5

CHAPTER 5
Prevalence of pemphigoid as a potentially unrecognized cause of pruritus in nursing home residents

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Bullous pemphigoid may commonly present as pruritus in elderly patients.[1] Approximately one in five patients with pemphigoid has nonbullous skin manifestations that resemble other pruritic skin diseases, termed nonbullous pemphigoid.[1,2] According to recently established minimal diagnostic criteria the diagnosis of bullous and nonbullous pemphigoid can be based on either a skin biopsy, or a serum sample.[2] The prevalence of bullous pemphigoid strongly increases with age and the disease is associated with neurodegenerative diseases, such as dementia and Parkinson's disease.[3,4] Our aim was to assess the prevalence of pemphigoid in a high-risk population of nursing home residents, with nonbullous pemphigoid a potential unrecognized cause of pruritus.

Methods

This prospective cross-sectional study was conducted in seven nursing homes affiliated with the University Network for Elderly Care of the UMCG in the Netherlands between July 2016 and December 2017. Participants aged 65 years or older were eligible when a routine vena punction was scheduled and one extra blood sample could be withdrawn. Exclusion criteria were systemic immunosuppressive therapy or life expectancy of less than four weeks. Written informed consent was required of cognitively capable participants, or legal representatives of cognitively impaired participants.

Pruritus was assessed by skin examination using the Bullous Pemphigoid Disease Area Index (BPDAI) excoriation score. Cognitively competent participants rated pruritus from 0 to 10, and for cognitively incompetent participants nursing staff was interviewed about signs of pruritus. Diagnostic criteria for pemphigoid were: 1) pruritus and/or skin blisters, and 2) positive epidermal side staining of IgG by indirect immunofluorescence on salt-split skin (IIF SSS).[2] A skin biopsy for direct immunofluorescence (DIF) was only performed on voluntary basis due to ethical considerations.

Results

We enrolled 125 nursing home residents (figure 1) on average 84.1 years [SD 6.9], with a history of neurodegenerative disease in 75%. Pruritus was present in 59 of 125 participants (47%) and of chronic duration (>6 weeks) in 48 participants (81%). Pemphigoid was diagnosed in seven of 125 participants, yielding an overall prevalence of 6%. Table 1 describes the clinical and serological findings. Three

participants with bullous pemphigoid had already been diagnosed. Nonbullous pemphigoid was unrecognized and newly diagnosed in four participants, all of whom had a history of chronic pruritus. Nonbullous skin manifestations consisted of erythematous papules/nodules, urticarial plaques and excoriations, mainly distributed on the back and extremities (figure 2). Non-specific serological findings in controls were single detection of IgA by IIF SSS (two cases), and low titers of IgG autoantibodies by BP180 NC16A (ten cases) or BP230 ELISA (three cases).

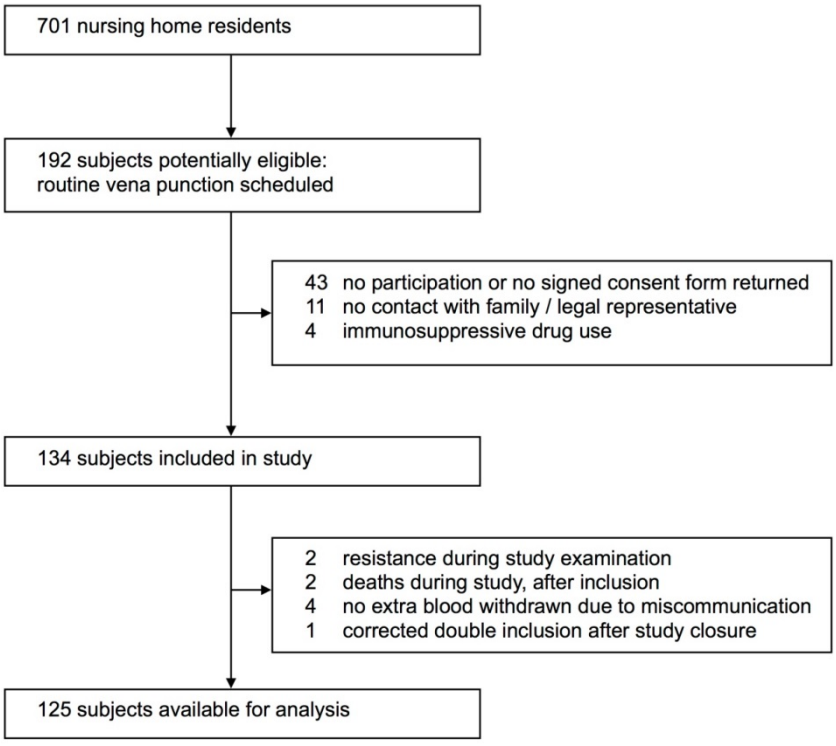

Figure 1. Flowchart of the study.

Discussion

We observed a prevalence of pemphigoid of 6% among nursing home residents. More than half of the cases did not show blisters and had not yet been diagnosed with pemphigoid.

Only two previous studies assessed bullous pemphigoid in nursing home residents, and reported a prevalence of 1% by survey[5], and an annual incidence of 5% by skin biopsy.[6]

Our study confirms that the prevalence of pemphigoid is substantially higher in nursing home residents than in the general population, which was estimated at 0.026% in total and 0.3% in persons aged ≥85 years (data provided by the authors).[3] Possibly this finding might be explained by neurodegenerative diseases preceding development of pemphigoid as a result of cross-reactivity between neuronal and epithelial isoforms of the pemphigoid antigens.[4] While the confirmative IIF SSS test is highly specific, the sensitivity is approximately 80% and a skin biopsy for DIF required to exclude pemphigoid in negative cases.[2]

The striking finding of this study that nonbullous pemphigoid was more frequent than bullous pemphigoid merits attention from clinicians. We therefore recommend to include pemphigoid in the diagnostic work-up of chronic pruritus in elderly patients.

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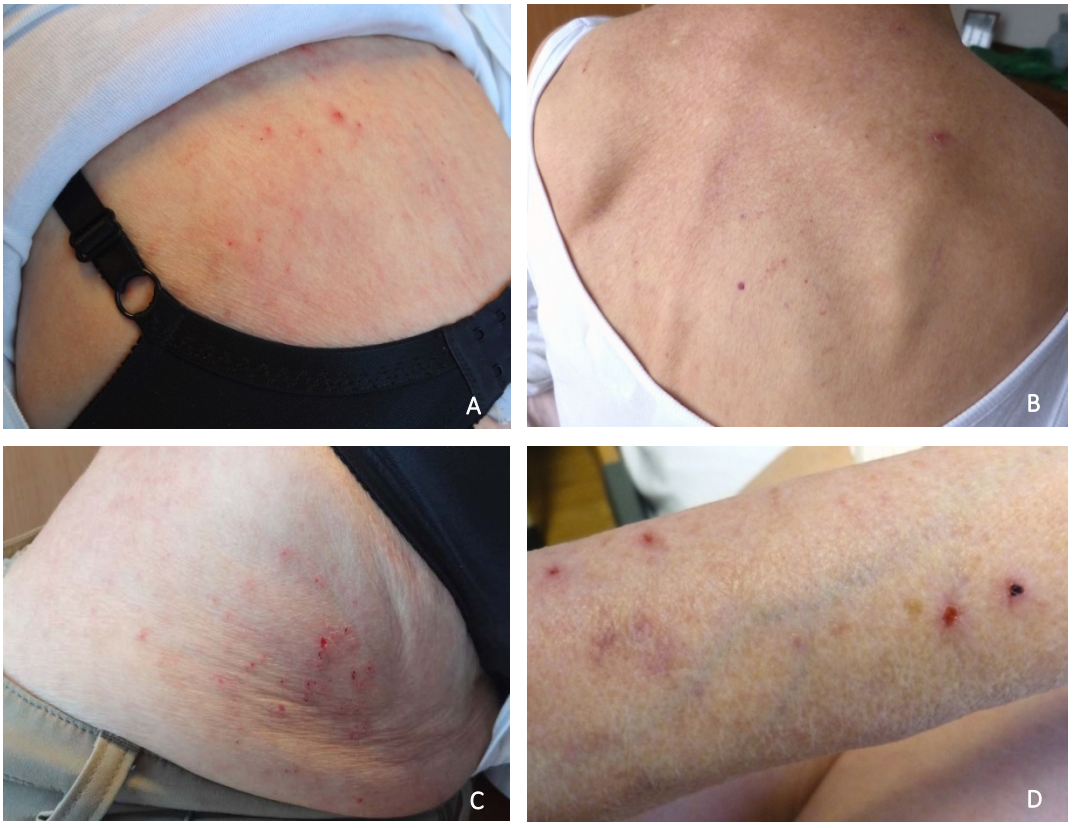

Figure 2. Clinical features of a 89 year old female nursing home resident with nonbullous pemphigoid. A) Excoriated erythematous papules and excoriations on the back.
B) Complete remission achieved after 6 weeks of treatment with methotrexate 7.5mg per week monotherapy. C) Excoriated papules and urticarial plaques on the right flank.
D) Excoriated erythematous papules and nodules on the left arm.

Table 1. Characteristics of nursing home residents diagnosed with pemphigoid

Sex / age (years), pemphigoid phenotype	Clinical findings, skin lesions and distribution	IIF SSS (roof staining)	IIF ME	Antigen by ELISA BP180 NC16A, BP230, immunoblot	DIF* anti-BMZ	Treatment and follow-up (duration)
F / 83, bullous	mild pruritus, moderate blisters, erythema, excoriations and hyper-pigmentation on abdomen, back and extremities	IgG 3+	IgG +	BP180, BP230	n.a.	Lesional super potent corticosteroids Partial remission (9 months), until death due to natural causes.
M / 81, bullous	severe pruritus, generalized blisters, erosions, erythema, papules and urticaria	IgG 3+ IgA 1+	IgG +/-	BP180	IgG, C3c linear	Oral corticosteroids, doxycycline, lesional super potent corticosteroids Death due to natural causes shortly after study examination
F / 73, bullous	mild pruritus, localized blisters on legs with excoriations, hyper-pigmentation and hematoma	IgG 1+	IgG +	BP180, BP230	IgG, C3c n-serrated	Oral corticosteroids, methotrexate (15 mg/wk) and lesional super potent corticosteroids Complete remission (18 months)
M / 84, nonbullous	severe generalized pruritus with excoriations, papules, erythema	IgG 1+	IgG +	BP230	IgA n-serrated	Doxycycline, whole-body super potent corticosteroids. Partial remission (17 months)
F / 89, nonbullous	severe pruritus with excoriations, erythema, papules and urticaria on back and extremities	IgG 3+	IgG +	BP230	negative	Methotrexate (7.5mg/wk) led to complete remission (11 months), flare after tapering and complete remission (9 months) after retreatment
F / 81, nonbullous	severe pruritus with excoriations, erythema and urticaria on back and extremities	IgG 1+	IgG +	BP230	negative	Methotrexate (7.5mg/wk) led to complete remission (7 months), flare after tapering and complete remission (1 month) after retreatment, until death due to natural causes.
F / 83, nonbullous	mild pruritus with erythema, papules and excoriations on extremities	IgG 2+	IgG +	BP230	negative	Topical steroid ointments Complete remission (18 months)

F, female; M, male; IgG, immunoglobulin G; IgA, immunoglobuline A; C3c, complement C3; +, positive; -, negative; +/-, doubtful positive; IIF, indirect immunofluorescence; SSS, salt-split skin; ME, monkey esophagus; ELISA, enzyme linked immunosorbent assay; NC16A, non-collagenous 16A domain of BP180; DIF, direct immunofluorescence; BMZ, basement membrane zone. *No study requirement, performed at voluntary basis

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