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MINI REVIEW

The pathogenesis of Prurigo nodularis – 'Super-Itch' in exploration

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Abstract

Prurigo nodularis (PN) is characterized by multiple hyperkeratotic nodules, papules and the presence of intensive pruritus. This leads to an impaired quality of life and high burden due not only to the severe itch but also the chronic, skin lesions and lack of treatment options.
The pathogenesis of PN is not completely clarified. Previous studies have demonstrated just how important the interaction between cutaneous nerve fibres and immune cells is. Besides a reduced intraepidermal nerve fibre density, there are increased dermal levels of neuropeptides such as substance P, calcitonin gene-related peptide and nerve growth factor, as well as a predominant presence of eosinophils and mast cells. An interaction of these factors results in a complex relationship which will be discussed in this article.

1. Introduction

Prurigo nodularis (PN) is characterized by the presence of symmetrically distributed multiple (up to hundreds), highly pruritic, hyperkeratotic, erosive or crusted nodules and papules (Fig. 1). PN is a long-term reaction to the chronic scratching of patients with chronic pruritus (CP). It has been determined that PN may arise from various origins, most notably from dermatological (e.g. atopic dermatitis), systemic (e.g. chronic kidney failure) and neurological (e.g. brachioradial pruritus) diseases. Usually, a single cause for pruritus is not identifiable; multifactorial origins have often been identified and, in some patients, a cause cannot be found (Ständer et al., 2013). The theory that PN is a disease in its own right, as it does not evolve in all but a subset of CP patients, still remains under debate. Even today, the exact pathogenesis and knowledge of predisposing factors that can contribute to PN, besides an atopic predisposition (Iking et al., 2013), continue to be ambiguous. However, this vicious cycle of repeated itching and scratching leads to a high burden and restricted quality of life. The goal of PN treatment is to break this cycle and allow the skin to heal.

An epidemiological study of PN incidence and prevalence does not exist. The availability of PN patients in the daily clinical practice is actually rare, and thus, studying the multiple contributing factors of PN is difficult. It can affect patients in every age group, even children (Amer and Fischer, 2009), but the elderly are the most commonly affected (Iking et al., 2013).

2. Histopathological changes in PN

Changes in almost all skin cell types such as the collagen fibres, epidermal keratinocytes, mast cells, Merkel cells, dendritic cells, eosinophils, endothelial cells, and the epidermal and dermal nerve fibres have been identified in histopathological studies of prurigo nodules (Weigelt et al., 2010; Schuhknecht et al., 2011). Thick compact orthohyperkeratosis, irregular epidermal hyperplasia or pseudoepitheliomatous hyperplasia, focal parakeratosis and hypergranulosis were found in the epidermis; fibrosis of the papillary dermis, an increased number of fibroblasts and capillaries, a dense dermal interstitial and perivascular infiltrate with increased number of

What does this review add?
- The interaction between cutaneous nerve fibres and immune cells play an important role in the pathogenesis of prurigo nodularis.

T-cells, eosinophil granulocytes and mast cells were observed in the dermis in PN lesions. However, modified nerve fibres are possibly of greatest importance.

3. Neuronal factors of prurigo nodularis

Intraepidermal and dermal nerve fibres play an important role in the formation of PN. A change in the density of dermal nerve fibres was able to catch the attention of Pautrier in 1934 (Pautrier, 1934). Other studies with different approaches soon followed, e.g. staining neuropeptides [substance P (SP), calcitonin gene-related peptide (CGRP), nerve growth factor (NGF) or other appropriate receptors (TrkA p75NGF) (Liang et al., 2000; Johansson et al., 2002; Schuhknecht et al., 2011]. These approaches demonstrated thickened and increased numbers of dermal nerve fibres. However, the density of intraepidermal protein gene product 9.5-positive nerve fibres (epidermal peptidergic and non-peptidergic, unmyelinated C-fibres) was reduced (Schuhknecht et al., 2011). This was revealed in a study involving 53 PN patients comparing lesional and non-lesional skin of PN (Fig. 2) with skin from healthy subjects. This reduction in intraepidermal nerve fibre density was independent from clinical parameters (Schuhknecht et al., 2011). Not only due to this observation but also because of the frequently positive response to gabapentin and pregabalin (Fostini et al., 2013), commonly utilized in the treatment of pain and neuropathy, it can be assumed that the intraepidermal nerve fibres are involved as a subclinical sensory small fibre neuropathy in the formation of PN. The hyperplasia of nerves in the dermis and hypoplasia of the epidermis is an interesting finding for PN and might be related to the ongoing generation of pruritus in PN.

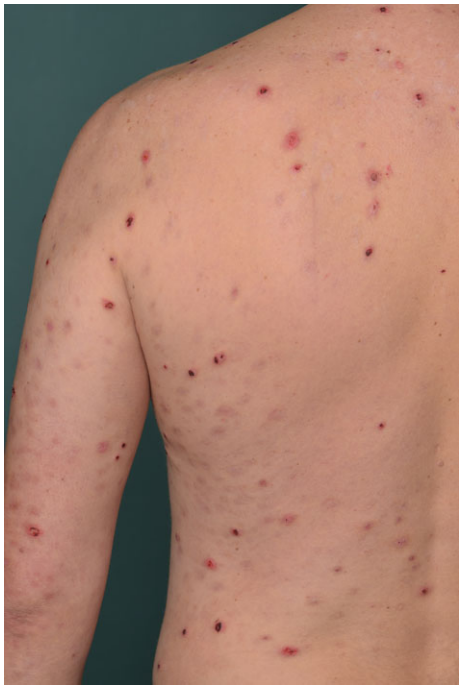

Figure 1 A 47 year old man with PN caused by alcoholic fatty liver disease and psychosomatic co-factors.

4. Interaction between nerve fibres and neuropeptides/neurotrophins

Neuropeptides like SP and CGRP have an increased expression in PN (Liang et al., 2000; Haas et al., 2010). SP is produced and secreted by nerve fibres. After binding to the neurokinin-1 receptor (NK1) in the skin, neurogenic inflammation, vasodilatation of short duration, mast cell degranulation, induction of leukotriene B4 and NGF keratinocyte expression take place. The essential role of SP in PN is underlined by the clinical observation that an SP antagonist (=NK1 antagonist), such as aprepitant, can successfully alleviate pruritus in PN patients (Ständer et al., 2010). CGRP has a similar mecha-

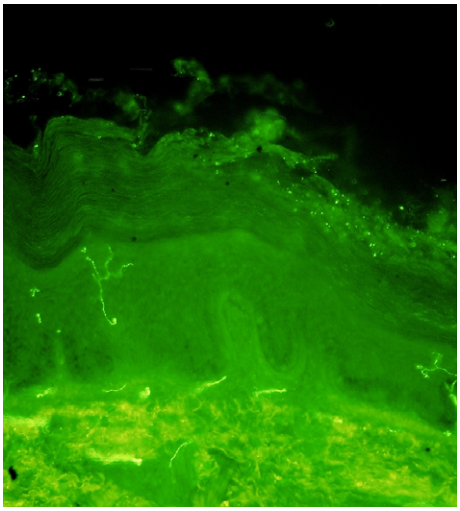

Figure 2 Reduced intraepidermal nerve fiber density in a prurigo lesion.

nism of action as a release of this neuropeptide results in neurogenic inflammation via recruitment and regulation of inflammatory cells, e.g. eosinophils and mast cells (Liang et al., 2000).

Neurotrophins, especially the NGF and NGF receptors such as tyrosine kinase (Trk) and the neurotrophin receptor p75 (p75NTR), are increased in nerve fibres (receptors) in PN (Johansson et al., 2002). NGF, which can be released from mast cells (Groneberg et al., 2005) and also by eosinophils (Kobayashi et al., 2002), leads to activation, sensitization and sprouting of skin nerves, as well as to proliferation and differentiation of keratinocytes. These observations may explain the dermal neuronal hyperplasia and hyperplasia of the epidermis (Matsumura et al., 2015). Topical NGF antagonists may be thus beneficial in treating PN, but have not been investigated in PN until now.

5. PN and inflammation

Inflammation caused by T lymphocytes, eosinophilic granulocytes and mast cells is involved in the development and chronification of PN (Raap et al., 2006). The number of dermal mast cells in skin afflicted by PN is not only increased but their morphology is also altered. The affected cells have an enlarged cell body, less cytoplasmic granules and maintain a dendritic appearance (Liang et al., 1999). Pruritus can be caused by the release of mast cell products such as histamine, tryptase and prostaglandins. Histamine acts directly on sensory nerve fibres via H1 histamine receptors, also inducing the proliferation of fibroblasts and collagen synthesis (Groneberg et al., 2005). Due to the high treatment failure rate of antihistamines, histamine cannot be the major mediator of pruritus in PN. In addition to histamine, mast cells also secrete neurotrophins such as NGF (Groneberg et al., 2005), which may directly induce pruritus by binding to cutaneous nerve fibres (Liang et al., 1998). Eosinophilic granulocytes seem to accumulate in the upper dermis in PN (Johansson et al., 2002). The exact mechanism underlying this remains uncertain. However, the observation that eosinophilic cationic protein (ECP), eosinophil-derived neurotoxin (EDN) and eosinophil protein X (EPX) which have a neurotoxic effect are found extracellularly in biopsies from PN skin supports the assumption that eosinophilic granulocytes are also important in the pathogenesis due to the inflammation and activation of nerve fibres.

The novel T-cell-derived cytokine interleukin-31 (IL-31) can induce severe pruritus in a mouse model (Arai et al., 2013). IL-31 binds to a heterodimerical receptor at TRPV1 (+)/TRPA1 (+)-C-fibres, keratinocytes, macrophages and eosinophils, and thus may be involved in transmission of pruritus and promotion of inflammation. Not limited to the skin, the densest area of this receptor seems to be at the dorsal horn of spinal cord. In addition, IL-31 can also be found in the circulatory system, as patients with atopic dermatitis have IL-31 serum levels correlating with disease severity and Th2 cytokines (Raap et al., 2008). Interestingly, skin biopsies from PN patients with an atopic background, in comparison to healthy skin from healthy individuals, showed a 50-fold up-regulation of IL-31 mRNA (Sonkoly et al., 2006). In sum, it seems likely that IL-31 is an important cytokine for the regulation of PN and represents a potential therapy target.

In summary, it can be concluded that the pathogenesis of PN is still not fully understood; however, there are many indications that neuronal plasticity and the interaction of mediators and nerve fibres play an important role in the onset of PN. An exact understanding of its pathogenesis is important for improving treatment of PN.

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