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Neuroanatomic Signatures in Brachioradial Pruritus, Chronic Prurigo, and Atopic Dermatitis

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Abbreviations:

AD (atopic dermatitis), BRP (brachioradial pruritus), CNPG (chronic nodular prurigo)

To the Editor

In September 2022, Agelopoulos et al., 2023 published an investigation on the density and distribution of intraepithelial sensory nerve fibers using pan-neuronal marker, protein gene product 9.5, in skin biopsies from patients with chronic nodular prurigo (CNPG), atopic dermatitis (AD), and brachioradial pruritus (BRP) and from healthy controls. In addition to a reduced number of intraepidermal nerve fibers in biopsies from all patients compared with those from healthy controls, different neuronal branching patterns were recognized in CNPG, BGP, and AD (Agelopoulos et al., 2023). The authors suggest that these patterns may reflect disease-specific local expression profiles and conclude that in pruritic dermatoses, nerve injury and subsequent sprouting may result from chronic scratching, whereas genuine neuropathy is expected to underlie BRP (Agelopoulos et al., 2023).

Indeed, as shown in Figure 3, the distribution of nerve fibers in biopsies of BRP is different from that occurring in CNPG, AD, and healthy skin (Agelopoulos et al., 2023). However, the most striking feature is the appearance of nerve bundles beneath the basement membrane in the upper dermis of biopsies from patients with BRP. It looks as if the nerve fibers retracted under the epidermal–dermal border to form bundles in the papillary dermis. This neuroanatomic characteristic was also found in another study on 16 patients with BRP (Wallengren and Sundler, 2005). The entrapment of cervical nerves has been described in most patients with BRP and is regarded as causative (Wallengren and Sundler, 2005). In patients living in temperate climates, BRP symptoms are seasonal, appearing in most patients at the end of summer, remitting in winter, and relapsing after summer (Wallengren and Dahlbäck, 2005). It seems that cervical spine disease is a prerequisite, but the symptoms are triggered by prolonged sun exposure. In our previous study on familial BRP, skin biopsies from the lower arm of four sisters were taken during a symptom-free period in winter as well as 6 months later, in late summer when the BRP was active (Figure 1a and b) (Wallengren and Dahlbäck, 2005; Wallengren and Sundler, 2005). Hypothetically, the nerve bundles in the upper dermis could fire spontaneously, starting the itch circuit. In such case, the neuroanatomic signature of BRP would be located in the upper dermis, beneath the basement membrane. Probably, it takes multiple nerve injuries to trigger the symptoms (Upton and McComas, 1973). The theory of double crush in entrapment syndromes suggests that the distal part of an axon is easily damaged when another part of this axon is under compression (Upton and McComas, 1973). Thus, individuals with cervical arthrosis would be more prone to develop BRP when exposed to the sun, damaging epidermal nerves. Interestingly, patients with BRP report scratching to intensify pruritus and put ice on itchy skin to cool it instead, the so-called ice pack sign (Bernhard and Bordeaux, 2005).

Figure thumbnail gr1

Figure 1 **Innervation in skin biopsies taken from a patient with BRP illustrated by PGP-IR. (a) Biopsy taken during the symptom-free period in the winter. (b) Biopsy taken during pruritic period in late summer. Note the (a) intraepidermal nerve fibers in winter biopsy and the (b) subepithelial bundles of PGP-IR in summer biopsy. This image originates from a project in cooperation with Frank Sundler (Wallengren and Sundler, 2005), reprinted from Wallengren and Sundler, 2005, with permission from Elsevier. BRP, brachioradial pruritus; PGP-IR, protein gene-product immunoreactivity.**

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In previous studies, reduced density of epidermal nerve fibers in CNPG was interpreted as subclinical cutaneous neuropathy alternatively as the effect of scratching (Pereira et al., 2017; Schuhknecht et al., 2011). The patients in these studies had no topical or systemic treatment for 2 weeks before biopsies were taken, and patients confirmed scratching of the prurigo nodules (Pereira et al., 2017; Schuhknecht et al., 2011). Also in this study, patients were left without systemic treatment for 4 weeks, and without topical treatment for 1 week before biopsies were taken (Agelopoulos et al., 2023). On the basis of the branching pattern, the authors suggest scratching to cause fragmentation and subsequent sprouting of nerve fibers in the epidermis (Agelopoulos et al., 2023). On the other hand, early studies on prurigo, demonstrated proliferation of nerve fibers in the dermis or even neurinoma which was believed to be a prerequisite of CNPG diagnosis (Pinkus and Mehregan, 1976). Later studies have shown conflicting results, but proliferation of sensory nerve fibers in the papillary dermis seems to be the most common finding in CNPG (Fostini et al., 2013).

Reduction of epidermal nerve fiber density in patients with AD in this study is to my knowledge previously unreported. In a recent publication, no difference in the density of epidermal nerve fibers was found; however, the nerves appeared elongated in AD (Tsutsumi et al., 2016). Some other investigations reported epidermal nerve fibers to proliferate in lesional AD skin (Emtestam et al., 2012; Järvikallio et al., 2003; Kubanov et al., 2015). Several studies have also shown an increased number of nerve fibers in the dermis of lesional skin of AD compared with that of healthy skin (Emtestam et al., 2012; Järvikallio et al., 2003; Kubanov et al., 2015; Lönndahl et al., 2019). The discrepancy between the present investigation and the other studies cited may be the status of the lesional skin that was investigated. Untreated dermatitis itches more, scratching being intensified. The question is whether the studied skin was intact or lichenified. Some authors pointed out that the biopsies were taken from early lesions that were probably not chronically scratched (Emtestam et al., 2012).

Maybe the proliferation of nerve fibers in the dermis of patients with CNPG and AD with the release of neurotransmitters with vasoactive and proinflammatory properties (neurogenic inflammation) is enough to activate itch (Wallengren, 1997). To exclude the effects of scratching, it would be interesting to perform studies on innervation in CNPG and AD by taking biopsies from lesions covered for about 10 days with hydrocolloid dressings to prevent the effect of scratching and to repair skin surface.

In conclusion, reduced density of intraepidermal nerve fibers seems to be secondary to trauma: sun in the case of BRP and scratching in the case of CNPG or AD. In BRP, epidermal nerves damaged by the sun seem to retract to the papillary dermis and form bundles that might fire spontaneously, whereas compression of nerve roots in the neck may potentiate conduction of itch (double crush). Reduced density of epidermal nerve fibers due to scratching is probably not responsible for the primary pruritus in CNPG and AD but gives an explanation for why scratching worsens pruritus. The neuroanatomical features described here are of clinical significance. They explain why drugs targeting neuronal receptors and channels relevant to itch transmission are very effective in severe BRP that requires treatment, whereas CNPG or AD respond better to immunomodulators.

Data availability statement

No datasets were generated or analyzed during this study.

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Conflict of Interest

The author states no conflict of interest.

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Author Contributions

Conceptualization: JW; Data Curation: JW; Formal Analysis: JW; Investigation: JW; Methodology: JW; Project Administration: JW; Supervision: JW; Validation: JW; Visualization: JW; Writing – Original Draft Preparation: JW; Writing – Review and Editing: JW

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