Neuroimmune gene signature of prurigo nodularis compared to psoriasis and atopic dermatitis

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Introduction: Prurigo nodularis (PN), atopic dermatitis (AD), and psoriasis are intensely itchy skin diseases associated with variable degrees of neuroimmune dysregulation. Psoriasis and AD are classically characterized by Th1/Th17 and Th2 polarization, respectively, but the neuroinflammatory profile of PN as compared to these conditions remains poorly defined.

Aims: To characterize the neuroimmune phenotype of PN compared to AD, psoriasis, and healthy controls (HC), we performed transcriptomic analysis of lesional and nonlesional skin biopsies from 25 PN patients, 27 AD patients, 15 psoriasis patients, and 12 HC using a custom neuroinflammation-focused NanoString® panel of 770 genes.

Results: Analysis of affected versus unaffected skin revealed differentially expressed genes (DEGs, fold change>1.5, p<0.05) associated with Th1, Th2, and Th17 activation in all three diseases. Upregulated DEGs in PN compared to AD and psoriasis were primarily associated with extracellular matrix (ECM) remodeling or neural function. Expression of IL-31 was upregulated in PN compared to psoriasis but not AD. Downregulated DEGs in PN compared to AD were associated with Th2 activation and glutamate receptors, while those compared to psoriasis were related to Th1 and Th17 activation. DEGs in nonlesional PN skin compared to HC included macrophage markers and indicators of complement activation, whereas no DEGs were seen in nonlesional AD skin compared to HC.

Conclusions: These findings suggest that PN has a distinct neuroinflammatory signature characterized by intermediate Th1/Th17 and Th2 immune axis activation in comparison to AD and psoriasis, with increased levels of ECM dysregulation, neuronal abnormalities, and IL-31 activity. Compared to HC, dysregulation of nonlesional skin was seen in PN but not AD; in particular, macrophage and complement abnormalities suggest immune-driven extralesional disease or predisposition to disease in PN. These results enhance our understanding of the underlying mechanisms of PN compared to other skin diseases.