Dermatological and immunological conditions due to nerve lesions

Domenico Bove, MD
Amalia Lupoli, MD
Stefano Caccavale, MD
Vincenzo Piccolo, MD
Eleonora Ruocco, MD, PhD

Second University of Naples, Italy

Correspondence to: Amalia Lupoli
E-mail: lupoliamalia@gmail.com

Summary

Some syndromes are of interest to both neurologists and dermatologists, because cutaneous involvement may harbinger symptoms of a neurological disease. The aim of this review is to clarify this aspect. The skin, because of its relationships with the peripheral sensory nervous system, autonomic nervous system and central nervous system, constitutes a neuroimmunoendocrine organ. The skin contains numerous neuropeptides released from sensory nerves. Neuropeptides play a precise role in cutaneous physiology and pathophysiology, and in certain skin diseases. A complex dysregulation of neuropeptides is a feature of some diseases of both dermatological and neurological interest (e.g. cutaneous and nerve lesions following herpes zoster infection, cutaneous manifestations of carpal tunnel syndrome, trigeminal trophic syndrome).
Dermatologists need to know when a patient should be referred to a neurologist and should consider this option in those presenting with syndromes of unclear etiology.

KEY WORDS: carpal tunnel syndrome, herpes zoster, neuropeptides, trigeminal trophic syndrome

Introduction

The skin is innervated by primary afferent sensory nerves, postganglionic cholinergic parasympathetic nerves and postganglionic adrenergic and cholinergic sympathetic nerves. Sensory as well as autonomic (sympathetic) nerves influence a variety of functions within the skin, both physiological (embryogenesis, vasoconstriction, vasodilatation, body temperature, barrier function, secretion, growth, differentiation, cell nutrition, nerve growth) and pathophysiological (inflammation, immune defense, apoptosis, proliferation, wound healing) (Roosterman et al., 2006).

The neuroanatomy and neurophysiology of cutaneous nerves

The anatomy and classification of cutaneous sensory nerves were extensively reviewed by Winkelmann (1988). Sensory nerves can be subdivided into four groups: Aα fibers (12-22 μm) are highly myelinated, show a fast conduction velocity (70-120 m/s), and are associated with muscular spindles and tendon organs. Aβ fibers (touch receptors) are moderately myelinated (6-12 μm). Aδ fibers have a thin myelin sheath (1-5 μm), an intermediate conduction velocity (4-30 m/s), and are generally polymodal. Finally, the slow-conducting C fibers (0.5-2 m/s) are unmyelinated and small (0.2-1.5 μm). The skin is innervated by afferent somatic nerves with fine unmyelinated (C) or myelinated (Aδ) primary afferent nerve fibers transmitting sensory stimuli (temperature changes, chemicals, inflammatory mediators, pH changes) via dorsal root ganglia and the spinal cord to specific areas of the central nervous system (CNS), resulting in the perception of pain, burning, burning pain, or itching. Aδ fibers constitute ∼80% of the primary sensory nerves sprouting from dorsal root ganglia, whereas C fibers make up ∼20% of the primary afferents (Lawson, 2002). Both C and Aδ fibers respond to a variable range of stimuli, both physical (trauma, heat, cold, osmotic changes, distension or mechanical stimulation, ultraviolet light) and chemical (toxic agents, allergens, proteases, microbes). Sensory nerves innervate the epidermis and dermis as well as the subcutaneous fatty tissue as a three-dimensional network (Kelly et al., 2005). Most of the nerve fibers are found in the mid-dermis and the papillary dermis. The epidermis, blood vessels and skin appendages, such as hair follicles, sebaceous glands, sweat glands and apocrine glands, are innervated by several subtypes of sensory nerves. Sensory nerves, as well as functioning as an afferent system to conduct stimuli from the skin to the CNS, also act in an efferent neurosecretory fashion through their terminals (Paus et al., 2006).

The neuroanatomy and neurophysiology of autonomic nerves

The anatomy of cutaneous autonomic nerves was reviewed in detail by Brain and Moore (1999). Autonomic nerve fibers in the skin derive almost completely from sympathetic (cholinergic) neurons. In the face, they also derive, rarely, from parasympathetic

(also cholinergic) neurons. Compared with sensory nerve fibers, they make up only a minority of cutaneous nerve fibers and, still in comparison with sensory nerve fibers, their distribution is restricted to the dermis, where they innervate blood vessels, arteriovenous anastomoses, lymphatic vessels, erector pili muscles, eccrine glands, apocrine glands, and hair follicles (Vetrugno et al., 2003). Thus, cutaneous autonomic nerves are involved in the regulation of blood circulation, lymphatic function and skin appendages (sweat glands, apocrine glands, hair follicles). Postganglionic autonomic nerves in the skin predominantly generate acetylcholine (ACh), but also release neuropeptides such as neuropeptide Y (NPY), calcitonin gene-related peptide (CGRP) and vasoactive intestinal polypeptide (VIP), as well as neuromodulators such as tyrosine hydroxylase (used as a marker for autonomic nerves in the skin). The fact that immunoreactivity for NPY and atrial natriuretic peptide is observed only in autonomic nerve fibers differentiates these fibers from sensory nerve fibers. The role of ACh as an important regulator of sweat gland function has been well explored; conversely, the exact role of autonomic nerve-derived neuropeptides is poorly understood. Like ACh, neuropeptides released by autonomic nerves may be involved in the regulation of sweat gland function and probably dysfunction of sweat secretion based on uncontrolled sympathetic innervation (congenital sensory neuropathy type IV, hypohydrosis, diabetic neuropathy, syringomyelia, leprosy). Adult human sweat gland innervation, however, is not only cholinergic but co-expresses all of the proteins required for full noradrenergic function (tyrosine hydroxylase, aromatic amino acid decarboxylase, dopamine β–hydroxylase and the vesicular monoamine transporter VMAT2). Sympathetic neurons specifically innervating the cutaneous arteriovenous anastomoses (Hoyer-Grosser organs) also possess a full cholinergic/noradrenergic co-phenotype. Sympathetic nerve fibers release norepinephrine and/or NPY to stimulate arterioles, arteriovenous anastomoses and venous sinusoids, which results in vasoconstriction, whereas parasympathetic nerves, by releasing ACh and VIP, mediate vasodilatation through activation of venous sinusoids (Weihe et al., 2005; Donadio et al., 2006).

Cutaneous neuropeptides

The skin, because of its relationship with the peripheral sensory nervous system (PNS), autonomic nervous system (ANS), and CNS, constitutes a neuroimmunoendocrine organ. It is well known that the skin contains numerous neuropeptides produced by the resident cells of the immune system, or by skin cells, and released from sensory nerves. Neuropeptides are a heterogeneous group of molecules consisting of two or more of the 40 amino acids that are present in the CNS and PNS. They are contained in and released from a wide range of nerves. Chemically distinct, neuropeptides exhibit characteristic patterns of localization within the PNS and CNS and, acting as neurotransmitters and/or neuromodulators, possess the ability to stimulate a range of diverse biological activities (Lotti et al., 1999). The concept of co-transmission within the ANS was first advanced by Burnstock (1976). His study of adenosine triphosphate in sympathetic nerves led to the realization that neuropeptides are also contained in both sympathetic and cholinergic nerves. However, while noradrenaline is generally considered to be the classical transmitter in sympathetic nerves and ACh in parasympathetic nerves, the predominant neurotransmitters released from the sensory fibers of non-adrenergic, non-cholinergic (NANC) nerves have been found to be one or more neuropeptides. The nerves that contain and release neuropeptides are primarily unmyelinated sensory C fibers, including both sensory and autonomic ones, and myelinated Aδ fibers (Bevan and Szolcsányi, 1990; Dray, 1992). In the skin, the Aδ fibers are preferentially responsible for vasodilatation, whereas the C fibers are responsible for plasma leakage (Baluk, 1977; Jänig and Lisney, 1989). Cutaneous nerve fibers can modulate inflammatory reactions through local release of neuropeptides. These neuropeptides are able to regulate both acute and chronic aspects of cutaneous inflammatory processes, such as vascular motility, cellular trafficking, and trophism (Baluk, 1977; Jänig and Lisney, 1989; Pincelli et al., 1996). They provide a dense innervation to most organs and tissues and, in particular, to blood vessels, where perivascular nerves often terminate in close association with endothelial cells.

Substance P (SP), the first neuropeptide to be discovered (V Euler and Gaddum, 1931), was characterized in 1970 (Chang and Leeman, 1970). It is the best characterized of the neuropeptides released from sensory C fibers in the skin and its activities require not only its secretion, but also the expression of the SP receptor on local target cells, and of tissue proteases that degrade neuropeptides, such as neutral endopeptidase (Ansel et al., 1996). SP is a member of the tachykinin family together with neurokinin A (NKA, also called neurokinin α, substance K or neuromedin L) and neurokinin B (NKB, also known as neurokinin ß or neuromedin K), and it is present in many areas of the nervous system, but especially in areas of immunological importance, such as the gastrointestinal tract, the respiratory tract, the eyes and the skin. In the PNS, SP occurs in a subpopulation of primary afferent neurons (Aδ and C fibers), which transmit impulses initiated by noxious stimuli. SP is synthesized in the dorsal root ganglia, from which it migrates centrally to the dorsal horn of the spinal cord and peripherally to cutaneous nerve terminals of the sensory neurons. Three distinct receptors, termed NK-1, NK-2 and NK-3, mediate the biological effects of tachykinins, with SP, NKA and NKB, respectively, as their preferred endogenous agonists. The peripheral actions in which SP is involved are cutaneous neuroinflammation with vasodilatation and increased vascular permeability and promotion of cell proliferation (Pernow, 1983). SP has also been implicated in the modulation of inflammation because the peptide pro-

motes the proliferation of various types of target cells. Both SP and NKA have been shown to stimulate proliferation of human cultured keratinocytes, fibroblasts and endothelial cells (Tanaka et al., 1988), but under certain circumstances they instead suppressed keratinocyte growth. In addition, they also stimulate the proliferation of arterial smooth muscle cells, thereby aiding healing processes. *In vivo*, SP stimulates neovascularization (Ziche et al., 1990) and may modulate melanocyte gene expression, is chemotactic for melanocytes, and can enhance their dendricity, but not to the same extent as nerve growth factor or CGRP (Hara et al., 1996).

Several secretory peptides belong to the glucagon-secretin family. Among these, VIP and peptide histidine methionine (PHM) appear to be the most important in human skin. VIP and PHM have a widespread tissue distribution in both the CNS and PNS, and are known to co-localize in peripheral autonomic nerves (Christofides et al., 1982). In human skin, innervation with nerves containing these peptides occurs around the glandular cells, ducts and myoepithelial cells of the eccrine sweat glands, where they increase sweat secretion, around the arterial segment of the deep and superficial vascular plexuses, and close to hair follicles. VIP is a very important vasodilator agent and intradermal injection of VIP produces rapid vasodilatation and increased vascular permeability; primary effects of VIP are erythema and sometimes edema. When released from sensory nerve endings and/or mast cells, VIP promotes the proliferation of keratinocytes by stimulating adenylate cyclase activity by means of specific VIP receptors (Vaalasti, et al., 1985). VIP is known to be a potent releaser of histamine from mast cells into the extracellular space, which indicates a common pathway of activation for VIP and other histamine-releasing substances, distinct from that of IgE-dependent activation. VIP has anti-inflammatory qualities in that it suppresses delayed hypersensitivity *in vitro* and inhibits phospholipase A2.

Calcitonin gene-related peptide, discovered by Amara and colleagues (1982) and derived from the calcitonin/CGRP gene by alternative RNA splicing, along with the tachykinins SP and NKA, is the major peptide present in primary afferent C-fiber neurons. It occurs in two forms, designated CGRP-α or CGRP-1 and CGRP-ß or CGRP-2. In human skin, two CGRP-containing populations of unmyelinated sensory nerve fibers have been visualized, one co-localizing with SP in small-diameter sensory nerves, occurring in the dermal papillae and free epidermal nerve endings of glabrous skin, suggesting that these neuropeptides have a common role in cutaneous sensory innervation. Release of CGRP from efferent neurons contributes to the neurogenic inflammatory response, and it may even be considered the primary mediator of neurogenic vasodilatation. It is an essential mediator of NANC vasodilatation both in the gastric mucosa and in the skin. The vasodilator effect of CGRP is of pathophysiological significance for the protection of the gastric mucosa from injury and for the process of neurogenic inflammation in the skin. Like SP, somatostatin and VIP produce dose-related weal and flare reactions in human skin, but only relatively high doses of CGRP cause these reactions, which, moreover, are much weaker than those produced by SP.

Calcitonin gene-related peptide also exerts an important mitogenic effect, increasing endothelial cell proliferation (Haegerstrand et al., 1990), and has been found to have an important trophic effect in the regeneration of UV-damaged skin (Benrath et al., 1995). In fact, CGRP synthesis is also increased after nerve injury, suggesting that this peptide may also play a role in nerve regeneration. Indeed, CGRP promotes Schwann cell proliferation through activation of certain cAMP pathways (Luger and Schwartz, 1995).

Although neuropeptides have been widely implicated in inflammation, the precise mechanisms underlying neuropeptide-induced extravasation of leucocytes from blood vessels into tissue are not known. This process is central to the development of an inflammatory response and requires adhesion molecule-mediated interactions between the vascular endothelium and circulating leucocytes (Springer, 1990).

Neuropeptide Y, a 36-amino-acid peptide, has been shown to coexist with noradrenaline in sympathetic nerves localized around blood vessels in various vascular beds. In the skin, NPY has been identified in the periarteriolar nerve fibers of the deep and superficial dermal plexuses and in basal cells of the epidermis (Tatemoto et al., 1982), but it has also been found to innervate eccrine sweat glands, myoepithelial components of sweat glands and, to a lesser degree, apocrine glands, sebaceous glands and hair follicles. With this distribution around the cutaneous vasculature, NPY causes vasoconstriction of blood vessels and this vasoconstriction is mediated by post-junctional Y2 receptors (Doods and Krause, 1991). Thus, NPY plays a role in the regulation of skin blood flow and possibly eccrine sweat production. Finally, NPY has also been demonstrated to modulate adrenergic neurotransmission through an endothelium-dependent mechanism (Daly and Hieble, 1987).

There have been many reports on the occurrence of neuropeptides in human skin both under normal and under pathological conditions. Neuropeptides are set to become, in the near future, a new approach to skin therapy. An increasing body of evidence supports the setting up of clinical trials using topical neuropeptide agonists and/or antagonists in the treatment of chronic inflammatory skin disorders, such as post-herpetic neuralgia, prurigo nodularis, localized pruritus, psoriasis, atopic dermatitis, contact dermatitis, cold urticaria, notalgia paresthetica, diabetic neuropathy and Raynaud's phenomenon (Claudy, 1996).

Some syndromes are of interest to both neurologists and dermatologists, because cutaneous involvement may harbinger symptoms of a neurological disease. The aim of this review is to clarify this aspect. Dermatologists need to know when a patient should be referred to a neurologist and should consider this option in those presenting with syndromes of unclear

etiology. Patients with chronic itch, for example, should first be evaluated by dermatologists, but if no dermatological or systemic causes are identified, the possibility of neurological causes should be considered. Twycross et al. (2003), in neuropathic itch syndromes, classified itch as cutaneous or pruritoceptive itch, neuropathic itch and neurological itch. Dermatologists should include neuropathic itch syndromes in their differential diagnoses and should perform an appropriate diagnostic evaluation. Two peripheral diseases, i.e. post-herpetic itch after shingles and a condition caused by several trigeminal nerve root injuries (known by dermatologists as trigeminal trophic syndrome), and one type of brain lesion, i.e. stroke affecting the central trigeminal pathways, are the best known causes of neuropathic itch. The dermatological disorders known as brachioradial pruritus (focal itch on the shoulders or arms) and notalgia paresthetica (itch on the lower part of the torso) are most often caused by underlying radiculopathy from spinal osteoarthritis (Eisenberg et al., 1997; Raison-Peyron et al., 1999); other common causes of radicular pruritus are shingles, truncal diabetic radiculitis and leprosy (Oaklander, 2012).

Cutaneous and nerve lesions following herpes zoster infection

Neuroepidermal tropism of varicella-zoster virus (VZV) accounts for the cutaneous and nerve lesions following herpes zoster infection. Mucosal and skin lesions appear as characteristically grouped vesicles that heal spontaneously in a few weeks and may or may not leave visible scars. Nerve lesions involve peripheral sensory fibers, sometimes causing permanent damage that results in partial denervation of the affected dermatome.

Skin biopsies of VZV-infected dermatomes show a reduction in the dermal nerve network, in particular a reduction of the unmyelinated C fibers and thinly myelinated Aδ fibers. In patients with severe post-herpetic neuralgia, the density of nerve endings in the papillary dermis and epidermis of the affected dermatome is reduced significantly. Interestingly, the extent of this reduction parallels the severity of the patient's neuralgia.

The nerve injury induced by VZV infection affects sensory function. In fact, the predominating symptoms are largely sensory. The main sensory disturbance is post-herpetic neuralgia (PHN), which ranges from constant pain (burning, aching, throbbing), through intermittent pain (stabbing, shooting), to stimulus-evoked pain, also known as mechanical allodynia. This is pain elicited by stimuli that do not normally induce pain. The lancinating pain of early PHN is presumably due to the VZV-induced demyelination of sensory nerve fibers. In fact, loss of the myelinic sheath in two or more adjacent neurites results in the close apposition of denuded axons, which permits action potentials to spread laterally from one axon to another (ephaptic neurotransmission). As a consequence of this "electrical" neurotransmission, multiple nociceptors are triggered on minimal stimulus, causing severe jolts of pain. Demyelination mainly involves fast-conducing afferent fibers (Aδ) and somehow preserves slowly-conducting ones (C fibers). This is why even the lightest mechanical stimuli generate abnormally long-lasting and painful sensations (hyperesthesia including mechanical allodynia). In some cases, a prolonged period of hyperesthesia may unexpectedly bring about a complete loss of touch and pain sensitivity (anesthesia) in the VZV-affected dermatome. Put simply, a reduction in incoming signals from the periphery due to afferent nerve injury produces enhanced electrical activity of the target central neurons, resulting in an initial increase and subsequent decrease or total loss of the sensory function. In addition, some patients complain of severe itching in the affected dermatome. Generation of post-herpetic itch (PHI) may be related to spontaneous firing of denervated central itch-specific neurons or, alternatively, it may be due to relative preservation of peripheral itch-specific neurons from adjacent, uninjured dermatomes after PHN. If neuropathic itch is co-localized with anesthesia, patient scratching can cause painless injuries. Oaklander's report is emblematic in this regard: after an ophthalmic zoster, a patient developed such irrepressible PHI with concomitant loss of pain sensitivity that her persistent painless scratching of her scalp and skull led to self-induced brain injury (Oaklander, 2012; Ruocco et al., 2012).

In the VZV-infected dermatomes, reduction of the sensory nerve fibers, which contain and release neuromediators (such as SP, VIP, CGRP), can result in immunity-related disorders. A large series of "opportunistic" disorders, namely primary or metastatic tumors, infections and immune reactions, may appear in the dermatomes that have been infected by VZV as a consequence of the destabilization of local immunity produced by the viral damage of sensory nerve fibers (Ruocco et al., 2012). Zoster-affected dermatomes become privileged sites for subsequent development of heterogeneous skin disorders characterized by the well-defined "Wolf's post-herpetic isotopic response" (PHIR). The term isotopic response was coined by Wolf et al. (1995) to describe the occurrence of a new skin disorder at the site of a previous, unrelated and already healed cutaneous disease, in most cases a herpetic infection, with an extremely variable latency (days, weeks, months, years, decades). The first report of this phenomenon dates back to 1955, when the world-famous British neurologist Wyburn-Mason (1955) described a series of 26 patients in whom malignant tumors developed at the site of a previous herpes zoster (25 cases) or herpes simplex (1 case) lesion. One of the most striking examples of the connection existing between zoster infection and tumor onset in healed herpes sites is the report by Hudson et al. (1985) of a patient with an angiosarcoma of the head whose topography traced precisely the trigeminal areas (first and second branches) that had been affected by herpes zoster 10 years previously. A wide variety

of cutaneous lesions have been described as occurring within areas cleared of a previous herpetic infection after a highly variable interval. In the zoster-affected dermatome, the immune response may become compromised or generally destabilized (either reduced or amplified). In some cases, this destabilization leads to a defective immune response (as denoted by the local outbreak of opportunistic infections, primary tumors or metastases from internal malignancies); in other instances, destabilization results in excessive local immune reactions (lichen planus, lichenoid chronic graft-versus-host disease, psoriasis, acneiform lesions, drug reactions, post-zoster eosinophilic dermatosis). While post-herpetic sensory symptoms have been well known for a long time, it is only in the last two decades that immunity-dependent disorders occurring in a zoster-affected dermatome have been recognized, focused on and named (Wolf's PHIR) (Ruocco et al., 2009). Regular signaling between sensory fiber-secreted neuropeptides and locally recruited immune cells is a basic requirement for a normal immune response in a given cutaneous district. When nerve integrity is compromised, as occurs in zoster infection, the neuropeptide release is altered and thus inevitably affects local immune control, even if there is no reduction in the immune cell "contingent". If this contingent is reduced or lost, local immune control is obviously knocked out. Bearing in mind that some neuropeptides (e.g. SP) are immune function stimulators, while others (e.g. VIP) are immune suppressors, one could argue that the PHIR can be either reduced or amplified depending on the type of neuropeptide involved in the nerve fiber damage. However, SP, VIP and CGRP all co-localize in C fibers, while Aδ fibers contain and release CGRP rather than SP. It is also known that neuropeptide amounts may vary greatly in sensory nerve fibers, with different proportions of a single neuropeptide being present in different subsets of nerve fibers. Furthermore, depending on incidental circumstances, some neuropeptides can either enhance or inhibit particular immune/inflammatory cell functions. In any case, to the best of our knowledge, neuropeptide amounts in zoster-affected dermatomes have never been evaluated (Ruocco et al., 2012).

Cutaneous manifestations of carpal tunnel syndrome

Carpal tunnel syndrome (CTS) is a frequent neurological impairment caused by compression of the median nerve throughout the carpal tunnel, characterized by numbness, rather than pain, weakness, paresthesia, and loss of sensory discrimination (Foti et al., 2011; Cox et al., 1992; Fast et al., 1989).

There are a few reports of prominent dermatological signs of CTS in the literature, including ulceration, blistering, hypohidrosis, Raynaud's phenomenon, and irritant contact dermatitis (Foti et al., 2011; Cox et al., 1992; Fast et al., 1989).

Recurrent blistering of the fingertips is the most frequently reported of these rare cutaneous signs of CTS, and it affects the fingertips innervated by the median nerve (Foti et al., 2011; Cox et al., 1989). Several pathogenetic theories have been proposed to explain this singular phenomenon including trauma, infections, and autonomic factors (Foti et al., 2011; Cox et al., 1992; Fast et al., 1989). Trauma would be an interesting explanation because of the sensory loss associated with CTS, and it would suggest either thermal or physical trauma; nevertheless, trauma is rarely reported by patients and not all dermatological signs and symptoms could be explained by this hypothesis (Cox et al., 1992).

Primary infections inducing blisters of the fingertips, e.g. blistering distal dactylitis, are reported, but bacterial cultures obtained from bullae rarely give a positive result (Cox et al., 1992).

Autonomic and vasomotor dysfunction caused by nerve compression produces symptoms such as hypohidrosis, swelling, and increased hand temperature, and may be implicated in the pathogenesis of dermatological signs (Cox et al., 1992).

A new pathogenetic theory, based on the immunocompromised district concept (Ruocco et al., 2009), has recently been proposed (Baroni et al., 2012). The suggestion is that dysregulation of neuropeptide release by peripheral terminations of the median nerve, secondary to compression, creates an imbalance between immunostimulating and immunosuppressive neuropeptides, favoring the onset of different dermatological signs (Baroni et al., 2012). According to this hypothesis, the variegated expression of cutaneous signs in CTS would depend on the prevalence of either immunosuppressive or immunostimulating neuropeptides, which would explain, respectively, the presence of infections and blistering or contact dermatitis (Baroni et al., 2012).

Trigeminal trophic syndrome

Trigeminal trophic syndrome (TTS) is a rare cause of facial ulceration, which develops following self-manipulation of the skin after an injury of the trigeminal ganglia or other parts of the PNS/CNS involved in the trigeminal pathway (Rashid and Khachemoune, 2007; Mishra et al., 2011; Kautz et al., 2009). It was first reported by Wallenberg in 1901 (Kautz et al., 2009) as an ala nasi ulcer associated with brainstem infection.

The classical clinical triad of TTS comprises facial paresthesia, trigeminal anesthesia, and crescentic lateral ala nasi ulceration. Ulceration may also involve the cheek and upper lip, and is often preceded by a sensation of burning, itching, crawling and tingling (Rashid and Khachemoune, 2007; Mishra et al., 2011; Kautz et al., 2009).

The syndrome occurs in 18% of patients with post-trigeminal ablation, and usually presents following alcohol injection, surgical ablation, rhizotomy of the sensory compartment of the trigeminal nerve, or coagulation of the Gasserian ganglion (Rashid and Khachemoune, 2007). Ischemic damage of the trigeminal ganglion or Wallenberg's syndrome are also com-

mon preceding events (Rashid and Khachemoune, 2007). Other rarely reported causes are vertebrobasilar insufficiency, acoustic neuroma, post-encephalitis, and amyloid deposits in the CNS and trigeminal nerve (Rashid and Khachemoune, 2007).

The pathogenesis of TTS is still unclear, although several hypotheses have been advanced. It seems to be associated with a physical mechanism of self-mutilation secondary to trigeminal anesthesia and paresthesia (Rashid and Khachemoune, 2007; Mishra et al., 2011; Kautz et al., 2009). Nevertheless, since only a minority of patients experience paresthesia or report picking, other theories should be proposed. In the past, a trophic theory was proposed to explain the ulcer formation (Rashid and Khachemoune, 2007). According to this theory, a CNS disorder, involving the alteration of certain (as yet undiscovered) trophic factor secretions, was at play, rendering them unable to play their role in the maintenance of facial skin (Rashid and Khachemoune, 2007). Moreover, the lack of neurotrophic factors like SP and α-MSH has also been discussed in relation to the pathogenesis of TTS (Mishra et al., 2011).

It is likely that this rare disease, too, involves a more complex dysregulation of neuropeptides, but further investigations are necessary to demonstrate this.

Sarcoidosis

Sarcoidosis is a systemic disease characterized by the presence of non-caseating granulomas. The etiology of this disorder remains obscure, although it is probable that a complex interplay of a variety of host factors and infectious and non-infectious processes, coinciding with a susceptible genetic background, lead to systemic granulomatous inflammation. The disease most commonly affects the lungs, lymph nodes, liver, spleen, phalangeal bones, parotid glands, eyes, and skin (Thomas and Hunninghake, 2003). Although pulmonary involvement occurs in 90% to 95% of cases, cutaneous lesions are present in about a quarter of patients and are generally observed at the onset of the disease, coinciding with or following systemic involvement (Marchell and Judson, 2010). Eruptions caused by sarcoidosis are classified as “specific” (non-caseating granulomas are present in biopsy specimens of tissue) or “non-specific” (lesions develop as a result of a reactive process without the formation of granulomas).

The most common non-specific skin lesion is erythema nodosum. Other non-specific skin findings may occur, but they are exceedingly rare. The neutrophilic dermatoses, Sweet syndrome and pyoderma gangrenosum, sometimes qualify as non-specific cutaneous sarcoid lesions.

Specific lesions develop in 9% to 15% of all sarcoidosis patients. These lesions have a highly variable presentation (papular form, plaques, lupus pernio, angiolupoid sarcoidosis of Brocq-Pautrier).

The occurrence of sarcoidal lesions on traumatized skin sites that gave rise to scars (scar sarcoidosis) is a peculiar and uncommon form of cutaneous sarcoidosis in which old scars become infiltrated, tender and develop a reddish-brown color with non-caseating epitheloid cell granulomas. Clinically, there is spontaneous development of livid or reddish-brown plaques on scars that were previously mostly atrophic. Histologically, scar sarcoidosis presents with granulomas, often containing polarizable foreign bodies whose inoculation as a result of the previous trauma had gone unnoticed. Scar sarcoidosis has been associated with herpes zoster infection, surgery, trauma, tattooing and other events, such as chronic lymphedema, thermal burns, radiation dermatitis and vaccination sites, known to represent the origin of vulnerable skin areas labeled as “immunocompromised districts” (Ruocco et al., 2009). This concept embraces many and various clinical conditions capable of making the affected skin area prone to developing, over time, a wide range of secondary skin diseases, such as opportunistic infections, tumors, or dysimmune reactions, often of granulomatous type (in particular sarcoidosis). Therefore, scar sarcoidosis is probably pathogenically similar to a sarcoidal granulomatous reaction appearing on healed herpes zoster sites (Cecchi and Giomi, 1999). In fact, both clinical conditions result from a local destabilization of immune control caused by either traumatic or viral damage to the local neuroimmune network (Ruocco et al., 2012). In these circumstances, the local immune destabilization manifested by sarcoid reactions seems to be oriented towards an amplification of the local immune response, which can be countered by steroid treatment.

Vasculitic syndromes

Neurological involvement in vasculitic syndromes is frequent and may be the only manifestation of the underlying vasculitic disease; it is estimated to be present in 70% to 80% of vasculitides (Kernohan and Woltman, 1938; Kissel et al., 1989). Neurological involvement in a systemic vasculitis may manifest itself at the level of the CNS or, more frequently, the PNS (as mononeuritis or asymmetric sensorimotor neuropathy) (Kernohan and Woltman, 1938; Kissel et al., 1989; Mathew et al., 2007). Likewise, cutaneous involvement in vasculitic syndromes is not rare and is frequently associated with neurological signs. In particular, polyarteritis nodosa, Churg-Strauss syndrome, Wegener granulomatosis, and cryoglobulinemia commonly present with concomitant cutaneous and neurological involvement (Kernohan and Woltman, 1938; Kissel et al., 1989; Mathew et al., 2007).

Polyarteritis nodosa is a systemic vasculitc syndrome, whose characterizing features are necrotizing inflammatory lesions affecting medium-sized and small muscular arteries, in particular at vessel bifurcations. This histopathological damage results in microaneurysm formation, aneurysmal rupture with hemorrhage,

thrombosis, and, consequently, organ ischemia or infarction (Stone, 2002).

Churg-Strauss syndrome and Wegener granulomatosis are two closely related vasculitides affecting medium-sized and small vessels and associated with antibodies to neutrophil cytoplasmic antigens (Keogh and Specks, 2003).

Cryoglobulinemia is a vasculitic syndrome characterized by the presence of cryoglobulins in the serum and resulting in systemic inflammation, most commonly affecting the kidneys, skin, and PNS, provoked by cryoglobulin-containing immune complexes (Ramos-Casals et al., 2012).

Although clinically different, the above-mentioned vasculitic syndromes could all be characterized by simultaneous cutaneous and neurological involvement, possibly linked to a common pathogenic mechanism linking the PNS to the skin.

Segmental fibrinoid vessel wall necrosis and transmural inflammatory cell infiltration are the main pathological features of vasculitic diseases, while cell-mediated mechanisms seem to be more important in peripheral nerve disease. In particular, T cell-mediated processes against epineurial and endoneurial vessels seem to play a role in the pathogenesis of vasculitic neuropathies (Kernohan and Woltman, 1938; Kissel et al., 1989; Mathew et al., 2007; Stone, 2002; Keogh and Specks, 2003; Ramos-Casals et al., 2012). Moreover, necrotizing vasculitis causes neuropathy through ischemic injury to the vasa nervorum. Nerve injury would produce a local imbalance between immunostimulating and immunosuppressive neuropeptides, favoring the occurrence of different dermatological signs of vasculitic syndromes.

Concluding remarks

This review focuses on many aspects of some diseases that both dermatologists and neurologists can encounter in their clinical practice. The first important aspect is that the skin, given its relationships with the PNS, ANS and CNS, is a neuroimmunoendocrine organ. The skin contains numerous neuropeptides released from sensory nerves, and the molecular mechanisms by which neuropeptides link the neural-immune-endocrine axis is currently the focus of growing attention. Neuropeptides play a precise role in cutaneous physiology, pathophysiology and certain skin diseases. A complex dysregulation of neuropeptides is a feature of some diseases of both dermatological and neurological interest (e.g. cutaneous and nerve lesions following herpes zoster infection, cutaneous manifestations of CTS, TTS). Wolf's isotopic response is the occurrence of an unrelated cutaneous disorder in an area of healed skin previously affected by another pathology; VZV infection, or less often herpes simplex virus infection, is the most common skin disorder predisposing to an isotopic response. The dominance of fungal and viral infections hints at deficient local cellular immunity, as hypothesized by Ruocco et al. (2009), and neuropeptides act as neurogenic modulators of the immune system of the skin, participating in the regulation of cutaneous inflammation. When nerve integrity is compromised, as occurs in zoster infection, neuropeptide release is altered, thus inevitably affecting local immune control, even if there is no reduction in the immune cell "contingent". If this contingent is reduced or lost, local immune control is obviously knocked out. The new pathogenetic theory, based on the immunocompromised district concept (Ruocco et al., 2009), suggests that dysregulation of neuropeptide release from peripheral terminations of the median nerve, secondary to compression, creates an imbalance between immunostimulating and immunosuppressive neuropeptides, favoring the occurrence of different dermatological signs. Accordingly, the variegated expression of cutaneous signs in CTS would depend on the prevalence of either immunosuppressive or immunostimulating neuropeptides which would explain, respectively, the presence of infections and blistering or contact dermatitis. The lack of neurotrophic factors like SP and α-MSH has been discussed in relation to the pathogenesis of TTS.

The aim of this review was to clarify an important clinical and diagnostic aspect: in some clinical cases, cutaneous involvement (e.g. ulceration, blistering, hypohidrosis, Raynaud's phenomenon, irritant contact dermatitis in CTS; sensation of itching, ala nasi ulcer in TTS) may harbinger symptoms of a neurological disease and should prompt the dermatologist to consider referring the patient for a neurological consultation in order to arrive at the correct diagnosis; in other clinical cases, syndromes diagnosed by dermatologists could also be of interest to neurologists (e.g. cutaneous and nerve lesions following herpes zoster). The syndromes dealt with in this review are only some of a large group that might be defined borderline diseases between dermatology and neurology. We would welcome the introduction of two new medical fields that constitute possible new frontiers for close collaboration between dermatologists and neurologists – neuroendocrine-cutaneous-immunology and neurodermatology. Dermatology and neurology in the 21st century should reflect these data and opinions, thereby driving a change in the behavior of these specialist branches of medicine. Given the fascinating future perspectives in neurodermatological diseases, increasing collaboration between dermatologists and neurologists should be encouraged.

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