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Title: Prophylactic treatment with plasma-derived C1-inhibitor in idiopathic non-histaminergic angioedema

Running title: pdC1-INH as prophylaxis in InH-AAE.

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To the Editor

Idiopathic non-histaminergic angioedema (InH-AAE) is defined as localized and self-limiting edema of the subcutaneous and submucosal tissue, in which family history and known causes have been excluded and antihistamine treatment has been proved not being effective (1). It is due to a temporary increase in vascular permeability caused by the release of vasoactive mediators. Bradykinin seems to be the main mediator of this type of angioedema (2), suggesting a common pathogenetic pathway with C1-inhibitor deficiency hereditary angioedema (C1-INH-HAE). The evidence proving this hypothesis is still poor, so

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other mediators, such as cystenil leukotrienes, prostaglandins, or platelet-activating factor, should be considered.

Currently there are not treatments labelled for idiopathic non-histaminergic angioedema. Nevertheless recently some case reports and series have been published, suggesting that drugs with proved efficacy in C1-INH-HAE could be also used in patients with InH-AAE. Most of these papers deal with population of adults, or adults and children, but very few cases are focused only on children.

Two case reports describe the successful use of ecallantide, a plasma kallikrein inhibitor, for treatment of acute attacks in a child and in a teenager affected by InH-AAE (3,4). A number of studies involving InH-AAE patients from puberty to elderly suggest the efficacy of tranexamic acid (1-3 g/daily) as a prophylactic treatment (5,6,7).

Recently three case reports have been published about adults and teenagers with InH-AAE requiring prophylactic treatments. In each of them the replacement therapy with pdC1-INH treatment appeared effective as preventive care (8,9). No experience in the use of pdC1-INH as prophylaxis in children has been published until now.

We report the first case of a 11-year old child affected by InH-AAE and effectively treated with pdC1-INH in prophylaxis. Written informed consent was obtained from the patient and his parents for publication of this case report.

At the age of 9, the child referred to the outpatient department of our Allergy and Immunology Clinical Center for recurrent attacks of angioedema without wheals.

He reported to suffer from beta major talassemia, so from birth the patient had been undergone periodically to blood transfusions and administration of iron chelating drugs.

From the age of 7 the patient reported recurrent episodes of limbs swelling and abdominal pain without urticaria and itch. The frequency of attacks was about four times a month; they lasted for about 12 hours regardless of treatment with betamethasone 1 mg per *os on demand*.

He had no history of allergy and no sensitivity to indoor or outdoor allergens on the basis of skin and in vitro allergy tests.

In the next weeks he underwent a diagnostic evaluation. Lymphoproliferative and autoimmune diseases were excluded. The child was evaluated for FXII- and C1-INH-HAE. C4 and functional C1-INH levels were normal, while C1-INH antigenic levels were borderline (median value 0,194 g/l-normal value 0,21-0,39 g/l) at baseline and during acute attacks. In order to exclude that blood transfusions could temporarily normalize C1-INH antigenic levels, we withdrew blood sample before and after the transfusion and we found no differences between the two samples. Gene testing for factor XII (*F12*) and C1-INH gene (*SERPING1*) was performed and no causative mutations were found.

The patient was provided with a diary where number, affected organs and severity of attacks were recorded. Because of the high frequency of attacks, up to twice a week, we prescribed prophylaxis with antihistamines. Patient took cetirizine once daily for three months, without improvement in frequency and severity of attacks. Owing to unresponsivity to treatment and the lack of known causes, we performed the diagnosis of idiopathic non-histaminergic angioedema.

Then, in order to decrease the frequency of attacks, we prescribed tranexamic acid 500 mg twice a day, that he took for three months without improvement of symptoms. After some months he referred a worsening of symptoms, with increase in severity and frequency of attacks and recurrent involvement of eyelids and tongue. In this period he frequently referred to emergency rooms, where classical allergic therapy with steroids and antihistamine was administered without bringing down the duration of attacks. Based on previous reports about efficacy of plasma-derived C1-inhibitor in the treatment of C1-INH-HAE, we treated our patient with off label pdC1-INH (Berinert; CSL Behring, GmbH, Marburg, Germany) administered endovenously during acute attacks.

Interestingly he referred symptoms' improvement after about an hour from the administration of the drug, and a complete resolution in about ten hours (Fig.1).

In the next months, the patient showed worsening in frequency of attack up to 4 in a week. After using pdC1-INH on demand for about one year, because of worsening of symptoms, he started infusion of pdC1-INH 1000 UI every fourth days as preventive care. At this writing he has been using this approach for one year with improvement of symptoms. Currently he

rarely complaints just very mild symptoms before the next administration and he reports better quality of life.

The reason why InH-AAE, characterized by normal level and function of C1-INH, could benefit from infusion of plasma derived C1-INH is still unclear, probably it would involve the link among the plasma contact system, complement and fibrinolytic pathways. Further studies may demonstrate that InH-AAE and C1-INH-HAE share specific physiological mechanisms, and it could also help to better classify these patients. To our knowledge, this is the first published case report reporting the outcome of the use of pdC1-INH in the treatment of acute angioedema attacks and as long-term prophylaxis in a child with InH-AAE. Presently there are not treatments labelled for InH-AAE. The severity and high frequency of symptoms and the early age of patient, led us to start an off label therapy regimen with pdC1-INH, improving both frequency and severity of attacks. Larger trials are needed, but we believe that, if treating patients with other traditional drugs is ineffective, pdC1-INH should be used and may be beneficial.

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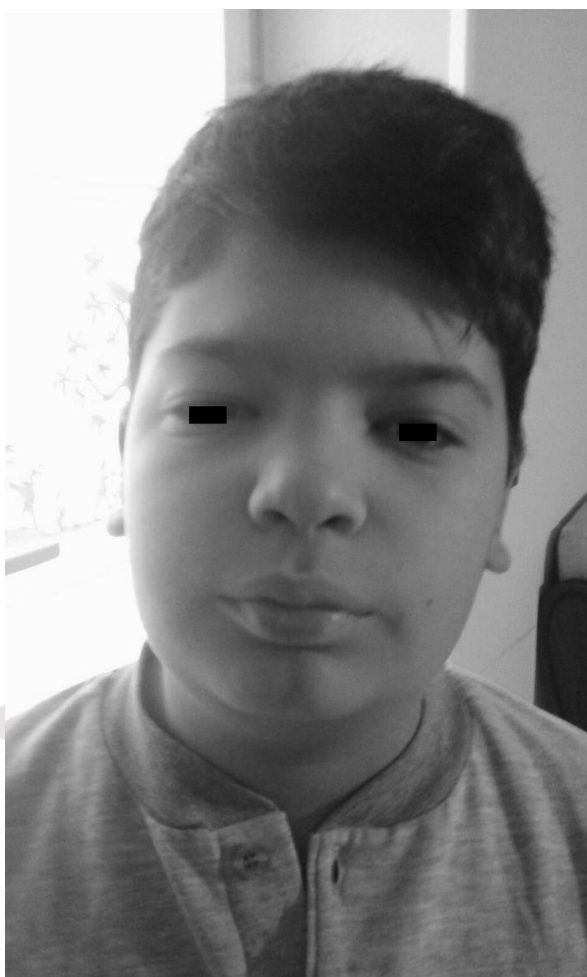
References:

1. Cicardi M, Aberer W, Banerji A et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the HereditaryAngioedema International Working Group. *Allergy*. 2014; **69**: 602-16.
2. Cugno M, Nussberger J et al. Bradykinin and the pathophysiology of angioedema. *Int Immunopharmacol*. 2003; **3**: 311-7.
3. Dy TB, Rasheed M et al. Resolution of an acute attack of idiopathic angioedema with ecallantide. *Ann Allergy Asthma Immunol*. 2013; **111**:224-6.
4. Berry A, Firszt R. Successful treatment of idiopathic angioedema with ecallantide. *J Allergy Clin Immunol Pract*. 2013;**1**:297-8.
5. Mansi M1, Zanichelli A et al. Presentation, diagnosis and treatment of angioedema without wheals: a retrospective analysis of a cohort of 1058 patients. *J Intern Med*. 2015;**277**:585-93.
6. Wintenberger C, Boccon-Gibod I et al. Tranexamic acid as maintenance treatment for non-histaminergic angioedema: analysis of efficacy and safety in 37 patients. *Clin Exp Immunol*. 2014; **178**:112-7.
7. Du-Thanh A, Raison-Peyron et al. Efficacy of tranexamic acid in sporadic idiopathic bradykininangioedema. *Allergy*. 2010;**65**:793e795.

8. Stahl MC, Harris CK et al. Idiopathic nonhistaminergic angioedema successfully treated with ecallantide, icatibant, and C1 esterase inhibitor replacement. *J Allergy Clin Immunol Pract.* 2014; 2:818-9.
9. Shroba J, Hanson J et al. Current treatment options for idiopathic angioedema. *Ann Allergy Asthma Immunol.* 2015;115:429-33.

Fig. 1

A.



B.



Fig 1. (A) Lips and eyelids angioedema. (B) Resolution of angioedema after treatment with plasma-derived C1-inhibitor