

Cold urticaria: A clue to a silent systemic disease

Urticária ao frio: um sinal de doença sistémica silenciosa

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Abstract

A previously healthy 2-year-old boy with a history of recurrent hives after exposure to cold air. A diagnosis of cold-induced urticaria was confirmed by a positive ice cube test but in the investigation, we found hepatic cytolysis and a lack of alpha-1-protein band level in protein electrophoresis. Deficiency of alpha-1-protein was confirmed which prompted genotype sequencing and genetic studies, unveiling the ZZ genotype and Glu342Lys mutation of *SERPINA1* gene respectively. Alpha1-antitrypsin deficiency (AATD) was identified in association with acquired cold urticaria.

In the last decades cases of AATD associated with cold urticaria have been described mostly in patients with Z allele. AATD results in inadequate inactivation of plasmatic proteases and, consequently, incomplete control of the inflammatory reaction, eventually predisposing to urticaria.

The authors suggest that AATD screening could be more frequently performed in the investigation of cold urticaria, since early AATD diagnosis is essential.

Keywords: Cold urticaria. Alpha1-antitrypsin deficiency. Z allele.

Resumo

Rapaz de 2 anos, previamente saudável, com história recorrente de lesões urticariformes após exposição ao frio. Da investigação salienta-se: teste do cubo de gelo positivo, padrão de citólise hepática e ausência da banda alfa-1 na eletroforese das proteínas. Foi confirmado o défice de alfa-1-antitripsina (DAAT) e a sequenciação e estudo genético revelaram genótipo ZZ e mutação Glu342Lys do gene *SERPINA1*.

Nas últimas décadas têm sido reportados casos de DAAT associados a urticária ao frio, sobretudo nos portadores do alelo Z. Apesar da causalidade ser desconhecida, o DAAT resulta na inativação inadequada de proteases plasmáticas e, consequentemente, no controlo incompleto da reação inflamatória, eventualmente predispondo ao aparecimento de urticária.

O caso descrito alerta para a importância do rastreio de DAAT no estudo da urticária ao frio, dado que é essencial o diagnóstico precoce desta patologia.

Palavras-chave: Urticária ao frio. Défice de alfa-1 antitripsina. Alelo Z.

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What does this case report add?

This case supports the possible association between urticaria and decreased levels of α 1AT activity with predominance of the Z gene, and recommendation to perform AATD screening upon cold urticaria.

Previous presentations

This case report was presented as a E-poster at the meeting 20° Congresso Nacional de Pediatria that took place in Lisbon on October 13, 2019.

A previously healthy 2-year-old boy, without relevant family history, was referred to our immuno-allergology clinic due to a history of recurrent hives during the previous four months. Episodes were characterized by pruritic coalescing erythematous papules developing on bare skin areas that started within minutes after exposure to cold air and disappeared in less than 24 h. Neither angioedema nor other symptoms (fever, gastrointestinal or respiratory complaints) were ever observed. Symptoms related to the contact with cold water were not referred.

He started levocetirizine 5 mg twice a day with complete resolution of symptoms. However, when he reduced the dose to half (5 mg/day), symptoms relapsed in contact to cold air.

In this context, Cold Stimulation Test (CST) was performed with an ice cube. Ten minutes after skin contact, he developed erythematous papules at the test site. Laboratory tests showed hepatic cytolysis (AST 104 U/L; ALT 145 U/L; with no cholestatic pattern nor hepatic dysfunction). Viral infections (Epstein-Barr virus, Cytomegalovirus, Hepatitis A, B, and C virus) were excluded, as well as celiac disease. Cytoplasmic-antineutrophil antibodies (C-ANCA) were negative. A serum protein electrophoresis showed a decreased alpha-1-protein band level (33 mg/dL), which prompted genotype sequencing and genetic studies, unveiling the ZZ genotype and Glu342Lys mutation of *SERPINA1* gene respectively. Family members were heterozygotes for this mutation.

Alpha1-antitrypsin deficiency disease (AATD) was identified, associated with cold urticaria, but the patient had no other manifestation of AATD.

More extensive vaccine prophylaxis was ensured (such as hepatitis virus A immunization) and patient's parents were advised to adopt lifestyle changes, specifically avoiding exposure to tobacco smoke, in order to slow further deterioration of target organs.

He maintains follow-up in gastroenterology and immuno-allergology, with stable levels of transaminases and normal hepatic ultrasound, and urticaria under complete control with a minimal dose of H1 anti-histamines.

Discussion

Our clinical case involves two different identities: AATD and acquired cold-induced urticaria.

Alpha1-antitrypsin (α 1AT) is the most important protease inhibitor in blood and acts as protection, at least to some degree, against trypsin, kallikrein, elastase, collagenase, and proteases derived from leucocytes (such as neutrophil elastase)¹.

AATD is inherited in an autosomal co-dominant fashion and is caused by mutations in the *SERPINA1* gene located in the long arm of chromosome 14². In patients with the Z allele, such as the presented case, the alpha1-antitrypsin has a lysine substituted for a glutamate amino acid resulting in spontaneous polymerization within the endoplasmic reticulum of the hepatocyte²⁻⁴. This leads to decreased serum levels of alpha1-antitrypsin and hepatocyte apoptosis which can manifest initially as laboratory abnormalities (the stage where our patient was) but can also progress to hepatitis, fibrosis and finally to juvenile liver cirrhosis¹⁻⁴.

This disease is also responsible for other organ dysfunction such as pulmonary emphysema, panniculitis, and vasculitis^{2,4}. Although panniculitis is the typical skin manifestation associated with the ZZ phenotype of AATD², our patient only presented urticaria lesions. No signs of vasculitis were ever observed.

Cold urticaria can be divided into acquired forms and familial forms. In our case, the early onset of urticaria would suggest a familial form, which includes delayed cold urticaria (DCU), familial cold autoinflammatory syndrome (FCAS), and familial atypical cold urticaria (FACU)⁵, however, clinical manifestations were not compatible neither the family history. Also, CST is characterized by negative results in the familial forms, except in delayed cold urticaria in which the result is positive only after a few hours. Therefore, our case is more compatible with acquired cold urticaria, which can be classified as either primary (usually idiopathic) or secondary, mostly to an underlying haematologic or infectious disease⁵. In this case, an idiopathic form seems more likely, since secondary causes have been excluded. Nevertheless, follow-up with no remission of urticaria within 5 years might support a diagnosis of a familial form⁵.

Since the 1970s there have been reports on the association between alpha-1-antitrypsin deficiency and urticaria¹. Doeglas and Bleumink confirmed the significantly decreased levels of α 1AT activity in patients with cold urticaria with predominance of the Z gene in these groups¹.

Deficiencies of protease inhibitors in general, and AATD in particular, predispose to the development of skin lesions¹. Although the casual relationship is not fully understood, a deficiency of alfa1-antitrypsin will lead to inadequate inactivation of plasmatic proteases and thus to faulty control of inflammatory reactions, eventually predisposing to the development of urticaria¹.

Conclusion

The authors suggest that AATD screening could be performed more frequently in the investigation of cold-induced urticaria, and emphasize the importance of recognizing these atypical presentations of AATD, as an early diagnosis is critical to enable the implementation of lifestyle changes and therapeutic options that will slow down further disease progression, decreasing morbidity and mortality.

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Conflicts of interest

The authors declare no conflict of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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