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Soy allergy complicating disease management in a child with coeliac disease

To the Editor,

Food allergy is an immune-mediated reaction that occurs reproducibly on exposure to a certain food or food component (most commonly a protein) and is distinct from other conditions causing adverse responses to food, including digestive/absorptive processes, toxic reactions and autoimmune disorders (1). Coeliac disease (CD) is an autoimmune condition, which typically presents with gastrointestinal symptoms and failure to thrive within the first years of life and is caused by an abnormal immunological response to ingested gluten, in genetically predisposed individuals (2,3). Its diagnosis is primarily based on the presence of characteristic duodenal biopsy findings (villous atrophy, crypt hyperplasia and intra-epithelial lymphocytosis) along with documentation of clinical or histological response to a gluten-free diet (GFD) (4). The presence of positive serology for CD-specific autoantibodies, mainly endomysial and antitissue transglutaminase antibodies (EMA and tTG, respectively), is also a strongly supportive diagnostic finding, but not essential for diagnosis (2,4).

We herein report a rare and diagnostically challenging case of a 13 ½-year-old child with biopsy-proven CD and concurrent soy allergy complicating disease management, and briefly discuss the potential pitfalls associated with differential diagnosis and treatment of refractory symptoms in patients with CD.

A 13 ½-year-old girl was referred to the Allergy Department at 'Sotiria' General Hospital, Athens, Greece, for further evaluation of refractory CD. The patient had been diagnosed

with CD at the age of 3 ½ years, approximately 6 months following the onset of gastrointestinal symptoms (vomiting, abdominal pain, flatulence and diarrhoea) along with tiredness. Personal and family history for atopy was negative. Laboratory workup at the time of initial diagnosis was significant for positive EMA, tTG and antigliadin autoantibodies (AGA); duodenal biopsy was compatible with coeliac disease. Both mother and child tested negative for *Helicobacter pylori* antibodies. Repeat upper endoscopy with duodenal biopsies, performed twice at the age of 7 and 13 years, revealed similar findings to the initial biopsies (partial villous atrophy, increased number of intra-epithelial lymphocytes and moderate eosinophilic mucosal infiltration). During this period and despite a strict GFD, the patient's symptoms persisted, CD-specific autoantibodies remained positive, and declining growth percentiles were noted.

At the patients' presentation to our department, routine laboratory tests (including complete blood count with differential, electrolytes, blood glucose, renal and liver function tests, lipase, amylase, erythrocyte sedimentation rate, c-reactive protein) were within normal limits; quantitative Ig determination showed a moderate elevation of IgA in the serum (233 mg/dl, normal range: 85–214), while IgM and IgG values were normal. Serological testing for AGA (IgA and IgG) and t-TG IgA antibodies gave positive results (AGA IgA and IgG: 24 and 62 units, respectively, t-TG IgA: 83 units, normal values in all cases <20 units), while EMA antibodies were borderline positive (1:20). Molecular HLA typing confirmed the presence of the HLA-DQ2 and HLA-DQ8 haplotype. Skin prick

testing (SPT) was performed on the volar surface of the forearm using commercial extracts of cow's milk, soy, egg, wheat, rice, corn, potato, chicken and beef; a positive reaction was defined as a wheal with a diameter of at least 3 mm larger than that produced by a negative control (normal saline) present 20 minutes later. Histamine (10 mg/ml) was used as a positive control. All skin prick tests were negative. Atopy patch tests (using fresh allergens) were also performed for the same foods and were applied and read as previously proposed by Heine et al. (5). More specifically, one drop of fresh cow's milk containing 3.5% fat, one drop of soy milk (1 unpacked level scoop of Isomil formula per 2 fl oz of water), whisked hen's egg (white and yolk), wheat, rice, corn, potato, chicken and beef powder dissolved in water (1 g/10 ml) were placed on non-irritated, non-abraded areas of the patient's back using large (12 mm) aluminium chambers with filter paper discs (Finn Chambers Large, Finland). A first reading was performed 20 min after the application of the allergens so as to exclude an immediate skin reaction. Patches were removed after 48 h and read at 48 and 72 h after the application. Atopy patch test (APT) results showed a weak positive reaction to soy (erythema and slight infiltration). The patient was then placed on a strict dietary exclusion of soy, with gradual resolution of symptoms, increase in growth percentiles and normalization of autoantibody titres, during a follow-up period of 2 years. A 14-day gluten challenge test was subsequently undertaken to further confirm the initial diagnosis of CD. Upon reintroduction of gluten into the patient's diet, re-emergence of symptoms and elevation of CD-specific autoantibodies were noted; furthermore, gradual resolution of clinical symptoms and serological normalization was documented following her return to a GFD. The patient was diagnosed with CD and non-IgE-mediated soy allergy, and was placed on strict dietary exclusion of both gluten and soy, with no recurrence of symptoms at 2-year follow-up.

Refractory CD (RCD) is characterized by persistence or recurrence of gastrointestinal symptoms and villous atrophy despite strict adherence to a gluten-free diet (GFD) for at least 6–12 months, when other causes of non-responsive CD have been excluded (3). RCD may be either of the primary type, when there is no history of response to GFD, or of the secondary type, when there is disease relapse after initial treatment response (4). As previously emphasized, evaluation of a potential case of RCD should include confirmation of the initial diagnosis (via repeat diagnostic tests and procedures and/or review of prior tests and histology slides), assessment of compliance to GFD and elimination of alternative causes of refractory disease comprising, but not limited to, microscopic or collagenous colitis, small-intestine bacterial overgrowth, pancreatic insufficiency and lactose intolerance (3,4). Other food intolerances are also included among the potential causes of persistent gastrointestinal symptoms in CD, but their occurrence and diagnostic significance in these patients are only rarely reported and discussed (4,6,7).

Our patient presented with clinical, serological and pathological findings highly suggestive of primary RCD. Additional

diagnostic evaluations, including the performance of SPT and APT for a variety of food allergens, revealed the presence of non-IgE-mediated soy allergy. Initial diagnosis of CD was confirmed by the repeat upper GI endoscopy and biopsy results (which were compatible with CD), the persistent presence of positive CD-specific autoantibodies and the results of gluten challenge. Furthermore, genetic compatibility with CD (positivity for HLA-Class II DQ2 and DQ8) was documented. Interestingly, strict exclusion of soy from the child's diet resulted not only in clinical improvement and an increase in growth percentiles, but also in normalization of autoantibody titres. We can only hypothesize that normalization of CD-specific serology following soy avoidance in our patient might be due to inadvertent removal of unknown sources of gluten. On a side note, it must be also emphasized that food patch testing is not a well-standardized procedure; the APT results herein presented may therefore not necessarily be generalizable or reproducible.

CD has been previously associated with a variety of other conditions – mainly autoimmune in nature – such as type 1 diabetes, autoimmune thyroiditis, Addison's disease, autoimmune liver diseases, pernicious anaemia and connective tissue diseases (2,8). A potential epidemiological association between coeliac disease, especially its 'silent' form, and atopy has also been suggested by some (8,9), but not all previous studies (10), and it remains to be further clarified whether coeliac disease may predispose or not to the development of an atopic condition, and vice versa. As previously hypothesized, decreased mucosal protection against allergens in patients with untreated or refractory CD may predispose to the development of an atopic condition, while, inversely, increased mucosal permeability, which is a common finding in atopics, may predispose as well to pathogenesis of CD-specific mucosal damage (8,9).

Our reported case highlights the importance of maintaining a high index of suspicion for the presence of alternative or additional causes of refractory gastrointestinal symptoms in patients with a diagnosis of RCD, especially of the primary type. A thorough clinical and laboratory workup is essential for the most accurate diagnosis and optimal management of these complex and diagnostically challenging cases. Simultaneous occurrence of CD with other types of food intolerances, including non-IgE-mediated reactions to proteins other than gluten, as documented in the present case, should be included in the differential diagnosis of RCD.

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NSAID hypersensitivity in twins

Dear Editor,

Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most prescribed drugs in the world. They may cause up to 25% of reported adverse drug events, which comprehend immunologic and non-immunologic hypersensitivity reactions and affect approximately 0.6–2.5% of the general population (1).

In recent years, the interest on the genetic mechanisms involved in hypersensitivity drug reactions has increased. Genes coding for enzymes and receptors in the prostaglandin and leukotriene pathways are often responsible for NSAIDs hypersensitivity (2, 3). Several studies on possibly involved genes have been performed and have widened the knowledge on NSAIDs hypersensitivity (4). However, so far, the international literature has not analyzed the possibility of a familial inheritance of NSAIDs hypersensitivity. We describe here the case of two homozygous fifteen year-old twin sisters who presented the same kind of hypersensitivity reactions to NSAIDs (2).

Both twins presented a hypersensitivity reaction to Ibuprofen, characterized by facial swelling, approximately eleven hours after the drug intake, 5 years before they came to our Unit. They both were taking the drug because of fever. The reaction spontaneously disappeared after two hours. For this reason, we hospitalized them to perform a drug provocation test (DPT). As shown by the study conducted by Çelik et al. (5), DPTs are to be preferably performed in a safe environment provided with emergency equipment and experienced professionals, and where patients can be observed for a certain amount of time in order to treat possible severe drug reactions. The first twin (A), who did not have a history of atopy or chronic urticaria (CU), underwent a DPT to ibuprofen (maximal dose: 752 mg) to confirm the diagnosis. On the

contrary, the second twin (B), who presented with a history of allergy to birch and hazel and who suffered from CU, was investigated for an alternative NSAID, since CU is a well-known risk factor for developing hypersensitivity reactions to analgesic drugs that mainly inhibit the COX-1 pathway (5, 6). She underwent a DPT to piroxicam (maximal dose: 36 mg). Twin A did not develop any clinical manifestation during the observation period. Nevertheless, the morning after the test, she presented with labial swelling and urticaria localized on her left arm. During the observation period, twin B presented a mild serous rhinitis and a modest left eyelid swelling, with no conjunctivitis associated, which actually worsened the day after the test, when labial swelling appeared as well. The two provocation tests were therefore considered as positive for both sisters.

Tryptase concentrations were stable in both twins before and after the tests (A: from 6.51 to 5.79 µg/l; B: from 5.94 to 5.51 µg/l). On the contrary, histamine blood levels significantly increased in both patients (A: from 0.58 to 1.91 ng/ml; B: from 0.58 to 1.28 ng/ml). Basophil activation test (BAT) resulted negative to ibuprofen for twin A. It was negative to both ibuprofen and piroxicam for twin B. Even though BAT seems to have low sensitivity and specificity for NSAIDs, we run it to complete the allergy work up in our patients. Blood samples for BAT were collected 6 weeks after the provocation tests, right before the twins came in our Unit to continue the investigations.

Indeed, 6 weeks after the first test, another DPT to a COX-2 selective NSAID (celecoxib) was carried out for both sisters, in order to find a therapeutic alternative. Five hours after the beginning of the DPT to celecoxib (administered dose: 4.7 mg/kg for a cumulative dose of 235 mg), twin A started to present facial and inferior lip swallow. Tryptase levels remained stable after the test (from 4.43 to 4.80 µg/l), while histamine concentration increased (from 0.91 to 3.42 ng/ml). It was not possible to perform a BAT for celecoxib due to basophils hyper-reactivity at basal state, even 6 weeks after this second

Abbreviations:

NSAIDs, nonsteroidal anti-inflammatory drugs; DPT, drug provocation test; CU, chronic urticaria; COX-1, cyclooxygenase-1; COX-2, cyclooxygenase-2; BAT, Basophils activation test.