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Use of subcutaneous-C1 INH for acute therapy and prophylaxis of a child with HAE

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Editor,

Hereditary angioedema (HAE) is a congenital disorder (1). It can be caused by heterozygous mutations in C1 inhibitor gene (SERPING1). This form of HAE **has** an autosomal dominant inheritance pattern and leads to recurrent episodes of swelling that may be very painful. There are two phenotypic variants: type I (low plasma levels of C1 inhibitor antigen and function) and type II (normal plasma levels of C1 inhibitor antigen and low function).

Patients with HAE suffer from **attacks** of local swelling in the face, extremities and gastrointestinal tract; laryngeal involvement is potentially life-threatening and needs emergency care.

Onset of symptoms may change: it rarely occurs before age of 3, but over 90% of patients are symptomatic within the second decade of life (2-3)

A 16 months old baby girl, with family history of HAE type I, was first seen at our Centre for Rare Diseases when she was 10 month old, for a painful swelling of the right arm. Based on the family history and on the absence of other causes of edema, she was treated with plasma derived C1 inhibitor (20 i.U./Kg Berinert,

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CSL Behring GmbH, Marburg Germany). Blood samples for C1 inhibitor and C4 measurement were obtained before infusion. Ten minutes from end of infusion the baby calmed down, we assume due to pain resolution, and 30 minutes later the swelling completely disappeared. After 6 hours observation the patient was discharged. Pre-infusion C1 inhibitor plasma level was 5 mg/dl (n.v. 15-35 mg/dl). Ten days later the baby suffered from painful leg swelling, but i.v. therapy could not be given due to inaccessible peripheral vein. Upon deterioration of patient's conditions with slight tachypnea, pdC1-INH Berinert 400 IU were administered subcutaneously. The treatment was well tolerated, the patient stopped crying within 15 minutes and after one hour the swelling was significantly reduced. Blood tests showed regular kidney, liver and coagulation functions. The patient was discharged after a 12 hours observation. To prevent further angioedema attacks, she was started on weekly s.c. pdC1-INH 200 IU. At this writing, 18 weeks after beginning of weekly s.c. ph C1-INH administration, the patient is treated at home by the parents and remains asymptomatic and in healthy conditions. **On** two occasions, in order to verify the actual need for continuing treatment, administration of pdC1-INH was delayed: on the 9-10th day after the last infusion an angioedema attack occurred.

To our knowledge this is the first report of efficacy of subcutaneous pdC1-INH in **reversing** acute angioedema in a 15 month old child HAE due to deficiency of C1 inhibitor. It is also the first report of efficacy of weekly s.c. pdC1-INH at such an early age. **Age of onset is variable (4-5); C1-INH deficiency is present at birth, and a minority can have perinatal angioedema symptoms; the patient might present at less than 1 year of age with colic or, rarely, swelling. Most commonly, symptoms begin at school age. Half of patients with HAE had symptoms within the first decade of life, and another third had symptoms by the second decade.** The therapeutic armamentarium for this early age is limited to pdC1 inhibitor i.v. for acute attacks and tranexamic acid for prophylaxis. Efficacy of tranexamic acid also as acute treatment is seldom reported, but without conclusive evidence (1). **Venous** access limitations, particularly in emergency condition, are not uncommon at this age and this was the case in our patient. The dramatic suddenness and severity of the symptoms along with the pending possibility of an unmanageable life threatening situation prompted the decision to start our patient on the off label regimen of programmed s.c. pdC1-INH 200 I.U. per week. After initial parents' training, this regimen was successfully administered at home. **As with** to previous reports home treatment prevented further hospital admissions and restored a normal life for the baby and her family (6-7).

The decision to immediately treat with pdC1-INH upon first appearance of an angioedema and relying on the family history, but in absence of confirmatory blood testing, was outside the guidelines. The severity of the clinical condition and the need to rule out the existence of a cause of pain different from angioedema, forced us to break guidelines. Pain attending angioedema symptoms is a critical point in treatment of these patients. Such a condition is characteristic when symptoms localize to the gastrointestinal mucosa. In this situations, improvement upon specific treatment is the only possibility to rule out other conditions causing abdominal pain in HAE patients. We successfully applied the same criterion to our patient.

In conclusion, here we report use of subcutaneous C1-inhibitor for both acute therapy and prophylaxis of HAE in a very young child; we believe that this report, directly originated from a clinical constrain, provides some hint to solve emergency situations in very young HAE patients whose therapeutic approach is still poorly defined.

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