HEREDITARY ANGIOEDEMA (HAE): A CASE REPORT AND LITERATURE OVERVIEW

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Abstract: Recognition of the unique clinical and immunological characteristics of the rare causes of Hereditary angioedema (HAE) is important in order to obtain proper and timely diagnosis and treatment of the patient. Hereditary angioedema is a rare disease with great heterogeneity of symptoms like edema of the skin, gastro-intestinal mucosa and larynx or pharynx. The changes are spontaneously withdrawn in 12 to 72 hours. Hereditary angioedema is autosomal-dominant but can occur spontaneously in a healthy family without clinical manifestations or immune defects. Based on the mechanism of occurrence, it is conventionally classified as angioedema mediated by mastocytic degranulation, bradykinin or idiopathic, while in terms of clinical and pathophysiological manifestation it is divided into acquired and congenital or congenital angioedema with or without urticaria.Three types of HAE are described. The most frequent is type I, which is a result from a mutations in the SERPING 1 gene, they cause hereditary angioedema type I and type II. The SERPING 1 gene provides instructions for creating C1 inhibitory protein, which is important for controlling inflammation. C1 inhibitory protein leads to blockage of the activity of certain proteins that lead to inflammation. Mutations that cause hereditary angioedema type I lead to decreased levels of C1 in the blood, deficiency of the complement C1 inhibitor. Without an adequate level of functional C1 inhibitor, excessive amounts of a protein fragment called bradykinin are generated. Bradycin causes inflammation due to the increased elimination of fluid through the walls of blood vessels in the body's tissues. Excessive accumulation of fluid in body tissues causes episodes of swelling observed in individuals with inherited angioedema type I and type II.

Case presentation: A 25-year old woman who was first diagnosed with Oedema Quincke, of the face, after an insect bite, when she was 9 years old. Since then, almost every month, swelling of the arms or legs occurs before the menstrual cycle, and swelling of the hands also occurs when blood is drawn from the finger, while several times a year there is swelling in the facial region. The patient was brought for the first time as an emergency to the Department of Dermatovenereology at the Clinical Hospital Stip with pronounced circuscribed edema of the face without erythema and without a feeling of itching and pain that appeared 3-4 hours before admission. Due to the frequent occurrence of swelling in the facial region, immunochemical analyzes have been performed. The analysis showed a reduced level of C1 inhibitor esterase 0.0365g / l (0.18-0.39) and the results are in favor of HAE typ I. The patient was treated few times with isogroup plasma 2x220 ml and within 24 hours the edema receded, later she was included in the program for patients with HAE, with parenteral inhibitor of C1 esterase, ie with amp. Beriner.

Keywords: hereditary angioedema; case report; C1 inhibitor esterase.

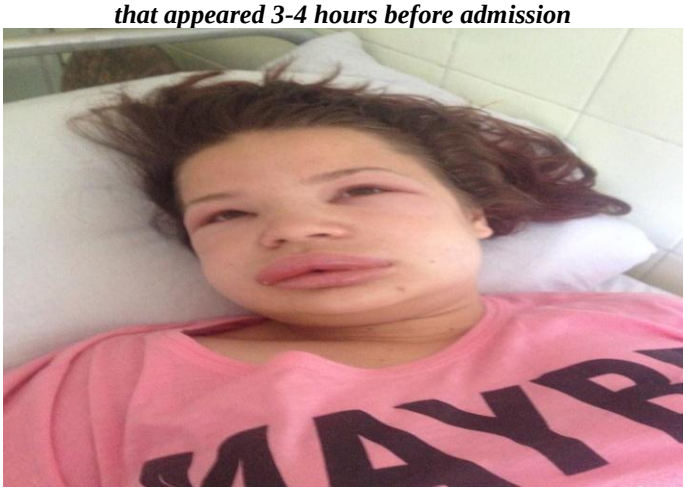
1. INTRODUCTION

Hereditary angioedema is a more or less pronounced circulatory-localized edema localized to the skin or mucous membranes, most commonly affecting the face, eyelids, lips, genitals, tongue, pharynx, and larynx. The skin colour over the edema is unchanged or pale pink, there is a feeling of tightness, and sometimes there may be itching of varying intensity. Based on the mechanism of occurrence, it is conventionally classified as angioedema mediated by mastocytic degranulation, bradykinin or idiopathic, while in terms of clinical and pathophysiological manifestation it is divided into acquired and congenital or congenital angioedema with or without urticaria. (Wolff, Johnson, 2009. Wolff, Goldsmith, Katz, Gilchrest, Paller, Leffel, 2008). Hereditary angioedema is a rare but serious disease that is autosomal-dominant but can occur spontaneously in a healthy family without clinical manifestations or immune defects. It is characterized by recurrent circus-edema without itching and erythema (Papamanthos, Matiakis, Tsirevelou, Kolokotronis, & Skoulakis,2010). The changes are spontaneously withdrawn in 12 to 72 hours.

2. CASE REPORT

A 25-year-old, mother of one child, with a positive family history of HAE (mother and mother's mother). The patient was diagnosed with the disease 5 years ago. In 2014, the patient was brought for the first time as an emergency to the Department of Dermatovenereology at the Clinical Hospital Shtip with pronounced circuscripted edema of the face without erythema and without a feeling of itching and pain that appeared 3-4 hours before admission. From EMC has been prescribed antihistamine and corticosteroid therapy (amp. Methylprednisolone a 120 mg).

Figure1. Pronounced circuscripted edema of the face without erythema and without a feeling of itching and pain that appeared 3-4 hours before admission



From the anamnesis we received data that at the age of 9 the patient was hospitalized in the children's ward as Oedema Quincke of the face, after an insect bite. Since then, almost every month, swelling of the arms or legs occurs before the menstrual cycle. Swelling of the hands also occurs when blood is taken from the finger, while several times a year there is swelling in the facial region. In our ward, the patient was treated with isogroup plasma 2x220 ml and within 24 hours the edema receded.

Figure 2. Patient after treatment with isogroup plasma 2x220 ml. Left pictures after 24 hours and right pictures after 72 hours.

Due to the frequent occurrence of swelling in the facial region, immunochemical analyzes have been performed. The analysis showed a reduced level of C1 inhibitor esterase 0.0365g / l (0.18-0.39) and the results are in favor of HAE typ I. On several occasions during the same year the patient was hospitalized in our ward, most often due to swelling of the face, and after conducting isogrup therapy (1-2x220 ml) the changes are withdrawn. In the next few years, in addition to edema in the facial region, the cause of frequent hospitalizations is edema in the neck region, intense

abdominal pain followed by nausea and vomiting, as well as laryngeal edema. After treatment with isogrup plasma or amp. Ruconest stable remission in a few hours is achieved. In 2015, the patient was included in the program for patients with HAE with parenteral inhibitor of C1 esterase, i.e. with amp. Beriner.

3. DISSCUSION

The prevalence of HAE is relatively low, 1 in every 10,000 or 1 in every 500,000 citizens (Frank,2010). Most people with HAE get a mutation in a C1 inhibitory protein from one of the parents. Mutations in the SERPING 1 gene cause hereditary angioedema type I and type II. The SERPING 1 gene provides instructions for creating a C1 inhibitory protein, which is important for controlling inflammation (Wolff, Johnson, 2009. Wolff, Goldsmith, Katz, Gilchrest, Paller, Leffel, 2008). C1 inhibitory protein leads to blockage of the activity of certain proteins that lead to inflammation. Mutations that cause inherited type I angioedema lead to decreased levels of C1 inhibitor in the blood, while mutations that cause type II result in the production of C1 inhibitor but its functioning is abnormal. Without a corresponding level of functional C1 inhibitor, excessive amounts are generated on a protein fragment called bradykinin (Wolff, Johnson, 2009. Wolff, Goldsmith, Katz, Gilchrest, Paller, Leffel, 2008). Bradykinin leads to inflammation due to the increased elimination of fluids through the walls of blood vessels in the body tissues. Excessive accumulation of fluid in body tissues causes episodes of edema observed in individuals with inherited type I and type II angioedema (Wolff, Johnson, 2009. Wolff, Goldsmith, Katz, Gilchrest, Paller, Leffel, 2008, Papamanthos, Matiakis, Tsirevelou, Kolokotronis, & Skoulakis, 2010). The symptoms of HAE can occur at any time in childhood. Attacks of swelling generally begin in school or adolescence. In 50% of the cases, the first changes appear when children are between 5 and 11 years old. The attacks are unpredictable, sometimes they appear without prior warning, but they can also develop in hours. The onset of edema may be preceded by prodromal symptoms such as: tingling in the area where the edema will develop, erythema rash, sudden mood swings, anxiety, fatigue, cramps or intense abdominal pain. Possible trigger factors are: stress, frequent infections in childhood, pregnancy, trauma, some drugs (ACE inhibitors, contraceptives), dental interventions, oral contraceptives, stings, certain foods, etc. In most cases the exact trigger is not known (Wolff, Johnson, 2009. Wolff, Goldsmith, Katz, Gilchrest, Paller, Leffel, 2008). The most common and earliest symptoms that occur: edema - can affect any part of the body, is most often localized in the facial region, swelling of the face and genitals can lead to severe impairment of normal patient function, edema of the respiratory tract - tongue, larynx accompanied by difficult breathing, difficult speaking and swallowing as well as the appearance of stridor (Sacha, Mmarcel, 2016.Bork, Frank, Grundt, Schlattmann, Nussberger & Kreuz, 2007). Such attacks can be fatal due to asphyxia, erythema marginatum - occurs in 42-58% of children, often can be interpreted as urticaria, abdominal symptoms - intense pain, cramps, nausea, vomiting, diarrhea, dehydration which many times it is misdiagnosed. The frequency of seizures without prior preventive treatment also varies and it is estimated that one third of patients have more than 12 seizures during the year, 40% of patients about 6 to 11 seizures per year, while one third occur much less number of seizures or have no symptomatology (Soni, Kumar, Alliu, & Shetty,2016). Concentrated C1 inhibitor (derived from plasma or recombinant) and icatibant (antagonist of B receptor for bradykinin) have been registered for the treatment of acute attacks of HAE in Europe, while eccalantide (an inhibitor of calicrain) has been registered only in the United States. The action of these drugs begins 30-60 minutes after their application and it takes several hours for the changes to completely subside. It is most effective if the drug is taken immediately after the first symptoms appear (Papamanthos, Matiakis, Tsirevelou, Kolokotronis, & Skoulakis, 2010, Sacha, Mmarcel,2016)

4. CONCLUSION

From the above we can conclude that the disease is very rare and it is not uncommon for patients to remain undiagnosed for many years or to be diagnosed as Oedema Quincke. Many patients reported that their frequent and severe abdominal pain was misdiagnosed as psychosomatic with referral to a psychiatric evaluation. We should always think that it is possible for a patient to have HAE if anamnesis gives us information that there is often abdominal pain attack, headache attack, family history of hereditary angioedema, occurrence of angioedema as a side effect of AKE inhibitor therapy.

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