Markers of non-coeliac wheat sensitivity in patients with myalgic encephalomyelitis/chronic fatigue syndrome

We recently reported in *Gut* that non-coeliac wheat sensitivity (NCWS) is associated with a state of systemic immune activation in conjunction with a compromised intestinal epithelium.[1] Patients with NCWS experience GI symptoms, most commonly including abdominal pain and bloating, as well as extraintestinal symptoms, among which fatigue, headache and cognitive difficulties feature prominently.[1 2] A principal component analysis of the generated data from our study, including markers of antibody reactivity to wheat gluten, intestinal cell damage and systemic innate and adaptive immune responses to microbial components, found clustering of the patients and controls into discernible groups and demonstrated the potential utility of the identified biomarkers for identifying patients with NCWS.[1]

Extreme fatigue, in particular one that does not improve with rest, is a hallmark of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).[3] Immune system abnormalities have been found to be associated with symptoms in a substantial number of patients with ME/CFS.[4 5] Furthermore, many patients complain of GI symptoms of unknown aetiology.[6–8] We considered whether a subset of patients with ME/CFS may exhibit serologic markers associated with NCWS, which might explain some of the corresponding symptoms. We screened serum samples from 131 patients with ME/CFS and 86 healthy controls (table 1), recruited as previously described,[9] for the same markers as those in the above-mentioned study on NCWS.[1] Questionnaires were used to assess GI symptoms within the past 6 months, including abdominal pain, bloating and nausea. Severity of individual symptoms was scored from 1 to 5 (1=absent; 2=mild; 3=moderate; 4=severe; 5=very severe), and a total score, based on the sum of individual symptom scores, was calculated for each subject.

Using the previously generated data from the original cohorts of NCWS, coeliac disease and control subjects (table 1),[1] we configured a discriminant function to identify potential cases of NCWS and coeliac disease among the subjects in the ME/CFS and associated control groups. Linear discriminant analysis (Minitab 17 (Minitab) software) was used to calculate the probability of each ME/CFS and control subject belonging to any one of the three categories of NCWS, coeliac disease and healthy control. The threshold for assigning a subject to a category was arbitrarily set at a calculated probability of 0.75. Accordingly, the algorithm identified one (0.76%) patient with ME/CFS and two (2.3%) control subjects as belonging to the coeliac disease group (P=0.3). In contrast, 20 (15.3%) patients with ME/CFS and 4 (4.6%) control subjects were categorised in the NCWS group (P=0.015). There was also a significant correlation between the calculated NCWS probability and the GI symptom severity total score in patients with ME/CFS (r=0.231, P=0.011).

Our results suggest that there may be a subset of patients with ME/CFS who have sensitivity to wheat and related cereals in the absence of coeliac disease, with potential relevance to some of their symptoms. ME/CFS is recognised as a condition with a spectrum of clinical phenotypes and underlying aetiologies. Characterisation of patients into subsets based on clinical and biological data is essential to gaining a better understanding of the condition and identifying useful biomarkers and therapeutic targets. The results of this analysis provide a rationale for examining the clinical and therapeutic relevance of food sensitivity, particularly NCWS, in the context of ME/CFS in future studies.

Table 1 Demographic characteristics of study cohorts

Subject group	Number of subjects	Mean age—years (SD)	Female sex—no. (%)	White race—no. (%)
Original cohorts*				
NCWS	80	34.6 (10.3)	62 (78)	80 (100)
Coeliac disease	40	34.5 (13.7)	30 (75)	40 (100)
Healthy†	40	35.0 (12.8)	30 (75)	40 (100)
Secondary cohorts‡				
ME/CFS	131	50.0 (11.4)	89 (68)	117 (91)
Healthy†	86	50.0 (12.8)	68 (79)	80 (93)

*Cohorts used to generate the discriminant function. For more information about these cohorts, see reference 1.
†There is no subject overlap between the two healthy control cohorts.
‡Cohorts on which the discriminant analysis was performed.
ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; NCWS, non-coeliac wheat sensitivity.

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