

of aggressive critical care, his multiorgan failure had no signs of improvement, and support was withdrawn. His second HSCT never fully engrafted. His initial respiratory arrest and cause of death were not related to a laronidase desensitization (separated by days and weeks, respectively).

Laronidase enzyme replacement therapy can be used before and after HSCT, which is the standard treatment in children with Hurler syndrome diagnosed before 2½ years of age.² In addition, ERT can be an effective treatment in children for whom HSCT has failed.⁵

However, serious hypersensitivity reactions to laronidase have been reported. In a phase 3 study to evaluate the long-term safety and efficacy of laronidase in 45 patients with MPS-1,⁶ 1 patient had an anaphylactic reaction, which included a generalized rash with urticaria, and respiratory difficulty. Because ERT is an integral part of treatment in young children, desensitization is indicated in patients with hypersensitivity reactions to laronidase.

We describe the use of a desensitization protocol in an 11-month-old boy with Hurler syndrome who developed anaphylaxis to laronidase shortly after a cord blood transplant. Our protocol allows for less total infusion volume compared with the previously published protocol, which is an important consideration in young children with decreased cardiac function. We found that additional laronidase desensitization can be safely and successfully completed during and after HSCT.

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Type 1 hereditary angioedema in a 72-year-old woman



Hereditary angioedema (HAE) is an autosomal dominant disease caused by a deficiency in functional C1 esterase inhibitor (C1INH). It is characterized by recurrent episodes of nonpruritic, nonpitting, subcutaneous, or submucosal edema that involves the arms, legs, hands, feet, bowels, genitalia, trunk, face, tongue, or larynx. Symptoms typically begin in childhood, worsen around puberty, and persist throughout life, with unpredictable severity.¹ HAE with decreased C1INH levels is fundamentally a consequence of a mutation in the gene encoding C1INH (*SERPINC1*), which is located on chromosome 11.² Different studies in various countries have been published reporting minimum prevalence and clinical data of patient and families with this disease, including the age of debut of symptoms.^{3–8} In all cases, the age of the first symptoms was before the eighth decade of life.

We describe a 75-year-old woman with frequent episodes of edema in the face, lips, and tongue with mild difficulty in breathing and swallowing since November 2012 when she was 72 years old. At that time she had been receiving treatment with imidapril (an angiotensin-converting enzyme inhibitor [ACEI]) during 30 months and was also undergoing treatment with vildagliptin/metformin, allopurinol, rabeprazole, trazadone, and dexibuprofen. Her paternal aunt, already dead, also had angioedema of unknown origin. Screening for HAE revealed a low value of C4 (3.44 mg/dL; reference range, 14–52 mg/dL), and measurement of antigenic C1INH revealed a decreased level (20.2 mg/dL; reference range, 22–45 mg/dL). Both values were determined by nephelometry. The C1INH activity assessed by a chromogenic method was also low (55%; reference range, 70%–130%). Normal results were obtained for C1q, C2, and C3. A few months later, the antigenic C1INH value was 15.7 mg/dL, and the activity of C1INH was 44%. All these complement levels were determined between attacks.

The patient has 3 daughters and a son without angioedema. Three had normal C1INH values, but a 46-year-old asymptomatic

daughter had repeatedly low levels of C4 and quantitative and functional C1INH. Thus, our patient was diagnosed as having type 1 HAE according to the diagnostic algorithm proposed in a recent consensus on the diagnosis, management, and treatment of angioedema mediated by bradykinin, including HAE.⁹ Her daughter was diagnosed as having asymptomatic HAE. A Spanish series of 444 patients with HAE described 61 patients (13.7%) who had never had an angioedema episode and were classified as asymptomatic.³

We tried to look for the possible mutations responsible of the disease in this family, but no mutations were found in either of the 2 patients. Johnsrud et al¹⁰ have reported that no mutations were found in some Norwegian families with HAE with decreased C1INH. They argued that *SERPINC1* mutations in those families cannot be excluded and perhaps mutations could be in regulatory regions or in deep intronic sequences.

Over time, the patient continued to have frequent attacks despite having stopped use of imidapril (substituted by barnidipine) and vildagliptin (antihyperglycemic agent of the dipeptidyl peptidase 4 [DPP-4] inhibitor class of drugs). She was treated occasionally with icatibant and had a good response in the emergency department. In September 2013, after checking that liver and kidney function test results were normal, we decided to start therapy with an attenuated androgen. She took 2 mg of stanozolol every 8 hours. Two months after beginning this therapy, the patient had not had new attacks, and antigenic and functional C1INH had reached normal levels. After reducing the dose of stanozolol, symptoms started again, including some episodes with abdominal pain and some that included a serpiginous erythema. At that time (spring 2014), C4 and antigenic and functional C1INH levels decreased (Table 1). Thus, we increased the dose of stanozolol with a good clinical response, and antigenic and functional C1INH levels were again normalized, although the C4 level remained reduced. We later decided to stop therapy with stanozolol and started treatment with danazol, which is another attenuated androgen.

Table 1
Evolution of Complement Levels With and Without AA Treatment

Date	C1INH, mg/dL	C1INH Activity, %	C4, mg/dL	AA
May 29, 2013	20.2	55	2.56	Without AA
September 11, 2013	15.7	44	2.18	Without AA
January 16, 2014	44.2	>150	10.1	Stanozolol, 2 mg every 12 hours
April 29, 2014	18.2	58	2.7	Without AA
May 20, 2014	15.6	66	1.89	Without AA
September 3, 2014	47.8	>150	8.71	Stanozolol, 2 mg every 8 hours
January 13, 2015	31.6	68	2.79	Danazol, 150 every 24 hours
July 15, 2015	23.2	77	4.69	Danazol, 100 mg every 48 hours

Abbreviations: AA, attenuated androgen; C1INH, C1 esterase inhibitor.

The patient started taking 200 mg every 24 hours. We slowly and progressively reduced the dose of danazol, but in August 2015 the patient had edema of the tongue. At that time, she was taking only 100 mg of danazol every 72 hours.

We describe a patient with type 1 HAE and a daughter with an asymptomatic form of HAE. The particularity of this case is the late onset of symptoms of HAE. Publications indicate that symptoms generally begin in the first years of life, although there is a considerable delay in the diagnosis. In a large Spanish series that included 444 patients with HAE, the mean (SD) age of onset of symptoms was 12.6 (10.5) years (range, 0–65 years).³

Recently, others studies have been published in different European countries and Japan reporting clinical data of patients with HAE, including the age at the first symptom.^{4–8} This age ranged from 9 years in Denmark⁴ to 26 years in Italy.⁸

The onset of symptoms in this patient could have been facilitated by the use of an ACEI or the concomitant use of an ACEI and a DPP-4 inhibitor. The ACEI produced an increase in local bradykinin as a result of inhibition of its catabolism by the blocking of the ACE, which is one of the main enzymes that contribute to the degradation of bradykinin. DPP-4 also contributes to the catabolism of bradykinin.

Perhaps the possible mutation in this family could produce only mild changes in the C1INH protein. This finding could explain the old age of the patient when the first symptoms appeared. She has normalized C1INH levels after taking low doses of attenuated

androgen and only has a decrease in those levels after taking very low doses of attenuated androgen or after stopping this therapy. Possibly this fact is because of the mild decreased level of C1INH observed in this case. Patients with HAE usually do not get normal values of C1INH after starting therapy with attenuated androgen, although the C1INH levels increase with this therapy.

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