E. Galdi, L.G. Cremonte

Acquired C1-inhibitor deficiency: a case report

SOS Dipartimentale di Allergologia ASL AL, Novi Ligure (AL), Italy - E-mail: lcremonte@aslal.it

Key words

Angioedema, acquired angioedema, lymphoproliferative disorder, C1 inhibitor

Corresponding author
Luigi Giovanni Cremonte
Dir. SOS Dipartimentale di Allergologia ASL AL
Via E. Raggio 12,
15067 Novi Ligure (AL)
Phone: +39 0143.332535
E-mail: lcremonte@aslal.it

Summary

Angioedema due to C1 - inhibitor deficiency may be hereditary (HAE) or acquired (AAE). AAE is a very rare condition, whose prevalence is possibly underestimated, as it is often unrecognized. AAE usually occurs after the fourth decade of life, and it is commonly associated to an underlying disease, mainly lymphoproliferative disorders. We report a 74-years old woman with recurrent episodes of angioedema involving upper airways in which diagnosis was obtained a long time after symptoms onset. A concomitant B cell leukaemia was also diagnosed. This report stresses the importance of the recognition of AAE: a delayed diagnosis is indeed associated to the risk of severe life-threatening episodes, unresponsive to the usual therapy of common form of angioedema. AAE should be considered as a possible diagnosis in subjects with adult onset of angioedema: a careful clinical history is basic, since the clinical features and the time-course are often suggestive of the disease.

Introduction

Angioedema (AE) is characterized by a sudden pronounced swelling of the lower dermis and subcutis, pain rather than itching, frequent involvement below mucous membranes (1).

AE is due to transient increase of endothelial permeability in the capillaries of the deep cutaneous and mucosal layers (2).

Causes of AE are miscellaneous: allergy, drugs (ACE inhibitors, salicylates, nonsteroidal antinflammatory drugs), idiopathic, C1 inhibitor deficiency (3).

Two types of AE are best defined, and can be taken as the prototypes of all the different angioedemas (2). The most common form of AE is allergic IgE mediated, and it is due to the release of histamine from mast cells. The other prototype of AE is hereditary AE due to C1-inhibitor (C1-INH) deficiency (2), in which there is a release of bradykinin (BK) from high molecular weight kininogen (HK) upon activation of the contact system, with generation of activated factor XII (FXIIa) and plasma kallikrein from their precursor zymogens FXII and plasma prekallicrein (4).

C1-INH deficiency is a rare disorder that may be due either to a genetic defect (as in Hereditary Angioedema, HAE) or to an increased consumption (Acquired Angioedema, AAE) (2).

AAE, first described by Caldwell in 1972 (5), is a syndrome characterized by acquired deficiency of C1-INH, hyperactivation of the classical pathway of human complement, and recurrent angioedema symptoms.

AEE is a very rare condition: approximately 100 case are reported in the literature (6), and its prevalence is estimated between 1:100000 and 1:500000 (7). Since AAE is

a frequently unrecognized condition, its prevalence is considered underestimated (7).
The pathogenesis of angioedema is mediated by episodic release of bradykinin due to an inappropriate activation of the contact-kinin system lacking its major regulator C1-INH (8, 9).
This mechanism is the same in AAE and HAE, in which the deficiency of C1-INH is due to mutations in one of the two alleles of the C1-INH gene (autosomal dominant defect) (10).
As a consequence of the common pathogenesis, clinical presentation of AEE and HAE is the same: recurrent episodes of angioedema of the skin, severe abdominal pain (due to edema of the bowel mucosa), edema of the tongue and of the oral mucosa, acute dyspnoea (due to edema of the upper respiratory tract) (7). AEE and HAE are life-threatening conditions, due to laryngeal edema.
The age of onset of symptoms is within the second decade of life for most (>90%) subjects with HAE, after the fourth decade for those with AAE (7).
AAE is associated with various diseases, particularly with lymphoma and different form of lymphoproliferative disorders (7). In the majority of these subjects neutralizing antibodies to C1-INH are present (11-13). Although lymphoproliterative disorders represent the main diseases group encountered in AAE, systemic lupus erithematosus, neoplasias, and infections have also been described in association with AAE (7).
Testing for C1-INH deficiency is done by measuring C4 levels in plasma and C1-INH antigen. In patients with C1-INH deficiency, C4 levels are markedly decreased. Due to the extremely wide range of variability of C4 levels, low levels are not uncommon also in normal subjects. Thus, when C4 levels are low, C1-INH deficiency needs to be directly demonstrated (2). Additional testing is necessary to distinguish between inherited and acquired deficiency; this testing includes determination of C1q (reduced in 70% of subjects with AAE and normal in HAE), and, if C1q is normal, autoantibodies to C1-INH, which presence at high titre allows diagnosing AAE (7).
The treatment of acute episodes is based on replacement therapy with plasma-derived C1-INH.
Non responsive subjects need invasive procedures to maintain patency of upper airways.
More recently the bradykinin B2 antagonist icatibant has been successfully used, also in subjects unresponsive to C1-INH (14).
Diagnosis is critical for the proper therapeutic management, since misdiagnosis exposes patients to the risk of death, due to laryngeal edema during spontaneous attacks. Physical trauma is a trigger of attacks, so manoeuvres on the oral cavity (i.e. dental works, endoscopic examination, endotracheal intubations) may induce an attack; subjects undergoing these procedures should be premedicated and monitored.

Case report

A 74-year-old woman was seen at our Unit for recurrent episodes of angioedema of the face, unresponsive to therapy with systemic corticosteroids and antihistamines, and lasting for about 4-5 days. In some occasions the tongue and the upper airways were involved. Urticaria was never associated to angioedema. The first episode occurred on December 2006, four years before the first examination at our Unit. The intervals between episodes were about two months. Several visits to the Emergency Room were reported.
Family history was negative for angioedema. Personal history was negative for atopy; adverse drug reactions to nonsteroidal antinflammatory drugs were referred. Drug history was negative for current therapy with ACE-inhibitors.
A recent blood cell count with differential showed WBC 13.85x10^3/UL, neutrophils 22%, lymphocytes 72%, and beta2-microglobulin was 4000 ng/mL. An hematological evaluation has already been scheduled.
The age of onset of angioedema, the absence of coexisting urticaria, the absence of response to usual treatment of AE suggested a AAE.
C4 measurement shown a decreased level: 6 mg/dl. A second measurement of C4 levels again resulted 6 mg/dL. C1-INH was measured and resulted unmeasurable. Diagnosis of C1-INH deficiency was made.
To distinguish between inherited and acquired deficiency, C1q was determined, and resulted unmeasurable. Diagnosis of AAE was made (15).
In the meantime hematological evaluation led to the diagnosis of B-chronic lymphocytic leukemia (B-CLL).
Antinuclear and anti ENA autoantibodies measurement ruled out systemic autoimmune disorders.
Replacement therapy with plasma-derived C1-INH for reversal of acute attacks was recommended, stressing the importance of having readily available the treatment. Since the treatment is rarely present in hospital emergency departments, the patient was instructed to keep the drug at home, and to carry it to the nearest hospital in the case of an attack.

We met the patient at two follow up visits (about 12 and 18 months after diagnosis), and no subsequent episodes were referred. Measurement of C1INH and C4 was repeated, and confirmed low levels.
In the meantime treatment with cyclofosfamide and vincristine has been given for concomitant leukemia. The patient was asymptomatic for angioedema both during therapy, and after its interruption, about one year before the last follow up examination at our Unit.

Discussion

Some important considerations can be drawn from this case report.
AAE is a well known condition, but it is frequently unrecognized due to its rarity; a delayed diagnosis is associated to a high risk of fatality due to inappropriate therapy. In our patient diagnosis was made about 4 years after the first episode.
In a subject with recurrent episodes of AE the importance of a careful clinical history has to be stressed, since the clinical features and the time-course often suggest the possibility of AAE. In our case the unresponsiveness to usual pharmacological treatment of AE, the involvement of upper airways and the late age of onset suggested a possible AAE.
Subjects with AE examined at the Emergency Room should always be referred to a subsequent allergological evaluation, and particularly when clinical presentation and persistence of symptoms after usual AE therapy are not typical of a common form of AE.
Moreover the confirmation of the hypothesis prompts the need for a lymphoproliferative and autoimmune disease screening, being abnormal B cell proliferation the most frequent disease association.
Similarly, haematologists should be aware of the possibility of AAE in subjects with lymphoproliferative disorders and recurrent AE episodes, in order to refer the patient to a specialist for appropriate diagnosis and treatment.
In our patient a long time without attacks was reported at the follow-up visit. We think that treatment given for leukemia didn't affect the course of AAE in our case, considering absence of episodes during a long period (about one year) after stopping therapy, and persistence of low level of C4 and C1 INH. We believe the course of the disease in our patient is consistent with its natural history. Frequency and severity of the recurrences are indeed variable, ranging from completely asymptomatic to recurrences of attacks every few days. This variability may occur in different patients, but also in the same patient, and the underlying mechanism is unknown (2).
In conclusion, acquired AE due to lymphoproliferative disorder should always be considered in the case of adult onset not associated with a family history of AE.

References

1. Zuberbier T, Asero R, Bindslev-Jensen C, et al. EAACI/GA2LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. Allergy 2009; 64: 1417-26.
2. Cicardi M, Zanichelli A. Angioedema due to C1 inhibitor deficiency in 2010. Intern Emerg Med 2010; 5: 481-86.
3. Grigoriadou S, Longhurst HJ. Clinical Immunology Review Series: An approach to the patient with angio-edema. Clin Exp Immunol. 2009; 155: 367-77.
4. Cugno M, Zanichelli A, Fieni F, Caccia S, Cicardi M. C1-inhibitor deficiency and angioedema: molecular mechanisms and clinical progress. Trends Mol Med 2009; 15: 69-78.
5. Caldwell JR, Ruddy S, Schur PH, Austen KF. Acquired C1 inhibitor deficiency in lymphosarcoma. Clin Immunol Immunopathol 1972; 1: 39-52.
6. Zingale LC, Castelli R, Zanichelli A, Cicardi M. Acquired deficiency of the inhibitor of the first complement component: presentation, diagnosis, course, and conventional management. Immunol Allergy Clin North Am 2006; 26: 669-90.
7. Cicardi M, Zanichelli A. Acquired angioedema. All Asthma Clin Immunol 2010; 6: 14-18.
8. Davis AE. C1 inhibitor and hereditary angioneurotic edema. Annu Rev Immunol 1988; 6: 595-628.
9. Nussberger J, Cugno M, Amstuz C, Cicardi M, Pellacani A, Agostoni A. Plasma bradykinin in angio-oedema. Lancet 1998; 351: 1693-7.
10. 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 bend. J Allergy Clin Immunol 2004; 114: 551-31.
11. Jackson J, Sim RB, Whelan A, Feighery C. An IgG autoantibody which inactivates C1-inhibitor. Nature 1986; 323: 722-4.
12. Alsenz J, Bork K, Loos M. Autoantibody-mediated acquired deficiency of C1 inhibitor. N Engl J Med 1987; 316: 1360-6.
13. Cicardi M, Beretta A, Colombo M, Gioffre D, Cugno M, Agostoni A. Relevance of lymphoproliferative disorders and of anti-C1 inhibitor autoantidodies in acquired angio-oedema. Clin Exp Immunol 1996; 106: 475-80-
14. Zanichelli A, Badini M, Nataloni I, Montano N, Cicardi M. Treatment of acquired angioedema with icatibant: a case report. Intern Emerg Med 2011; 6 (3): 279-80-
15. Bowen T, Cicardi M, Farka H, et al. 2010 International consensus alghoritm for the diagnosis, therapy and management of hereditary angioedema. Allergy, Asthma Clin Immunol 2010; 6: 24-37.