4A

CHAPTER 4A
Reply to: "Pruritus with pemphigoid autoantibodies is the tip of an iceberg"

Aniek Lamberts*[1], Joost M. Meijer*[1], Gilles F.H. Diercks[1,2], Hendri H. Pas[1], Barbara Horváth[1]

** Authors contributed equally*

Center for Blistering Diseases, Department of Dermatology[1], and the Department of Pathology[2], University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

In reply to: Byth LA. Pruritus with pemphigoid autoantibodies is the tip of an iceberg. Journal of the American Academy of Dermatology, 2019 Nov;81(5):e151.

Published in the Journal of the American Academy of Dermatology, 2019 Nov;81(5): e153-e154.

To the editor: We appreciate the response of dr. Byth to our article[1], and agree that nonbullous pemphigoid (NBP) deserves more attention in the clinical practice guidelines for chronic pruritus, as a rather unknown cause of chronic pruritus in elderly patients.[2,3] We politely disagree with dr. Byth that NBP patients with pruritus without rash should be referred to as '*pruritus with pemphigoid autoantibodies (PPA*)'. Firstly, we advocate for NBP as umbrella term for all pemphigoid variants without blisters, and believe that introducing the term PPA is needless and confusing. Secondly, PPA does not accurately describe the intended population of NBP patients without primary skin lesions, since all patients with bullous pemphigoid (BP) and NBP experience pruritus and have pemphigoid autoantibodies.

Dr. Byth questioned whether testing for pemphigoid autoantibodies in elderly patients with pruritus would be cost-effective. In our opinion, the burden of disease in these patients with chronic pruritus is too high to deny them a possible diagnosis of NBP and adequate therapy. Therefore, we included pemphigoid in the standard diagnostic workup of elderly patients with chronic pruritus.
We like to emphasize that caution is needed if only ELISA is used as screening method, as these have frequent false positive results. The recently published article of Wang *et al.*[4] reports positive BP180 and BP230 autoantibodies by ELISA in 208 patients with a negative skin biopsy for direct immunofluorescence (DIF). Various lesion morphologies were described in these patients, most commonly dermatitis, but also essential pruritus. The authors conclude that low positive levels of BP180 and BP230 autoantibodies should not be overinterpreted as evidence for BP in the setting of a negative DIF, and still consider DIF positivity to be the golden standard for diagnosis of NBP.

Recent work of our group assessed this clinical dilemma with a diagnostic accuracy study in 1125 patients suspected of NBP or BP, providing minimal diagnostic criteria.[5] IIF on salt-split skin (SSS) showed a positive predictive value for diagnosis of pemphigoid of 99.6%, and therefore plays an essential role for the serological diagnosis of pemphigoid. The BP180 NC16A ELISA showed frequent false-positivity (11,3%) and is not recommended for initial diagnosis, but only for disease monitoring in confirmed patients. The established minimal diagnostic criteria consists of a 2 out of 3 rule: (1) pruritus and/or predominant cutaneous blisters, (2) linear (n-serrated) IgG and/or C3c deposits by DIF on a skin biopsy specimen, and (3) positive epidermal side staining of IgG by IIF SSS on a serum

sample. Thereby, extending the spectrum of pemphigoid with the unrecognized nonbullous variant, and allowing a diagnosis with negative DIF.

Our article complements the study of Wang *et al*., demonstrating the use of the minimal diagnostic criteria in the broad spectrum of NBP. In conclusion, not all patients with '*pruritus with pemphigoid autoantibodies'* with ELISA positivity have pemphigoid, and IIF SSS positivity is essential for diagnosis in DIF negative cases.

References

1. Lamberts A, Meijer JM, Pas HH, Diercks GFH, Horvath B, Jonkman MF. Nonbullous pemphigoid: insights in clinical and diagnostic findings, treatment responses and prognosis. *J Am Acad Dermatol*. 2019 Aug;81(2):355-363. doi:10.1016/j.jaad.2019.04.029
2. Weisshaar E, Szepietowski JC, Dalgard FJ, et al. European S2k Guideline on Chronic Pruritus. *Acta Derm Venereol*. 2019;99(5):469-506. doi:10.2340/00015555-3164
3. Millington GWM, Collins A, Lovell CR, et al. British Association of Dermatologists' guidelines for the investigation and management of generalized pruritus in adults without an underlying dermatosis, 2018. *Br J Dermatol*. 2018;178(1):34-60. doi:10.1111/bjd.16117
4. Wang M, Lehman JS, Camilleri MJ, Drage LA, Wieland CN. Circulating bullous pemphigoid autoantibodies in the setting of negative direct immunofluorescence findings for bullous pemphigoid: A single-center retrospective review. *J Am Acad Dermatol*. 2019;81(2):472-479. doi:10.1016/j.jaad.2019.03.062
5. Meijer JM, Diercks GFH, de Lang EWG, Pas HH, Jonkman MF. Assessment of Diagnostic Strategy for Early Recognition of Bullous and Nonbullous Variants of Pemphigoid. *JAMA dermatology*. 2019 Feb 1;155(2):158-165. doi:10.1001/jamadermatol.2018.4390