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Classification of cutaneous manifestations in patients with non-celiac gluten sensitivity (NCGS) and wheat allergy (WA)

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1 **Article type:** Research letter

2 **Classification of cutaneous manifestations in patients with non-celiac gluten sensitivity**
3 **(NCGS) and wheat allergy (WA)**

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24 Skin symptoms associated to gluten related disorders (GRD) are becoming more
25 frequent, especially in non-celiac gluten sensitivity (NCGS) and wheat allergy (WA),
26 however, very few data exist¹. Our aim was to try to describe the cutaneous
27 manifestations in WA and NCGS.

28 A total of 339 patients (163 NCGS and 176 WA) have been analyzed with a
29 cutaneous, allergological and gastroenterological evaluation. They were 217 females
30 and 122 males. Mean age was 44 years (ranging between 3-85 years). All patients
31 showed gastro-intestinal symptoms: 80% reported abdominal pain and meteorism, the
32 remaining 20% referred changes in bowel habit (as diarrhea, constipation and/or
33 nausea).

34 Regarding NCGS, we found a higher incidence in women (115F:48M), while this
35 correlation was inverse in children (0-14 years). Respiratory symptoms were present in
36 70% of NCGS patients, consisting in seasonal rhinitis, conjunctivitis and/or asthma,
37 although only 23.3% was positive to grasses. The 65.6% showed cutaneous
38 manifestations as follows: eczematous dermatitis (45%), urticaria-
39 angioedema (36.4%), generalized itching (10%) and psoriasiform lesions (9%) (Fig. 1a).
40 Among eczematous dermatitis, we found that 35% consisted in atopic dermatitis
41 (AD), 10% chronic hand eczema (CHE), 15% AD localized to the hands (AD/CHE),
42 15% psoriasiform-dermatitis localized to the volar surface of the
43 hands (psoriasiform/CHE) and 25% generalized eczematous dermatitis (Fig. 1a and
44 Figs. 2a-b). Performing Chi² test, there was a significant inverse correlation between

positive test to grass pollen and NCGS($p<0.01$), highlighting that if the patients were tested positive on grass pollen, the probability was 97.57% lower to suffer from NCGS than patients who were tested negative. The multivariate confirmed the statistical significance.($p<0.001$).

Regarding WA, the incidence was higher in women(102F:74 M), showing a peak in the range 35-54 years; 93% of patients were positive to grasses, but only 26% reported seasonal respiratory symptoms. Cutaneous manifestations were present in 69.3% of cases and are classified in Fig.1b and Figs 2 c-d. Performing Chi² test we found a high correlation between grasses and WA($p<0.001$), highlighting that in patients tested positive on grass pollen, the probability was 40.24% higher to suffer from WA, than the negative ones. Multiple logistic regression confirmed the significance for the variable grasses($p<0.001$).

GRD can affect at least 3% of the population² and are divided in autoimmune (as CD, accounting 1% of GRD), allergic (as WA, accounting 10 % of GRD) and non-autoimmune and non-allergic disorders as NCGS, that accounts about 6% of GRD.³

Recently, Volta et al.⁴ showed a strong correlation between NCGS, female sex and adulthood. The authors observed a cutaneous involvement in 29% of patients, although in 18% of them it was not possible to establish a clear skin disease. Another study¹ enrolled 17 patients with NCGS and cutaneous manifestations, with a prevalence of the female sex and adulthood, highlighting that 59% of patients had skin disorders similar to a sub-acute eczema and/or to a dermatitis herpetiformis.

66 Regarding the presence of psoriasiform dermatitis in NCGS, while the association
67 between psoriasis, CD and GFD had been identified,²⁻⁴ no data exist on a possible
68 connection between NCGS/WA and psoriasis and/or psoriasiform dermatitis.

69 All NCGS patients reported the improvement of the symptoms (abdominal, cutaneous
70 and systemic) after a GFD. Moreover, as only 23.3% of patients showed sensitization
71 to grasses, the overall sensitization wasn't statistically significant, showing how in
72 NCGS the allergic IgE-mediated component is not predominant, as in WA.

73 In literature, regarding cutaneous manifestations in WA, there are reported cases of
74 urticaria, angioedema and AD.³ Specifically, Čelakovská et al. reported a correlation
75 between WA and the worsening of AD in 4.5% of adult patients.⁵ Also our 163(93%)
76 WA patients sensitized to grasses reported a worsening of cutaneous manifestations
77 after grain ingestion and during the pollen season, with a prevalence in aero-exposed
78 body areas. An important role in these immunological reactions is also played by
79 cross-allergies, although there are no data on cutaneous manifestations in WA
80 patients and the possible role of cross-reactivity between wheat and grasses.

81 GFD remains the only "therapy" currently available, resulting in a global
82 improvement in symptoms. Antihistamines and/or corticosteroids can be used only
83 for brief periods, in order to reduce the cutaneous symptomatology, together with
84 emollient creams. Immunotherapy may be also as a valid therapeutic option.

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104 **Figure legends.**

105 **Figure 1.** (a) Cutaneous manifestations and sub-classification of eczematous diseases
106 in NCGS group. (b) Cutaneous manifestations and sub-classification of eczematous
107 disorders in WA patients.

108 **Figure 2.** (a) 71-years-old man, affected by NCGS, with generalized eczematous
109 dermatitis; (b) psoriasiform/CHE in a 58-year-old man with NCGS. (c) 30-year-old
110 woman with WA and urticaria appeared after wheat intake; (d) CHE in a 68-year-old
111 woman with wheat and grass pollen allergy.

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