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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2009, 26(1):135

Clinical Immunology Quiz – Case 6

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A 15 year-old boy presented to the emergency department with severe abdominal pain, nausea and vomiting that began 8 hours earlier. His parents reported an additional episode one year ago that lasted for 2 days and complicated by diarrhea after the remission of the pain. Family physician attributed that episode to viral gastroenteritis. All clinical and laboratory exams were normal, with the exception of a slightly increased number of WBCs (12,100/mm^3). A more comprehensive history revealed that the patient also displayed two episodes of lip swelling 3 years ago and another episode on his right hand 2 years ago, which were rescued spontaneously two days later. There was no family history of angioedema.

Which is the next laboratory test?

A complete complement study was performed. The patient displayed low levels of C4 (5 mg/dL; normal range: 10–40), normal levels of C3 (147 mg/dL; normal range: 90–180), and extremely low levels of C1 inhibitor (5.6 mg/dL; normal range: 21–39). C1q levels were normal. Both parents displayed normal complement tests. According to these findings, the diagnosis of hereditary angioedema was emerged. Molecular analysis of *SERPING1/C1NH* gene was performed and revealed the presence of a nonsense mutation into exon 8 (W482X), characterized by a substitution of guanine by an adenine at position 18020 (GenBank accession number: *X54486*) (fig. 1), resulting in the generation of a truncated protein.

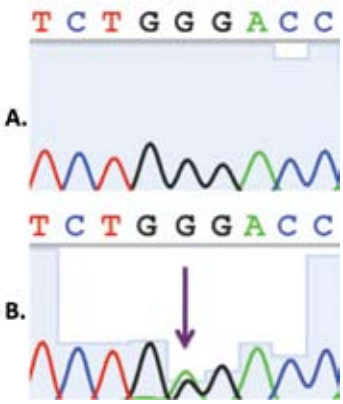

Figure 1. Sequencing analysis revealing the presence of a nonsense mutation (W482X) in *SERPING1/C1NH* gene. (A) Wild type-normal individual. (B) Patient with a G→A substitution at nucleotide 18020 (GenBank accession number: *X54486*) resulting in the replacement of tryptophane (W) by a stop codon (TGA) at position 482.

Comment

Hereditary angioedema (HAE) is an autosomal dominant disease characterized by recurrent angioedema episodes. The prevalence of the disease has been estimated at 1/50,000, with no reported difference in various ethnic groups. HAE patients present functional plasma levels of C1 inhibitor ranging from <10% up to 35% compared to normal subjects. This defect is associated to mutations in one of the two alleles of C1 inhibitor gene (SERPING1/C1NH), which is located in chromosome 11q11.2–q13. About 10% of patients result from brand new mutations; their parents and siblings are normal (as in the case presented above). The pathophysiology of HAE is complex, but it is now generally accepted that formation of bradykinin through activation of the kallikrein-kinin system, which is also controlled by C1 inhibitor, is the major inductor of the edema. Most HAE patients suffer from recurrent skin swelling, abdominal pain episodes and from rarely occurring, potentially life-threatening laryngeal edema. Nowadays, C1 inhibitor concentrate is available in European Union for the treatment of acute attacks and new drugs, such as recombinant C1-inhibitor, bradykinin antagonist (icatibant) and plasma kallikrein antagonist (DX-88) are under investigation in clinical trials with promising results. Prophylaxis treatment is the administration of androgens or transanemic acid, which can result in decreased frequency of attacks. The administration of fresh frozen plasma in acute attacks, when C1 inhibitor concentrate is not available, is controversial.

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