

## A case of hereditary angioedema with recurrent arthritis, erythema marginatum-like rash and chest pain

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**SUMMARY:** Ergin H, Başkan M, Akalın N, Gürses D. A case of hereditary angioedema with recurrent arthritis, erythema marginatum-like rash and chest pain. Turk J Pediatr 2003; 45: 261-264.

Hereditary angioedema (HAE) results from a congenital deficiency of C1 inhibitor and is characterized by submucosal and subcutaneous edema of skin, larynx and abdomen. Occasional reports have appeared linking HAE with autoimmune diseases. We report a case of HAE presenting recurrent nondeforming polyarthritis, erythema marginatum-like rash and chest pain. There were no significant radiographic joint changes. Serologic tests for rheumatologic and autoimmune diseases were negative. After danazol treatment, physical examination and laboratory findings were normal over five years. We suggest that pediatricians should be aware of this rare disease and treat patients accordingly.

*Key words: hereditary angioedema, C1 inhibitor deficiency.*

Hereditary angioedema (HAE), first reported by Quincke in 1882<sup>1</sup>, is characterized by episodes of well circumscribed, nonpitting subepithelial edema that primarily involves the extremities, larynx, face and abdomen<sup>2,3</sup>. The condition is inherited as an autosomal dominant trait. The localization of C1 inhibitor (inh) gene on chromosome 11 was demonstrated by Davies et al.<sup>4</sup>. The prevalence of HAE is estimated to be 1/100,000, affecting individuals of all races<sup>5</sup>. The disease can be biochemically differentiated into type 1, which is the most common form and is characterized by low serum levels of C1 inh, and type 2, characterized by having normal or high levels of C1 inh that are functionally inactive<sup>2,6</sup>.

We report a case of type 1 HAE who had recurrent arthritis, erythema marginatum-like rash and chest pain in addition to larynx, face, extremities and genitalia edema and abdominal pain, and thus who had been initially misdiagnosed as acute rheumatic fever (ARF).

### Case Report

A 15-year-old boy was admitted to Pamukkale University Hospital with dyspnea, hoarseness,



Fig. 1. The appearance of the edema of the face and neck.

and edema involving neck, face and scrotum (Fig. 1). There was a history of recurrent abdominal pain, and cutaneous angioedema involving arms, legs, face, trunk and genitalia at varying intervals since two years of age. The swelling, which was nonpruritic and painless, lasted for three to five days and gradually cleared. At seven years of age, he had developed cutaneous angioedema which was associated with chest pain, erythema marginatum-like rash, nondeforming

polyarthrititis, and arthralgias with involvement of knees, fingers, wrists, and elbows, without systemic or local increase in temperature. A diagnosis of ARF was made and the patient was treated with salicylates and administered benzatine penicillin as a prophylactic treatment every three weeks. He had been treated with epinephrine, diphenhydramine, and steroids during the first attack of larynx edema two years earlier. The family history was unremarkable except for consanguinity of his parents, and he had two healthy siblings.

On examination he was 75<sup>th</sup> percentile for weight (70 kg) and 25<sup>th</sup> percentile for height (168 cm). There were dyspnea, intercostals retractions and significant edema on the face, neck and scrotum. No fever, swelling of the joints, hepatosplenomegaly, lymphadenopathy or cardiac murmur was noted on physical examination. Routine laboratory investigations were within normal limits. The patient was found to have low antigenic C1 inh (0.04 g/L, normal 0.15-0.35 g/L) and C4 (8.50 mg/L, normal 15-50 mg/dl) confirming the diagnosis of angioedema (Behring Nephelometers). The C1 inh levels of this parents were within normal range (mother 0.36 g/L, father 0.43 g/L). The patient was admitted to the intensive care unit and treated with adrenaline, antihistaminic agents and corticosteroids. The swelling of the face and neck resolved at three days and dyspnea disappeared. In spite of benzatine penicillin therapy, we noted chest pain, erythema marginatum-like rash, and swelling of the joints involving finger and knee joints, without systemic or local increase in temperature during the recurrent episodes of HAE (Fig. 2). Physical examination, echocardiogram and laboratory investigations including complete blood count, urinalysis, blood biochemistry, sedimentation rate, ASO, C-reactive protein, fibrinogen, and serum immunoglobulins were reported to be in normal limits. Rheumatoid factor, antinuclear antibodies (ANA), and Brucella agglutination tests were negative. To distinguish from familial Mediterranean fever (FMF), the blood sample was sent for mutational analysis, but no mutation was found in exon II of C1qA gene by using allele specific polymerase chain reaction (PCR) and PCR restriction fragment length polymorphism<sup>7</sup>. We administered danazol for long-term prophylactic treatment

because tranexamic acid (an analogue of epsilon aminocaproic acid: EACA) was ineffective. C1 inh concentrate is currently not available. The patient was found to have low antigenic C1 inh (0.10 and 0.11 g/L) and C4 (13.5 mg/dl) levels while he was taking danazol and in an asymptomatic state. We did not observe any new attack involving joints and larynx with danazol treatment. But erythema marginatum-like rash and cutaneous angioedema developed whenever he did not take danazol during the five-year follow-up. Physical examination and recurrent laboratory investigations including



Fig. 2. The swelling of small joints of the hand.

thyroid functions showed no rheumatologic or autoimmune diseases in follow-up.

### Discussion

Hereditary angioedema is a rare autosomal dominant disorder characterized by a quantitative or functional deficiency of C1 inh, the regulatory protein of the initial classical pathway of complement system<sup>4</sup>. As observed in the present case, 25% of individuals with hereditary angioedema have no family history of the disease<sup>8</sup>. The absence of a family history of angioedema is not inconsistent with this conclusion, given its variable penetrance<sup>9</sup>. Cases of new genetic mutations whose parents had normal C1 inh levels may be found<sup>9,10</sup>. In a report, Chin<sup>9</sup> described a pair of siblings with HAE, with normal parental C1 inh levels.

Attacks of angioedema are reported to be induced by a variety of factors, such as tissue trauma, infection, anxiety, or fatigue. Dental

extractions and tonsillectomy can initiate edema of the upper airway. The symptoms of HAE apparently are influenced by sexual hormones and precipitated by emotional stress<sup>6</sup>. There is no identifiable precipitating event in over half of the patients, as noted in the present case<sup>11,12</sup>.

The skin lesions are described to be nonpruritic, pale, usually not warm, and most frequently involving the extremities, face or genitalia<sup>12,13</sup>. Occasionally mottling, a transient serpiginous erythema, or frank erythema marginatum may precede the edema, suggesting an immediate hypersensitivity reaction<sup>11</sup>. A diagnosis of allergic reaction and ARF were made in the present case because of transient erythema and erythema marginatum, respectively.

Abdominal attacks due to edema in the submucosa and serosa of the bowel wall are often associated with nausea, vomiting, and pain severe enough to necessitate the use of narcotic medications. Although attacks are usually self-limited, severe episodes are difficult to distinguish from acute abdominal conditions, and many patients with HAE have undergone exploratory laparotomy<sup>3,8,11,14</sup>. In countries where FMF is prevalent, FMF should also be included in the differential diagnosis<sup>15</sup>. The present patient was admitted to the hospital because of concurrent or isolated severe abdominal pain.

Life-threatening upper airway edema may result in asphyxiation, and approximately 25% of patients died of this complication before modern prophylactic therapy<sup>4,11,14</sup>. The patients of larynx edema do not respond to treatment with antihistamines, epinephrine, epsilon amino-caproic acid, or corticosteroids<sup>14</sup>. Our case did not show any marked clinical response with these therapeutic agents, and the clinical symptoms resolved spontaneously in three to five days. Infusions of fresh frozen plasma and C1 inh concentrate are effective for prevention and treatment of life threatening attacks of HAE<sup>14</sup>. For HAE patients who have had laryngeal obstruction or have suffered frequent and debilitating attacks, long-term prophylactic agents, such as EACA and attenuated synthetic androgens have been used successfully<sup>2,11,12</sup>. Both the antigenic concentration and functional activity of C1 inh need to be kept at least between 35% to 50% of normal level in order to prevent clinical symptoms<sup>4</sup>. Although the exact mechanism of action is not clear, synthetic

androgens enhance the synthesis of the C1 inh and C4 by the liver<sup>11</sup>. Treatment with danazol increased C1 inh levels over the critical value and prevented new attacks in our case.

A wide variety of symptoms and signs, such as bladder retention; pleural effusions with cough; mild pleuritic chest discomfort; extreme headaches, aphasia, hemiplegia, and seizures. (possibly due to localized brain tissue edema)<sup>13</sup>; arthralgia and nondeforming polyarthritis have been reported in patients with HAE<sup>5,16</sup>. Of these findings, only polyarthritis and chest pain were noted in our patient. An increased frequency of autoimmune and other immunoregulatory diseases have been described in patients with HAE<sup>16</sup>. Brickman et al.<sup>16</sup> reported 19 cases who had clinical immunoregulatory disease in 157 patients with HAE. Two of these 19 patients had symptoms or signs of arthritis. A 21-year-old white male with a history of nondeforming polyarthritis at six years of age, and no significant radiographic joint changes, showed complete IgA deficiency and negative ANA. The patient had been diagnosed as a juvenile rheumatoid arthritis (JRA) with IgA deficiency. A 22-year-old woman who developed symmetric polyarthritis at the age of 19 years was diagnosed as probable rheumatoid arthritis with secondary Sjögren's syndrome. IgM levels were slightly elevated, and the rheumatoid factor was positive. Arthritic complaints require careful evaluation in HAE, since angioedema overlying a joint may mimic the symptoms and physical findings of intraarticular inflammation<sup>16</sup>. The case of HAE also may have ARF or JRA independently. After a first attack at age seven years, our patient experienced a few attacks including chest pain, arthralgia, polyarthritis involving different small hand joints, erythema marginatum-like rash and skin edema, in spite of benzatime penicillin prophylaxis. There were no significant radiographic joint changes. Serologic tests for rheumatologic disease were negative. Therefore, we believe that recurrent polyarthritis and chest pain may develop as the result of HAE with normal immunoglobulins and negative rheumatologic serology. We did not find any other case report with polyarthritis who had normal immunoglobulins and negative rheumatologic serology. A deficiency of C1 inh may also be acquired with the onset of symptoms usually in the fourth decade of life, and this is usually

associated with lymphoproliferative, neoplastic and autoimmune diseases<sup>17</sup>. In the present case, an acquired angioedema was less likely because of the age of the patient and the symptoms persisting since two years of age. We did not find any symptom, or physical or laboratory finding of autoimmune, lymphoproliferative or neoplastic diseases during the five-year follow-up.

We suggest that pediatricians should be aware of this rare disease and treat patients accordingly.

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