Cold Urticaria and Celiac Disease

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Abstract

Cold urticaria can be associated with blood and thyroid disorders, drugs, or infections. Celiac disease is an autoimmune enteropathy caused by permanent gluten intolerance. It is often associated with other autoimmune diseases, such as chronic idiopathic urticaria. Nevertheless, association with cold urticaria has not yet been described. A boy aged 3 years 8 months presented local urticaria-angioedema when exposed to cold temperatures. An ice cube test was positive and iron deficiency anemia was demonstrated. He later developed legume intolerance, rhinoconjunctivitis related to pollen sensitization, and asthma. Due to persistence of cold urticaria symptoms and refractory anemia, a test for immunoglobulin A autoantibodies to tissue transglutaminase and an intestinal biopsy were performed. Results of both tests were compatible with celiac disease. A study of human leukocyte antigen indicated a high risk phenotype (HLA, DR6/DR7; DQA 0501, 0201; DQB 0301, 0201). After 7 months of a gluten-free diet, the boy's anemia resolved and he is free of symptoms when exposed to cold. This is a first description of the possibility of an association between celiac disease and cold urticaria. A poor course of cold urticaria in the absence of evidence of another underlying condition should lead to suspicion of celiac disease.

Key words: Urticaria. Physical urticaria. Celiac disease. Antigliadin. Gluten.

Resumen

La urticaria a frigore (UF) puede asociarse a trastornos hematológicos, tiroideos, fármacos o infecciones. La enfermedad celíaca es una enteropatía autoinmune causada por intolerancia permanente al gluten. Con frecuencia se asocia a otras enfermedades autoinmunes como urticaria crónica idiopática. Sin embargo nunca se ha descrito su asociación con UF. Niño de 3 años y 8 meses con urticaria-angioedema tras exposición al frío. Se objetivó anemia ferropénica y test del cubito de hielo positivo. Posteriormente desarrolló intolerancia a legumbres, y rinoconjuntivitis y asma por pólenes. Ante la persistencia de síntomas y anemia se realiza prueba de inmunoglobulina A a anticuerpos a transglutaminasa de tejido biopsia intestinal, compatibles con enfermedad celiaca, y fenotipo antígeno leucocitario humano de alto riesgo (DR6/DR7. DQA0501,0201. DQB0301,0201). Tras 7 meses de dieta sin gluten la anemia y los síntomas se resuelven a pesar de exposición al frío. Se describe por primera vez posible asociación entre UF y enfermedad celiaca. Ante UF de evolución desfavorable sin otra causa subyacente, se debe descartar esta posibilidad.

Palabras clave: Urticaria. Urticarias físicas. Enfermedad celíaca. Antigliadina. Gluten.

Introduction

Cold is the third leading cause of urticaria in children: only dermographism and cholinergic urticaria are more common than cold urticaria, which accounts for 1% to 3% of all urticariae [1]. Affected patients develop rash and/or angioedema after physical exposure to cold agents such as cold water, air, or foods. The mean age of presentation is 18 to 25 years (range, 3-74 years) and the duration of symptoms is 4.8 to 9.3 years; it is more frequent among females (63%) [2,3].

The diagnosis is based on a suggestive clinical history and a cold stimulus test, commonly called the "ice cube test." In this test, an ice cube protected by plastic (to avoid possible false positives due to aquagenic urticaria) is applied to the patient's skin for increasing periods of exposure (1, 3, 5, and 10 minutes). Positivity is established when erythema and edema are still present in the contact area after a waiting period of rewarming of 10 minutes. The area where the ice cube is applied must be changed each time in order to avoid desensitization of the skin [2,4,5].

Cold urticaria may be a sign of many conditions, as summarized in Table 1, so differential diagnosis must be made before the primary form may be diagnosed. Symptoms are classified according to 3 grades of severity. Grade 1 includes symptoms affecting only the local area where stimulus has been applied. Grade 2 comprises a systemic reaction where urticaria and angioedema affect the whole body. Grade 3 also includes signs of hypotension and shock [2].

Table 1. Class	sification of	Cold L	Irticaria	Syndromes
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Typical Primary (72 %) Secondary (28 %) Cryoglobulinemia Leukocytoclastic vasculitis Infectious diseases Hypothyroidism Cryoagglutinins, cryohemolysins, cryofibrinogens Drugs: penicillin, oral anticoagulants, antifungal agents
Atypical Systemic form Cold-dependent dermographism Cold-induced cholinergic urticaria Delayed cold urticaria Cold reflex urticaria
Familial forms

Treatment includes avoidance of cold and drugs to alleviate symptoms. Usually antihistamines are enough to control symptoms, but systemic reactions including hypotension requiring the administration of epinephrine have been reported [2,3].

We report the case of a 3-year-old boy with 3 episodes of cold urticaria in relation to exposure to cold water.

Case Description

A 3-year-old boy was brought to our outpatient clinic because of 3 episodes of urticaria and edema in relation to cold water exposure. His parents also reported perioral erythema when contacting cold foods. He had suffered mild symptoms of rhinoconjunctivitis in the spring of the previous year and an episode of vomiting and watery stools 4 hours after having eaten lentils. A diagnosis of atopic dermatitis and iron deficiency anemia had been made and treated by his general pediatrician. He had no relevant family history.

His initial evaluation included in vivo and in vitro tests. Skin prick tests (SPT) were performed with aeroallergens and lentil, even though his medical history was not suggestive of allergy. Positivity was determined only for grasses and *Olea europea*. The total immunoglobulin (Ig) E serum concentration was 78 kU/L and specific IgE against *O europea* was class 1, *Lolium* species class 4, and lentil class 0. A cold stimulus test was positive in the first minute of application.

Tests to rule out possible causes of cold urticaria were undertaken. A blood cell count revealed microcytic hypochromic anemia (hemoglobin, 10.8 mg/dL; hematocrit, 33.4%; mean corpuscular volume, 73.9 fL; mean corpuscular hemoglobin: 23.8 pg) and hypertransaminasemia was demonstrated (aspartate aminotransferase [AST], 54 IU/L). The rest of his chemistry panel, complement profile, cryoglobulins, and cryoagglutinins were within normal ranges. Screening tests for hepatotropic virus, *Salmonella, Toxoplasma* and *Brucella* species were negative. Urine analysis and a chest x-ray were also normal.

The patient was diagnosed with atopic dermatitis, iron deficiency anemia, primary cold urticaria, legume intolerance, and allergic rhinoconjunctivitis. Avoidance measures and antihistamine treatment were prescribed, in addition to symptomatic treatment for rhinoconjunctivitis.

Over a period of 10 years of annual follow-up visits in our department, the patient developed allergic sensitization to legumes (SPT and specific IgE positivity). At the last visit he still reported symptoms of urticaria when in contact with cold stimuli, even though the cold stimulus test had been negative for 2 years. He was still receiving iron supplementation therapy.

As the course of cold urticaria was unusual and iron deficiency anemia was still present despite treatment, we reevaluated the patient. He insisted that urticaria lesions appeared when he was exposed to a cold stimulus. No relevant family history was identified and no one in his family had similar symptoms. Blood cell counts and blood chemistry tests to determine levels of cryoglobulins, cryoagglutinins, immunoglobulins, complement, C-reactive protein, erythrocyte sedimentation rate (ESR), rheumatoid factor, and antinuclear antibodies were carried out. Only slight elevation in AST and ESR, and microcytic hypochromic anemia were revealed. Familial cold autoinflammatory syndromes were also screened for, but no mutations or polymorphisms were identified. An iron metabolism study showed low serum iron levels (16 µg/mL; normal range, 59-158 µg/mL), serum ferritin (2 ng/mL; normal range, 30-300 ng/mL) and low transferrin saturation (4%; normal range, 15%-50%). Transferrin (329 mg/dL) and iron binding capacity (418 µg/dL) were normal. Parasites in stools were negative. Feces were normal in amount, consistency, and appearance.

To screen for the possibility of celiac disease, IgA autoantibodies to tissue transglutaminase (aTTG) were determined and found to be elevated, at 100 arbitrary units (AU) per liter (normal, <7 AU/L). Biopsy specimens of the small intestinal wall were therefore taken (Figure 1). Microscopy revealed subtotal atrophy



Figure. Small intestine biopsy specimen. The superficial epithelium shows regenerative signs, with loss in height, nuclear hyperchromatism and cytoplasmic vacuolization with intraepithelial lymphocytes (more than 40 lymphocytes per 100 enterocytes). There is an increase in the number of cells in the lamina propria.

of the intestinal villi. A study of human leukocyte antigen indicated a high risk of celiac disease phenotype (HLA, DR6/DR7; DQA 0501, 0201; DQB 0301, 0201).

Discussion

Causes of iron deficiency anemia are summarized in Table 2. As growth does not explain anemia for such a prolonged period, the possibility of celiac disease was explored. As laboratory markers and intestinal biopsy were positive for celiac disease, the patient was diagnosed and started on a gluten-free diet. Seven months later anemia had resolved, transaminases had decreased, iron metabolism had returned to normal and symptoms had improved significantly. No new episodes of cold urticaria had presented despite having been exposed to snow and cold temperatures. IgA aTTG titers were within normal range (<7AU/L).

Celiac disease is an immunologic disorder leading to a permanent intolerance to gluten proteins contained in cereals such as wheat, barley, rye, and oat. This leads to mucosal atrophy and then poor utilization of nutrients. Celiac disease affects genetically predisposed individuals (HLA DQ2, DQ8) [6]. This condition appears associated to other immune diseases such as type 1 diabetes mellitus, autoimmune thyroiditis (Graves and Hashimoto diseases), Sjögren syndrome, rheumatoid arthritis, IgA nephropathy, or autoimmune hepatitis [7].

In recent years many cases of chronic idiopathic urticaria associated with celiac disease have been reported [8,9]. Placement on a gluten free diet led to resolution of urticaria symptoms. As previously reported by Menenghetti et al [9] avoidance of gluten in these cases results in the ceasing of immune system stimulation, in which case autoantibodies do not develop. Those authors recommended screening for celiac disease in all patients suffering from chronic urticaria. Nevertheless, the association of celiac disease and cold urticaria has never been previously described.

Table 2. Differential Diagnosis of Iron Deficiency Anemia

Transport alterations Atransferrinemia Autoantibodies against transferrin receptor
Increased blood loss Mecker diverticulum Parasites Hemorrhoids Gastritis Polyps Neoplasm
Increased iron needs Growth
Insufficient intake Inadequate diet Malabsorption Inflammatory bowel diseases Intestinal resection Parasites Celiac disease

The fact that both conditions have an immunologic background raises the possibility of a dysregulation of the underlying immune system that would have predisposed our patient to suffer both diseases.

Recently, the American Association of Gastroenterology has recommended screening for celiac disease in patients with compatible gastrointestinal symptoms, increase in transaminases, short stature, delayed puberty, or iron deficiency anemia [10]. Screening should be considered in cases of irritable bowel disease, aphthous stomatitis, peripheral neuropathy, or autoimmune diseases. We consider it to be of utmost importance to rule out this disease in cases of cold urticaria that have an atypical presentation, that persist for years, and especially if other symptoms coincide.

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Manuscript received June 20, 2007; accepted for publication October 9, 2007.

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