Cold urticaria and infectious mononucleosis in children

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ABSTRACT

Physical urticaria includes a heterogeneous group of disorders characterized by the development of urticarial lesions and/or angioedema after exposure to certain physical stimuli. The authors present the case of a child with severe acquired cold urticaria secondary to infectious mononucleosis. Avoidance of exposure to cold was recommended; prophylactic treatment with ketotifen and cetirizine was begun and a self-administered epinephrine kit was prescribed. The results of ice cube test and symptoms significantly improved. Physical urticaria, which involves complex pathogenesis, clinical course and therapy, may be potentially life threatening. Evaluation and diagnosis are especially important in children. To our knowledge this is the first description of persistent severe cold-induced urticaria associated with infectious mononucleosis in a child.

Key words: Children. Cold urticaria. Infectious mononucleosis. Physical urticaria.

RESUMEN

La urticaria física incluye un grupo heterogéneo de trastornos caracterizados por el desarrollo de lesiones de urticaria y/o de angioedema, después de la exposición a ciertos estímulos físicos. Los autores presentan un caso clínico de un niño con urticaria al frío adquirida grave, secundaria a la mononucleosis infecciosa. Se le recomendó evitar la exposición al frío; comenzó tratamiento profiláctico con ketotifeno y cetirizina y se prescribió kit de epinefrina para auto-administración. La prueba del cubo de hielo y la sintomatologia tuvieron una mejoría significativa. La urticaria física, con etiopatogenia, evolución clínica y terapéutica complejas, puede en ocasiones amenazar la vida del paciente, y al tratarse de niños cobra gran importancia la evaluación y el reconocimiento. De los casos descritos que tenemos conocimiento ésta es la primera descripción de la urticaria frío-inducida grave persistente asociada a mononucleosis infecciosa en niños.

Palabras clave: Mononucleosis infecciosa. Pediatría. Urticaria al frío. Urticaria física.

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INTRODUCTION

Physical urticaria is a unique subgroup of chronic urticaria, characterised by the development of urticarial lesions and/or angioedema, in exposed skin areas, after application of the physical stimuli, such as heat, cold, solar irradiation, water, exercise, pressure and vibration. Although generally benign and self-limiting, severe systemic reactions are known life-threatening complications[1,2].

The exact prevalence of physical urticaria is unknown; it is estimated to be low in the general population, building up however 10 to 20 %, of all chronic urticaria forms. Dermatographism is the most frequent type, present in 2 to 5 % of the general popu-

lation. Heat-induced urticaria, essentially cholinergic urticaria, represents 2 to 7 % and cold urticaria 3 to 5 % of physical urticaria. The rarest forms, with an incidence under 1 %, correspond to pressure, solar, vibratory and aquagenic urticaria[1-3].

There are some common particular characteristics: all forms are clinically quantifiable (measurable stimulus) and reproducible, with well-defined challenge tests, making diagnosis easier and turning monitorization of therapy efficacy possible. They are usually solved in a spontaneous way in time (months to years, on an average of 5 years), except for the familial forms; they affect mostly young adults, being rare at paediatric age; their etiopathogenesis is unknown[1,3].

CASE REPORT

M.C.N., born in September 1990, male, Caucasian, with a familial and personal history irrelevant, was referred to our outpatient clinic in May 1997, due to a clinical history started in August 1996, characterised by 3 syncope episodes, associated with generalised urticaria and angioedema, appearing about 3 minutes after body immersion in sea or river water, episodes of lip angioedema about 1 to 5 minutes after ingesting cold food and also face, hand and leg localised urticaria after contact with rain. Skin lesions regressed spontaneously in 30 to 60 minutes, with no other symptoms, such as respiratory or gastrointestinal. Eight weeks before the beginning of the mentioned symptoms, he had a fever episode, with two-week evolution, accompanied by sore throat, cervical lymphadenopathy and hepato-splenomegaly, with myalgia and getting tired easily, which he maintained during more than 12 months, though softened; at that time atypical lymphocytes (10.4 %) and a positive heterophile antibody test were found in the blood tests performed.

In the Immunoallergy Department of D.Estefânia Hospital, analytical tests revealed: complete blood count with monocytosis (9.6 %), relative (57 %) and absolute lymphocytosis (3.220) and presence of atypical lymphocytes (4.3 %); positive Epstein-Barr virus serology with positive EBV-VCA IgM – Viral Capside Antigen (that persisted with low titers for about 1 year), EBV-VCA IgG and EBNA – Epstein-Barr Nuclear Antigen; antibodies anti-EA were negative – Early Antigen; CMV serology with negative IgM and positive IgG; total IgE 318 IU/ml; IgG, IgA and IgM immunoglobulins within normal parameters; negative syphilis serology; negative antinuclear antibodies; negative cold cryoglobulin and agglutinin; sedimentation rate, complement (C3, C4, C1q and CH100), transaminases, protein electrophoresis and serum immunoelectrophoresis within normal parameters.

The presence of cold urticaria was confirmed by a positive response to the ice cube test: a 28 mm 33 mm wheal appeared after application of cold stimulus (0 to 4 °C) during 1 minute on the child's forearm. Measures such as avoidance of cold exposure, including aquatic activities, were recommended; prophylactic treatment was begun with ketotifen (2 mg/day) and cetirizine (5 mg/day) and an epinephrine auto-injector kit was prescribed.

Two months after the institution of prophylactic therapy, the ice cube test was repeated, with positive response after a 3 minute stimulation (wheal – 42 mm 40 mm). The child maintains symptoms up to this date (about 8 years), although with significant clinical improvement, mentioning short periods immersion of distal extremities of superior limbs in cold water with no induction of skin lesions; ingestion of cold foods is well tolerated. At the present time the ice cube test is still positive for a stimulation of 10 minutes or longer; in serum, anti-EBNA is positive.

DISCUSSION

To our knowledge this is the first description of acquired persistent severe cold-induced urticaria secondary to infectious mononucleosis in children, started at five years of age.

Cold urticaria, first described by Bourdon in 1866[4], is characterised by the development of urticaria and/or angioedema after exposition to cold (aquatic activities, cold air, rain, snow, ingestion of cold food or drink or contact with cold objects)[1,5,6]. Cold urticaria can be acquired or familial, the inherited form is very rare and determined by dominant autossomic transmission. Cold urticaria can be classified according to its response to cold challenge test: if the ice cube test turns positive, it is primary or secondary, according to its aetiology; if the response is atypical (late or in a distant place from where stimulus was applied) or negative with suggestive clinical symptoms, it is atypical acquired urticaria[1,3,6]. Primary or idiopathic acquired urticaria is the most common form: Neittaanmäki[7] found a prevalence of 96 % in 220 patients studied with cold urticaria, Santaolalla et al[8] in a review of 12 paediatric cases found an infection cause in only one case and Alangari et al[9], in a series of 30 children with cold urticaria didn't find any secondary cause.

According to several studies symptoms usually start in children or young adults, with an average age of 7 to 25 years old[5,7-9]; appearance at paediatric age, as in the case reported, is less frequent. Typically,

Table I

Cold urticaria associated with infectious mononucleosis

Author	Age (years)	Sex	Atopy	Clinical manifestations	Duration (weeks)	Ice cube test	Serology to EBV	Cryoglobulins
Tyson et al[8]	24	M	+	Urticaria, angioedema, wheezing, shock	7	+	+	+
Barth[9]	19	F	IgE	Urticaria	5	ND	ND	–
Lemanske et al[10]	17	M	ND	Urticaria, angioedema, hypocomplementemia	< 3	+	+	+
Bonnetblanc et al[11]	21	M	ND	Urticaria, angioedema, hypocomplementemia	1	+	+	+
Anderson[12]	15	M	ND	Urticaria, angioedema	28	ND	+	ND
Wu et al[13]	26	M	+	Urticaria, angioedema	1.5	+	+	–
Wu et al[13]	17	M	+	Urticaria	3	+	+	+
Case report	5	M	IgE	Urticaria, angioedema, shock	(*)	+	+	–

(*) Still symptomatic (after > 7 years – at the moment aged 14 years-old).
ND, not done: information not available from the case report or not performed.

cold urticaria lesions show up few minutes after cold stimulus, disappearing in 30 to 60 minutes; they appear mainly on the face, hands and legs. Lip, tongue and pharynx angioedema can occur after ingestion of cold food or drink. Cardiovascular, respiratory and gastrointestinal symptoms are often associated[5,6]. Cold urticaria can be classified according to the severity of clinical signs presented in types I to III[6]. The child in study presented a type III clinical pattern, with generalised urticaria and angioedema, associated to anaphylactic shock symptoms.

The clinical diagnosis of cold urticaria was confirmed by the ice cube test, which was strongly positive, with induction of response after one minute of stimulus. The time needed for the cold stimulus to induct positive response presents a predictive value of the type of clinical pattern[1,5]; there are an inversely proportional relation between the time needed to induct response and the severity of symptoms. Several studies indicate that severe systemic reaction (type III) occurs more frequently in patients with positive ice cube test for three minute or shorter stimuli[5,6], such as in the presented case.

Secondary acquired cold urticaria is a rare form and it is diagnosed in presence of suggestive clinical history, positive cold stimulation test and evidence of a causal pathology. Malignancies, systemic leukocytoclastic vasculitis and infectious diseases, such as syphilis and infectious mononucleosis, have been implicated in the aetiology of cold urticaria[1,6,7].

As in this case, the existence of a clinical history compatible with infectious mononucleosis, just before the appearing of physical urticaria signs, with a haematological pattern of monocytosis, lymphocytosis and presence of atypical lymphocytes and positive serology for Epstein-Barr virus, lead to the diagnosis of secondary acquired cold urticaria associated with infectious mononucleosis.

In the table I, a summary of the seven clinical cases, previously described in literature of cold urticaria associated with infectious mononucleosis[10-15], is presented, showing the similarities and differences between them. The first case was reported by Tyson et al in 1981[10].

Levels of specific anti-EBV antibodies were found in our patient and in two of the other mentioned patients[10,12]; in one patient[11] specific anti-EBV antibodies were not investigated.

The mechanism, through which infectious mononucleosis triggers cold urticaria, is unknown. Cold cryoglobulins and agglutinins can appear during infectious mononucleosis and have been pointed as eventual causing factors. However, Kaplan[16] demonstrated the presence of cryoglobulins in 20 out of 21 studied patients with infectious mononucleosis and none of these patients exhibited cold sensitivity. Cryoglobulins were not detected in our child and also in two of the described patients[11,15]. Autoimmunity mechanisms could explain the association between Epstein-Barr virus, as well as other infectious agents, and the appearance of cold urticaria[6].

Our clinical case presents some particularities, such as the patient's age, the duration of cold sensitivity and the severity of clinical symptoms. The patient in study is within paediatric age, contrarily to the 7 described patients[10-15], aged between 15 and 26 years old. In all 7 cases the duration of cold urticaria was transitory (maximum 28 weeks) and paralleled to the clinical course of infectious mononucleosis; on the opposite, the child we reported had a much longer clinical evolution, still presenting symptoms at the present time. Only one of the cases referred, reported by Tyson et al[10], presented systemic anaphylaxis, as well as the child we studied, occurring after immersion in sea water.

The incidence of atopy in cold urticaria is similar to that of general population and atopic patients show no difference in what concerns the severity or duration of symptoms[6,7]. If atopy existence is a factor that contributes to the development of cold urticaria in patients with mononucleosis, is still very controversial; in the 7 cases described, 3 of the patients were atopic and 1 presented high serum levels of total IgE, like the child in study.

Urticaria and other skin lesions occurs in about 5 % of patients with infectious mononucleosis[17], a reason for which some authors raise the hypothesis that sensitivity to cold in these patients may be more frequent that the one mentioned. Since cold urticaria can be potentially life threatening, it is important that patients who present urticaria and mononucleosis be carefully evaluated as to their cold sensitivity.

The main goal of cold urticaria treatment is preventing shock reactions, thus cold avoidance measures (namely aquatic activities), are fundamental. In what concerns drug therapy, the most reliable symptomatic control is obtained from H_1 antihistaminic. Recent H_1 antihistaminic, such as cetirizine, loratadine and fexofenadine with less sedating effects, high potency and quick action, are of first choice[8,18]. Therapeutic efficacy of ketotifen was also documented[19], including a double-blind study performed in children with cold urticaria[20]. The association of H_2 antagonists with H_1 antagonists, as well as doxepin, are other therapeutic alternatives[21,22].

Patients with type II (generalized urticaria/angioedema) or type III clinical patterns or positive ice cube test after 3 minutes or less of stimulation, are candidates for prophylactic therapy[5]. Serial use of ice cube test is recommended to evaluate the efficacy of the treatment[5,6]; in the child in study, we verified that there was an improvement in test responsiveness and a significant clinical amelioration.

The clinical case here presented stresses the importance of diagnosis of cold urticaria in children. This entity thus rare in this age group can be related to severe forms. Counselling, preventive and emergency medical therapy may be lifesaving for these children.

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