptom is pruritus in the left or right infrascapular region, but burning, hyperalgesia and tenderness are described [4,7,9]. Secondary lichenification and/or pigmentation frequently occur.

The cutaneous innervation is known to have putative neurotransmitter or neuromodulator peptides in addition to the classic neurotransmitters noradrenaline and acetylcholine. In humans, these peptides include substance P and other tachykinins, calcitonin gene-related peptide (CGRP), vasoactive intestinal polypeptide (VIP), peptide histidine methionine (PHM) and neuropeptide with tyrosine (NPY) [10–17]. Substance P and CGRP are found principally in sensory nerve fibers and are believed to be involved in neurogenic inflammation and plasma extravasation by antidromic activation [18,19]; substance P is also involved in the response to noxious stimuli [20]. The precursor of VIP also contains PHM; the two peptides therefore are colocalized, and are found in autonomic nerves [21]. They have vasodilator and secretomotor actions [22,23]. NPY also is found in autonomic nerves, and is a potent vasoconstrictor [24,25]. Localization of these nerves is possible by using immunohistochemical techniques with specific antisera to each peptide. The innervation overall may be detected using a variety of antisera to so-called general neural markers, such as neuron-specific enolase and neurofilament proteins, the presence of Schwann cells by glial markers such as S-100 [26]. We have previously found [17] the best of the general neural markers to be protein gene product 9.5 (PGP 9.5) which was originally isolated from human brain [27].

Because there is no morphologic information on the cutaneous innervation in nostalgia paresthetica, but there are neurologic symptoms, and because we have seen changes in the distribution and peptide immunoreactivity of nerves in skin from patients with other neuropathies [28,29], we have investigated five cases. The results of immunostaining for PGP 9.5, S-100 and neuropeptides in biopsies of affected skin areas were compared to those in contralateral unaffected skin from the same patients and site-matched biopsies from patients with no skin or neurologic lesion.

**MATERIALS AND METHODS**

**Patients** Details of the nostalgia paresthetica cases (n = 5) are summarized below. All five patients complained of distressing localized irritation and/or abnormal sensation in one or other infrascapular region. With the exception of case 1, neurologic examination outside of this area was normal. In none of the cases was there a family history.

**Case 1:** A 69-year-old man developed intense irritation and pain in an area over the lower part of the right shoulder blade 11 years ago. Initially intermittent, it has become continuous over the years. One year after the onset of the problem, he sustained a traumatic fracture at T8/T9 resulting in paraplegia. Examination revealed some li-
Table I. Characteristics of Primary Antisera

<table>
<thead>
<tr>
<th>Antigen*</th>
<th>Species</th>
<th>Code</th>
<th>DIL¹</th>
<th>Source*</th>
<th>ABSN²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropeptides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substance P</td>
<td>Mammalian</td>
<td>910 (SP35)</td>
<td>1:500</td>
<td>RPMs</td>
<td>1.0</td>
</tr>
<tr>
<td>α-CGRP</td>
<td>Rat</td>
<td>1208 (CGRP7)</td>
<td>1:200</td>
<td>RPMs</td>
<td>1.0</td>
</tr>
<tr>
<td>VIP</td>
<td>Pig</td>
<td>652 (V128)</td>
<td>1:2000</td>
<td>RPMs</td>
<td>0.5</td>
</tr>
<tr>
<td>NPY</td>
<td>Pig</td>
<td>1086 (YN12)</td>
<td>1:400</td>
<td>RPMs</td>
<td>1.0</td>
</tr>
<tr>
<td>General markers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGP 9.5</td>
<td>Man</td>
<td>1648 (RA95103)</td>
<td>1:600</td>
<td>Ultraclone, Cambridge, U.K.</td>
<td>0.5</td>
</tr>
<tr>
<td>S-100</td>
<td>Cow</td>
<td>1508 (Z311)</td>
<td>1:800</td>
<td>Dako</td>
<td>Not done</td>
</tr>
</tbody>
</table>

* CGRP, calcitonin gene-related peptide; VIP, vasoactive intestinal polypeptide; NPY, neuropeptide with tyrosine; PGP 9.5, protein gene product 9.5.
¹ DIL, dilution used for immunostaining.
² RPMs, Royal Postgraduate Medical School, in collaboration with Professor S.R. Bloom, Department of Medicine.
³ ABSN, antibody absorption; amount of antigen in nmol/ml of diluted antiserum required to abolish immunoreactivity.

Chenicification and pigmentation in the involved area, which was situated in the T5/T6 dermatome lateral to the spine on the right side. Sensation was normal and there was no hyperalgesia. X ray of the spine showed an old crush fracture at T8/T9 and some degenerative changes at T4/T5. The following treatments produced minimal or no benefit: topical and intraluminal steroids, local radiotherapy, local anesthetic creams and injections, and subcutaneous derenervation of the area of maximal irritation, transdermal nerve stimulation, acupuncture, and cryotherapy. Oral carbamazepine produced temporary relief.

Case 2: A 55-year-old woman noted the onset of episodic irritation at the base of the left scapula. There was no pain but some numbness in the area. On examination there was an area of faint pigmentation in the left infraocular region. Sensation to light touch was reduced in the area corresponding to T4-T6 but examination was otherwise normal. She obtained some relief from the application of a potent topical steroid.

Case 3: A 74-year-old man began to notice an icy patch on the left mid back 6 years ago. The sensation became worse at night. Examination showed no abnormality and no sensory loss but the patient delineated a localized area 5 x 5 cm in the left infrascapular region corresponding to the T2-T6 dermatome. X ray of the spine showed degenerative changes and spondylosis in the cervical region. The symptoms were well controlled by the daily use of transdermal nerve stimulation.

Case 4: A 67-year-old woman gave a 3-year history of irritation on the right mid back. It was intense enough to affect her sleeping. On examination, there was a localized area of scaling and chenicification in the right infrascapular region corresponding with the dermatomes of T3-T6. Sensation was normal. Her symptoms were improved by the regular use of a potent topical steroid.

Case 5: A 67-year-old man developed a localized area of irritation and aching on the left side of the mid back 12 years ago. The problem was intermittent. Examination of the skin and sensation in the area were normal but the patient indicated that the area corresponded with the T2-T6 dermatomes. Some relief was obtained by the use of a potent topical steroid. Carbamazepine was beneficial but side effects limited the dosage.

Biopsies Punch biopsies were taken under local anesthesia (lidocaine with adrenaline) from the affected area and the unaffected contralateral side. Skin specimens from similar sites were obtained from patients (n = 5) having no neuropathy or skin disorders who were undergoing surgery that entailed some skin removal. The tissues were fixed immediately in a solution consisting of 85 volumes of 2% (w/v) paraformaldehyde in 0.1 M phosphate buffer, pH 7.2, and 15 volumes of saturated aqueous picric acid [30] for 16 h at 4°C and then washed at 4°C for 24 h in several changes of phosphate-buffered saline (PBS—0.01 M phosphate buffer, pH 7.4, containing 0.15 M NaCl) containing 15% sucrose and 0.01% sodium azide. Tissues were then embedded in mounting medium (OCT Compound; Miles Inc, USA) on a cork mat and frozen rapidly by immersing all in melting dichlorodifluoromethane (Arcton,ICI, U.K.) previously frozen in liquid nitrogen. Care was taken to orientate the tissue to permit sectioning at right angles to the skin surface. Sections (6–7 μm) were taken up on glass slides coated with poly-L-lysine to ensure good adhesion [31], dried 1 h at room temperature and then immunostained or stained for morphologic assessment.

For histology, part of the biopsy from the affected skin of one case was fixed in formal saline for 12 h, processed routinely to paraffin wax and sectioned (5 μm thick). For the other cases, frozen sections were used for morphologic assessment, to conserve tissue. Sections were stained with hematoxylin and eosin or with crystal violet.

Immunohistochemistry Sections were stained by a modified indirect immunofluorescence method [32]. Briefly, slides were placed in PBS containing 0.2% (v/v) Triton X-100 and then incubated overnight in a drop chamber at 4°C with primary antisera (Table I) diluted in PBS containing 0.1% (w/v) bovine serum albumin and 0.01% (w/v) sodium azide. After washing the slides thoroughly in PBS (three changes of 10 min each), the primary antisera was reapplied for 4 h at room temperature. The slides were then washed (3 x 5 min changes) and fluorescein-conjugated goat anti-rabbit IgG (ICN Biomedicals Ltd, UK) was applied at a dilution of 1:200 for 60 min. Slides were washed as before and sections mounted in PBS: glycerol (1:9 v/v) and viewed and photographed using a fluorescence microscope (Olympus AH-2).

The number of immunoreactive nerves was assessed visually in all specimens and graded from absent (−) to abundant (+ + +) in epidermis and dermis and around hair follicles, sweat glands, and blood vessels. The grading was performed independently by two observers who were unaware of the study group to which each of the specimens belonged.

RESULTS

Histology Hematoxylin and eosin stained sections of affected skin from all cases showed occasional necrotic keratinocytes within the epidermis and melanin within macrophages in the dermis typical of those reported to occur in natalgia paresthetica [9] (Fig 1). No amyloid deposits were seen in any of the crystal violet stained preparations.

Immunocytochemistry Nerve fibers immunoreactive for neuropeptides and PGP 9.5, and Schwann cells and epidermal cells im-
immunoreactive for S-100, were seen in all sections from controls and
notalgia paresthetica cases. The results are summarized in Table II.

Controls: The specimens from normal controls and the unaffected
skin from the notalgia patients had identical distributions and num-
bers of nerves. Subsets of the nerves were immunoreactive for neu-
ropeptides. Substance P and CGRP had similar distributions al-
though the latter predominated (Fig 2). They were seen in varicos
fibers in the dermis, surrounding small arteries and arterioles, and
occasionally around sweat glands. Scattered fibers were also seen
below and penetrating the epidermis (Fig 2A,C). VIP and NPY
immunoreactive nerves had similar distributions, mainly in nerves
around sweat glands and blood vessels. Fibers and bundles immu-
noreactive for PGP 9.5 were seen throughout the dermis, around
blood vessels, sweat glands and hair follicles, running below the
epidermis and occasionally penetrating into it (Fig 3B,D). Immuno-
reactivity for S-100 was seen in Schwann cells of nerves in the
dermis only, and occasionally in epidermal dendritic cells (Fig 3F).

Notalgia Cases: No obvious changes were detected in the number
or distribution of neuropeptide-immunoreactive nerves (Fig 2B,D)
compared with controls. In the affected areas of skin, the number
of PGP 9.5 immunoreactive fibers and S-100 immunoreactive
Schwann cells was greater than in the controls and the unaffected
skin (Fig 3). This increase was seen in all areas of the skin, but was
most noticeable in the PGP 9.5-immunoreactive epidermal fibers
(Fig 3A,C). A large number of S-100 immunoreactive dendritic
cells was seen in the epidermis (Fig 3E), and around hair follicles.

**DISCUSSION**

This study demonstrates for the first time that in patients with
notalgia paresthetica, a condition characterized by pruritus and hy-
peralgesia, there is an increase in the cutaneous PGP 9.5 immuno-
reactivity but not in neuropeptides, particularly in the epidermis,
compared to controls. There is also a dramatic increase in the num-
ber of S-100 immunoreactive dendritic cells in the affected epider-
mis. Furthermore, it is also possible that notalgia paresthetica is not
such a rare condition as has been thought up to now.

There is now much evidence that anti-PGP 9.5 stains more nerve
fibers than are revealed by other neural markers, and that these
nerves are of all subtypes [29,33–35]. The converse, that PGP 9.5

**Table II. Results of Immunostaining of Nerves in Skin**

<table>
<thead>
<tr>
<th>Skin Area</th>
<th>PGP 9.5&lt;sup&gt;a&lt;/sup&gt;</th>
<th>S-100&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Substance P</th>
<th>CGRP</th>
<th>VIP</th>
<th>NPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidermis</td>
<td>++++ (++)</td>
<td>– (–)</td>
<td>– (–)</td>
<td>++ (+)</td>
<td>– (–)</td>
<td>– (–)</td>
</tr>
<tr>
<td>Dermis</td>
<td>++++ (++)</td>
<td>+++ (++)</td>
<td>+ (+)</td>
<td>+++ (++)</td>
<td>– (–)</td>
<td>– (–)</td>
</tr>
<tr>
<td>Hypodermis</td>
<td>++++ (++++)</td>
<td>+++ (++)</td>
<td>+ (+)</td>
<td>+++ (++)</td>
<td>– (–)</td>
<td>– (–)</td>
</tr>
<tr>
<td>Hair follicles</td>
<td>+++ (++)</td>
<td>+++ (++)</td>
<td>– (–)</td>
<td>+ (+)</td>
<td>++ (+)</td>
<td>+ (+)</td>
</tr>
<tr>
<td>Sweat glands</td>
<td>+++ (++)</td>
<td>+++ (++)</td>
<td>– (–)</td>
<td>– (–)</td>
<td>++ (+)</td>
<td>+ (+)</td>
</tr>
<tr>
<td>Blood vessels</td>
<td>++ (++)</td>
<td>++ (++)</td>
<td>– (–)</td>
<td>– (–)</td>
<td>– (–)</td>
<td>++ (++)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Results are the mean of visual estimates of the density of immunoreactive innervation in or around the main tissues of skin; controls are given in parentheses. They are graded: –, none; +, few; ++, moderate; ++++, abundant.

<sup>b</sup> Protein gene product 9.5.

<sup>c</sup> Glial marker.
immunoreactivity is not present in other tissue structures that have a morphologic appearance similar to nerves, is suggested by the absence of immunoreactivity following complete denervation in animals, such as skin flaps in mice [36], or blood vessels [35], or in human subjects with advanced peripheral diabetic neuropathy [29] or leprosy [28]. It is therefore proposed that the increased PGP 9.5 immunoreactive structures found here are indeed nerves.

The location of the increased nerves in the epidermis is of great interest because nerves in this site are believed to be sensory in nature [11], due to their type (mostly fine, varicose C-fibers) and because they are present in much greater number in the more sensitive areas of skin, such as lip, nose, and digits [14,17]. If these increased nerves are sensory, this could help to explain the symptoms of nostalgia paresthetica, such as pruritus and hyperalgesia, and it is notable that the increase was only seen in the affected areas of

patients, stained by immunofluorescence for the neuropeptides substance P fibers in the dermis and epidermis (arrows), but there is no distinguishable difference in their densities in the affected skin. Bar, 25 μm.

Figure 2. Infrascapular skin of control (A,C) and nostalgia paresthetica (B,D) (A,B) and CGRP (C,D). Immunoreactivity for both peptides is seen in nerve fibers in the dermis and epidermis (arrows), but there is no distinguishable difference in their densities in the affected skin. Bar, 25 μm.
Figure 3. Immunostaining for (A–D) PGP 9.5 and (E,F) S-100 in affected (A,C,E) and control (B,D,F) infrascapular skin. Nerve fibers overall, shown by immunoreactivity for PGP 9.5 (A,B), are increased in the upper dermis and epidermis (A,C; arrows) of affected skin in comparison with controls (B,D; epidermis is above the dashed line in C and D). There is also a marked increase in the number of dendritic cells immunoreactive for S-100 in the epidermis (E; arrows) compared with controls (F). Bar, 25 μm.
ical denervation procedures can lead to hyperplasia of other nerve types in the denervated tissues [37–39]. It is possible that a similar mechanism, reportedly due to excess of nerve growth factor [39] occurs in these cases.

It would be of interest to compare the results of this study with a similar investigation of patients having the type of noxious mechanoesth

ectica with hyperalgesia but a diminished sense of touch and temperature, which has been suggested as being due to an underlying pre- 

position to peripheral neuropathy [4]. Similar numbers of epidermal nerves in such patients would substantiate that the free epidermal nerve endings are principally involved in sensing pain and itch rather than in touch or temperature.

The finding of large numbers of S-100 immunoreactive dendritic cells in the epidermis is also interesting. These could either be melano-nocytes or Langerhans cells, both of which are reported to be immu-noreactive for S-100 [40]. The latter seems more likely because melanoocytes are usually confined to the basal layer of epidermis and, furthermore, some authors do not find them always to be immunoreactive for S-100 [41]. Unfortunately, appropriately processed tissue was not available to permit verification of their identity by immunostaining with OKT6, which is reported to be positive in Langerhans cells but requires unfixed sections [42].

This study shows that neural changes may be evident in neuropathies having increased sweating, as has been shown for those involving reduced sensation such as leprosy [28] and diabetes [29], and suggests that immunohistochemical examination of the nerves in skin biopsies may be helpful in the diagnosis of these cases. Further- 

more, the incidence of noxious mechanoesth

etica may be much greater than previously reported. Many doctors are unfamiliar with noxi-

ous mechanoesth

etica and tend to label the patient as neurotic or to treat the secondary changes of lichenification without appreciating the true cause of the pruritus. It is concluded that the itching and painful symptoms associated with noxious mechanoesth

etica may be due to those neural changes and are therefore, at least in these cases, not psycho-

somatic.

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