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Case Report

Probable "Escitalopram induced" angioedema in a patient with hereditary angioedema

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Abstract

Hereditary angioedema (HAE) is an autosomal dominant disorder. Considerable rate of mortality determines the importance of disease. In this paper, a patient with HAE who developed severe facial angioedema after the first dose of an antidepressant (Escitalopram) prescribed by a psychiatrist because of diagnosis of depression, was presented and discussed. In the presented case, severe facial angioedema was not found to be clearly associated with a particular cause. There were possibilities such as sporadic/idiopathic attack or depression related attack. However, occurrence of an acute attack soon after a newly started drug had to draw attention to Escitalopram. So, in patients with HAE under an antidepressant treatment, antidepressant related angioedema must be kept in mind when the HAE control deteriorated.

Keywords: Hereditary Angioedema, Escitalopram, Non-Histaminergic Angioedema.

INTRODUCTION

Hereditary angioedema (HAE) is an autosomal dominant disorder. It is rare (1/35.000 to 50.000) but can sometimes result in serious consequences. The disease presenting as non-histaminergic angioedema without urticaria, which is affects skin and mucous membranes. The underlying pathophysiology is the increased production of Bradykinin in the tissues caused by the incomplete or incorrect production of a complement control protein called as C1 esterase inhibitor (C1inh) (1).

Considerable rate of mortality determines the importance of disease. The leading cause of HEA associated death is asphyxia due to larynx or pharyngeal angioedema. Despite current effective therapies deaths secondary to laryngeal attacks still occur. The reported mortality rate as high as 13 percent (2).

Control of the triggering factors is undeniable in the management of patients with HAE. Several factors which may cause to acute attacks have been defined, and the number is increasing day by day. Among these factors, mental stress and depression have a special importance (3,4). Emotional instability increases the frequency of attacks, which in turn may cause to worsening psychological disorder. To break this vicious circle, antidepressant may sometimes provide additional benefit to classic prophylactic treatments.

In this paper, a patient with HAE who developed severe facial angioedema after the first dose of an antidepressant (Escitalopram) which was prescribed by psychiatrist because of diagnosis of depression, presented and discussed.

CASE REPORT

The patient is a 43-year-old female, who had diagnosed as HAE type 2 (C4: 0,003 g/L [0.16-0.38 g/L] C1 esterase level: 41 mg/dl [18-32 mg dl] and C1 esterase activity: 14% [70-130%]) 15 years ago and following up in our clinic for the last 7 years. She has been under treatment of human C1-esterase inhibitor concentrate infusions, by if needed, for two years. Attacks were acceptable number and severity (nearly 1 attack per month and mostly angioedema of extremities). However, the frequency of attacks was increased during the last 6 months without any obvious reason. Fortunately, angioedema was limited to skin and mild in severity.

All options for long-term prophylaxis to prevent attacks of HAE were evaluated. Tranexamic acid was ineffective in the prevention of HAE attacks and epsilon aminocaproic

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acid was not available in our country. Danazol treatment, which is also available for prophylactic therapy, was not accepted by the patient. She had unpleasant experiences with danazol previously, such as menstrual irregularity and hair growth in male pattern. So, the only option in our hand was to increase the frequency of C1-esterase inhibitor concentrate infusions.

All possible factors that may provoke HAE attacks were reassessed. Known general precautions to limit attacks were taken such as restriction of vigorous physical activities, avoidance of traumas, and early intervention of infections. However, uncomplicated but seriously disturbing HAE attacks were not controlled.

Failure in disease control was negatively affect the patients' mood and symptoms such as sleep disturbance, reluctance to work and poor concentration were aroused. These additional symptoms were also negatively affect the course of HAE further increased the frequency of attacks. The patient consulted with a psychiatrist and escitalopram 20 mg/day was given with the diagnosis of depression.

The patient received the first dose of escitalopram approximately 1 hour before sleeping as recommended. Approximately 6 hours later, at 05.00 the patient waked up with discomfort complaint on the face, she realized that his whole face was swollen and could not see around because of the swelling in the eyelids and was brought to emergency by her relatives.

At first examination on the emergency service, angioedema was detected in the lips, on the cheek and in the forehead, completely closing the eyes in the bilateral, lower and upper eyelids (Figure 1).

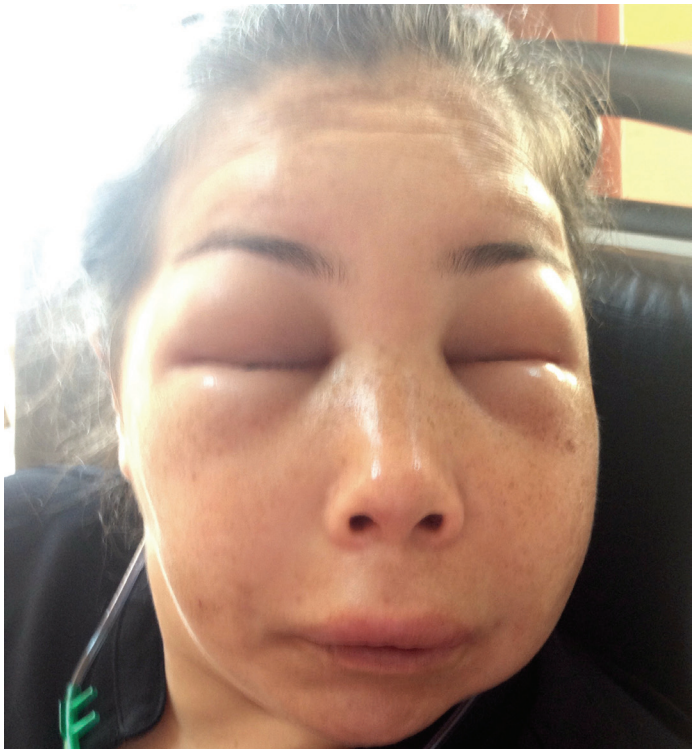

Figure 1. 6 hours after the patient receives the drug, Escitalopram

The patient transferred to our clinic a few hours after the emergency department admission. Since she had experienced this severe attack soon after a newly started drug (Escitalopram), we focused on primarily "a drug induced" angioedema. Also, all other possible triggers were evaluated in detail, including;

- Firstly, any other drug especially non-steroidal anti-inflammatory drugs (NSAIDs) use asked; she had not taken any other drug.

- She was not using oral contraceptives.

- Presence of any infection, especially upper respiratory tract was investigated. Oropharyngeal exam was normal; CBC, ESR and CRP were in normal limits. Urine analysis was also normal.

- There was no history of dental exam or face trauma prior to attack.

- There was no vigorous activity or exercise that could cause general body fatigue.

- Skin prick test with standard allergens was negative

- Immunological evaluation was normal which she had normal IgG, IgM, IgA and IgE levels

- She was not in the menstrual or premenstrual phase where the attacks can be frequent.

- She was not used a face mask, face cream or lotion at that night which may cause chemical irritation on face.

In consequence, we had three possibilities; a) A sporadic/idiopathic attack b) A poor mood (depression) related attack c) An ordinary angioedema and/or HAE attack induced by Escitalopram.

As the presence of widespread facial angioedema that can progress to oropharynx or larynx, this attack was accepted as "severe". Antidepressant treatment was discontinued immediately, because we had a strong suspicion about Escitalopram. The possibility of severe reaction discouraged patient from provocation testing with the suspicious drug. So we could not prove exact relationship between angioedema and Escitalopram.

DISCUSSION

HAE is still an incurable chronic disorder. Basic principles of the control of the disease include prophylactic treatments to reduce the number of attacks, intervention in acute attacks, and pre-treatments before elective traumatic medical procedures (surgery, endoscopy, dental treatment, etc.). Today, we have effective therapeutic agents (such as C1-esterase inhibitor concentrate, İcatibant, Ecallantide) which can be used for both acute attack and for long term prophylaxis. Once diagnosis of HAE is established, most of patients clearly benefit from these treatments and reaches a better quality of life.

As in most chronic illness, management of the disease should be personalized to the patient. In particular, the factors that initiate acute attacks must be investigated in detail and, if possible, should be removed. Well-defined triggers are usually reviewed in this purpose, but rare

exceptions or unidentified "possible" triggers may be overlooked. There are many examples of rare and/or possible triggers in the medical literature: severe upper airway obstruction caused by piercing of the tongue (5), snoring-induced recurrent edema of the soft palate (6), vaginal and vulvar angioedema after sexual intercourse (unpublished our clinical observation), excitement, cold exposure, prolonged sitting or standing, bacteriuria, menstruation (2,7) and Helicobacter pylori infections (8).

Particular groups of medicines deteriorate the course HAE by initiating acute attacks. Well-known examples are estrogen-containing contraceptives (9) and angiotensin-converting enzyme (ACE) inhibitors (10). HAE attacks due to tamoxifen, a selective estrogen-receptor modulator, have also been reported (11). In addition, there are some other drugs which may cause non-histaminergic angioedema, albeit not directly related with HAE, including; Sitagliptin (13) and Risperidone (14). However, it can be speculated that, this kind of medicines may also worsen course of disease if they used in patients with HAE.

In the presented case, severe facial angioedema could not clearly associate with a particular cause. Of course, as mentioned before, there were possibilities such as sporadic/idiopathic attack or depression related attack. However, occurrence an acute attack soon after a newly started drug had to draw attention to Escitalopram.

We have reached some data about "Escitalopram and Angioedema" with surfing on internet. Although there was no published paper in the PubMed database, there were some reports based on FDA data: by 25th November 2017; 21,118 side effects associated with Escitalopram have been reported and among these, 59 were angioedema (0.28%). Angioedema was found especially in female patients (68.42%) and in patients older than 60 years (43.64%). In 37.5 percent of cases, angioedema was occurred within first month of the treatment. This report is created by eHealthMe based on reports of 21.118 people who have side effects when taking Escitalopram from FDA (www.ehealthme.com/ds/escitalopram/angioedema/).

However, it is important to highlight that Escitalopram is not the only antidepressant that may cause to angioedema. There are some publications, although limited in number, reported different antidepressant induced angioedema cases (15-18). But, it is unclear whether these reactions are histaminergic or non-histaminergic, or by which mechanism.

CONCLUSION

In conclusion; we have decided to publish this case for three interests: 1) Escitalopram is one of the most prescribed antidepressant. Patients taking Escitalopram should be informed and observed in terms of angioedema. 2) Antidepressants may sometimes use in HAE patients to provide additional benefit to classic prophylactic treatments. However, such interventions may not be always safe, especially with new generation SSRI drugs. 3) In patients with HAE under an antidepressant treatment, antidepressant related angioedema must be kept in mind when the HAE control deteriorated. In our opinion, it is not important whether these reactions are histaminergic or non-histaminergic. Because, "drug related angioedema" may cause a "minor trauma" by increasing tissue tension, and may initiate a "true HAE attack".

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REFERENCES

1. Altman KA, Naimi DR. Hereditary angioedema: a brief review of new developments. Curr Med Res Opin 2014;30:923-30.
2. Agostoni A, Aygoren-Pursun E, Binkley KE, et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. J Allergy Clin Immunol 2004;114:S51-131.
3. Fouche AS, Saunders EF, Craig T. Depression and anxiety in patients with hereditary angioedema. Ann Allergy Asthma Immunol 2014;112:371-5.
4. Caballero T, Aygoren-Pursun E, Bygum A, et al. The humanistic burden of hereditary angioedema: results from the Burden of Illness Study in Europe. Allergy Asthma Proc 2014;35:47-53.
5. Trachsel D, Hammer J. A vote for inhaled adrenaline in the treatment of severe upper airway obstruction caused by piercing of the tongue in hereditary angioedema. Intensive Care Med 1999;25:1335-6.
6. Bork K, Koch P. Episodes of severe dyspnea caused by snoring-induced recurrent edema of the soft palate in hereditary angioedema. J Am Acad Dermatol 2001;45:968-9.
7. Zotter Z, Veszeli N, Kohalmi KV, et al. Bacteriuria increases the risk of edematous attacks in hereditary angioedema with C1-inhibitor deficiency. Allergy 2016;71:1791-3.
8. Visy B, Fust G, Bygum A, et al. Helicobacter pylori infection as a triggering factor of attacks in patients with hereditary angioedema. Helicobacter 2007;12:251-7.
9. Bork K, Fischer B, Dewald G. Recurrent episodes of skin angioedema and severe attacks of abdominal pain induced by oral contraceptives or hormone replacement therapy. Am J Med 2003;114:294-8.
10. Ricketti AJ, Cleri DJ, Ramos-Bonner LS, et al. Hereditary angioedema presenting in late middle age after angiotensin-converting enzyme inhibitor treatment. Ann Allergy Asthma Immunol 2007;98:397-401.
11. Rousset-Jablonski C, Thalabard JC, Gompel A. Tamoxifen contraindicated in women with hereditary angioedema? Ann Oncol 2009;20:1281-2.
12. Skalli S, Wion-Barbot N, Baudrant M, et al. Angio-oedema induced by dual dipeptidyl peptidase inhibitor and angiotensin II receptor blocker: a first case report. Diabet Med 2010;27:486-7.
13. Gunes F, Batgi H, Akbal A, et al. Angioedema - an unusual serious side effect of risperidone injection. Clin Toxicol (Phila) 2013;51:122-3.

14. Tuman TC, Demir N, Topal Z,et al. Angioedema probably related to fluoxetine in a preadolescent being followed up for major depressive disorder. J Child Adolesc Psychopharmacol 2013;23:697-8.
15. Tuman TC, Tuman B, Polat M, et al. Urticaria and Angioedema Associated with Fluoxetine. Clin Psychopharmacol Neurosci 2017;15:418-9.
16. Mithani H, Hurwitz TA. Paroxetine-induced angioedema and tongue swelling. J Clin Psychiatry 1996;57:486.
17. Lin CE, Chen CL. Repeated angioedema following administration of venlafaxine and mirtazapine. Gen Hosp Psychiatry 2010;32:341:e1-2.