



Alimentary Tract

The perspective of celiac disease patients on emerging treatment options and non-celiac gluten sensitivity



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ABSTRACT

Background: Non-celiac gluten sensitivity (NCGS) and emerging treatment options are hot topics in the celiac disease (CeD) scientific literature. However, very little is known about the perspective on these issues of CeD patients.

Methods: We performed a large patient survey among unselected CeD patients in Switzerland.

Results: A total of 1689 patients were analyzed. 57.5% have previously heard of NCGS. 64.5% believe in the existence of this entity. Regarding a potential influence of NCGS on CeD awareness, 31.7% show a positive and 27.5% a negative perception. Patients with prior use of alternative medicine and women more often have heard of and believe in the existence of NCGS vs. those never having used alternative methods and men, respectively (66.9 vs. 56.9%, $p = 0.001$ and 78.5 vs. 69.0%, $p = 0.001$; 60.7 vs. 44.2%, $p < 0.001$ and 71.0 vs. 60.8%, $p = 0.002$). Women and patients ≥ 30 years more often show a negative attitude towards NCGS (32.2% vs. 24.8%, $p = 0.024$ and 32.2% vs. 24.2%, $p = 0.018$). With regard to emerging treatment options for CeD, 43.3% have previously heard of novel agents, more women than men (46.0 vs. 38.0%, $p = 0.019$).

Conclusions: Perception of and attitude towards NCGS differ depending on sex, age and prior use of alternative medicine. Knowledge of the progress towards emerging treatment options is currently limited.

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1. Introduction

Non-celiac gluten sensitivity (NCGS) is a condition in which symptoms are triggered by gluten ingestion, in the absence of celiac-specific antibodies and/or classical celiac villous atrophy, with variable HLA status and variable presence of first generation anti-gliadin antibodies [1]. HLA DQ2 and DQ8, which are present in virtually all celiac disease (CeD) patients [2], are only found in 50% of all NCGS cases, which is only slightly higher than its prevalence in the general population [3]. NCGS along with CeD and

wheat allergy belong to the group of gluten-related disorders [3]. While CeD is autoimmune-mediated and wheat allergy shows an allergic IgE-mediated immune response, NCGS is neither based on an autoimmune, nor an allergic immune mechanism [4]. In 2010, NCGS was first described as an entity clearly distinct from CeD [5]. Despite the initial skepticism about the concept of this disorder among CeD experts, NCGS has matured to become a major topic in the scientific literature [1] and the lay press within the last few years. Although details remain elusive, pathogenesis of NCGS might involve innate immunity [4] as suggested by prior studies demonstrating increased toll-like receptor expression in NCGS patients compared to controls [5,6]. Nonetheless, it remains unclear, if gliadin [7–9] or other wheat, rye and barley derivatives are the causative agents [10]. Hence, the term non-gluten wheat sensitivity is preferred by some experts and peptides different from gluten might be the target of the pathogenic immune response. Finally, the possibility that NCGS might be a variant of nutrient-dependent irri-

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table bowel syndrome (IBS) has been proposed: a diet restricted in fermentable oligo-, di-, mono-saccharides and polyols (FODMAP) is an effective treatment of IBS [11]. Since many gluten-containing foods are an abundant source of FODMAPs, restriction of gluten also entails restriction of FODMAPs. After FODMAP withdrawal and blinded re-challenge with gluten only a minority (8%) of NCGS-patients showed gluten-specific effects, suggesting that the main effect results from FODMAP rather than gluten intake.

As a consequence, proper diagnosis of NCGS is a clinical challenge. NCGS is characterized by onset of symptoms appearing soon after gluten ingestion and disappearing upon gluten withdrawal. Symptoms reported are non-specific [1] and include IBS-like symptoms and systemic manifestations such as fatigue, headache or muscle pain [5,12]. For NCGS diagnosis, CeD and wheat allergy have to be ruled out first; then an elimination diet follows. In ambiguous cases, an open label gluten challenge can be used for confirmation [4]. Only little is known about the exact prevalence of NCGS; however, observational studies suggest there is a higher number of patients with NCGS than with CeD [13]. Among IBS patients with a diarrhea subtype, frequency of NCGS was reported to be as high as 28–30% [14,15]. No differences between CeD and NCGS have been found regarding personality, level of somatization and depression [16]. Besides this increasing knowledge of NCGS, little or nothing is known about CeD patients' perspective on NCGS and their opinion regarding the possibility of a shift in public and doctor's attention away from CeD towards NCGS.

While the best management of NCGS remains unclear, there is universal agreement that CeD should be treated with a gluten-free diet (GFD). GFD still represents the main – and only effective – treatment option in CeD [17]. However, GFD is costly for patients and not universally available. Furthermore, GFD leads to restriction in daily life and can even decrease social function scores [18]. A non-negligible proportion of patients are dissatisfied with GFD [19]. So patient compliance with GFD is limited and strict adherence to GFD challenging since even small amounts of gluten (50 mg/d) can be immunogenic and only a quantity of less than 20 ppm is universally accepted as gluten-free [20–22]. Thus, in the last few years, several attempts to replace GFD by other treatments have been made. Innovative treatment strategies include: reduction of gluten exposure, gluten peptide hydrolysis and even HLA DQ2/DQ8 blockage. Most of these approaches currently remain in an experimental stage [17]. So far, two agents have been tested in a phase II trial [23–25] with ALV003, an endopeptidase hydrolyzing gluten peptides, demonstrating potential regarding reduction in mucosal injury. However, ALV003 is envisioned as an additive treatment rather than an alternative to GFD [26].

To the best of our knowledge, this large patient survey among unselected Swiss CeD patients is the first investigation on CeD patients' perspective on NCGS and novel CeD treatment options regarding their needs, perceptions and demands.

2. Material and methods

2.1. Study design

This large patient survey collected information about patients' perspective on NCGS and emerging CeD treatment options. The call to CeD patients was made through announcements in the print news of the Celiac Community Foundation of the German speaking part of Switzerland and on its website. All members of the Celiac Community Foundation were eligible. Patients or their caregivers (if patients were children) were prompted to report their own case to the database using a standardized questionnaire (see Supplementary Table S1). All data were anonymized. The study

was presented to the local ethics committee and no concerns were raised due to an anonymized data collection.

2.2. Patients and data collection

All patients diagnosed with CeD were eligible for inclusion in this study. Data were collected by a standardized questionnaire, which included sections about (1) patient characteristics, (2) disease characteristics, (3) NCGS including questions about knowledge of, attitude towards and belief in this new entity, (4) patient's perspective on novel therapeutic options, knowledge of emerging drugs and patient's demands for new CeD medications. For comparison between the adult and pediatric study population, children were defined as patients under 16 years of age according to prior CeD studies [27].

2.3. Statistical analysis

For all statistical analyses, IBM software SPSS version 22.0.0 (2013 SPSS Science, Inc., Chicago, IL) was used. Categorical data are summarized as the percentage of the group total. Comparisons between categorical data were performed using Chi-square test, or the Fisher's exact test in case of small sample size ($n < 10$). A two-sided p -value of < 0.05 was regarded as statistically significant. For a more detailed subgroup analysis, patients who were under the age of 16 years at study enrolment were excluded given unknown demographic data on their caregivers reporting the individual CeD case.

3. Results

3.1. Patient demographics

From a total of 3800 printed questionnaires, 1689 (44.4%) were returned and finally analyzed. Demographic data has been published elsewhere: 1284 patients were female (76%), mean age was 41.3 years (range 0–92 years) with a mean age at CeD diagnosis of 31.1 years (range 0–83 years), mean duration of CeD was 10.0 years (range 0–70 years) and 269 patients (15.9%) were less than 16 years old [28]. Details on how CeD diagnosis had been established in the studied patients have been published elsewhere: diagnosis was made based on duodenal biopsies in nearly 80% [29].

3.2. Patients' perspective on NCGS

With 971 out of 1689 patients (and their caregivers, respectively), corresponding to 57.5% of the study population, more than half are aware of the concept of NCGS. Even more (64.5%) agree to the statement that gluten has a potential to cause undesirable complaints and medical conditions also in humans without CeD. On the other hand, only 26.5% of patients are not convinced of the existence of NCGS, while 9.0% are uncertain.

Regardless of their opinion on the existence of NCGS, patients were also asked, whether they appraise NCGS positively, as it may indirectly also support and increase awareness for CeD, or negatively, as it may shift away the public attention from CeD. The former positive perspective is adopted by 31.7%, the latter negative by 27.5%. One third (33.3%) do not believe in any relevance regarding CeD awareness, 7.5% are uncertain. Patients with prior use of alternative medicine (22.0%) more often have heard of and believe in the existence of NCGS compared to those never having used alternative methods (66.9 vs. 56.9%, $p = 0.001$ and 78.5 vs. 69.0%, $p = 0.001$), while no difference was seen regarding negative attitude towards NCGS (26.0% vs. 30.5%, n.s.).

For a more detailed subgroup analysis, patients, who were under the age of 16 years, were excluded given unknown

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