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REMISSION OF HEREDITARY ANGIOEDEMA ATTACKS ASSOCIATED WITH STARTING TERIFLUNOMIDE IN A PATIENT WITH MULTIPLE SCLEROSIS

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ABSTRACT

Background: Hereditary angioedema is a rare hereditary and potentially life-threatening disorder characterized by recurrent attacks of cutaneous and submucosal swelling. In spite of the advances made in terms of pathophysiology, underlying mechanisms are not fully clear and this, in turn, hinders the development of effective therapies. Currently, on demand treatment is considered first-class, with few cost-effective, long-term prophylactic options.

Case presentation: Here we describe the case of a 34-year-old man diagnosed with hereditary angioedema at the age of 10, who used to suffer several angioedema attacks per month. He was given prophylactic treatment with antifibrinolytic agents and androgens without improvement. Moreover, he was treated with plasma-derived C1-INH concentrate or icatibant for on-demand treatment of moderate and severe angioedema attacks. At the age of 33, after suffering sudden vision loss and lower limb paresthesia, he was studied and diagnosed with multiple sclerosis. Teriflunomide was administered at a dosage of 14 mg/day. Angioedema attacks disappeared 40 days after starting treatment.

Conclusion: Thus, we suggest considering the pathophysiologic mechanisms on which teriflunomide could be active and consider this drug carefully as an option for prophylaxis purposes. Yet, its effectiveness on this condition should be further studied.

KEYWORDS

Hereditary angioedema, autoimmunity, multiple sclerosis, teriflunomide

LEARNING POINTS

- Underlying mechanisms in hereditary angioedema lack clarity and hence hinder the development of effective therapies.
- On-demand treatment of hereditary angioedema is considered first class, with few cost-effective, long-term prophylactic options.
- The mechanisms of action and effectiveness of teriflunomide on hereditary angioedema should be studied further.

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INTRODUCTION

Hereditary angioedema (HAE) is a rare autosomal dominant condition with an estimated prevalence ranging from 1 in 10,000 to 1 in 50,000 individuals. It is characterized by recurrent and self-limited angioedema episodes that mainly affect the skin, the gastrointestinal tract, and the larynx. It is caused by functional deficiency of the plasma protein C1 inhibitor (C1-INH). Classically, two variants with identical clinical symptoms have been described. Type I HAE is characterized by low antigen and functional levels of plasma C1-INH in 85% of cases. Type II HAE has normal or high antigenic levels of C1-INH yet is dysfunctional, in the remaining 15%[1]. The onset of clinical symptoms usually occurs in childhood and attacks may happen at any time, with no clear cause or may be triggered by medication, stress, trauma, menstruation, or upper airway infection[1]. Location, frequency, and severity of attacks can vary among patients and even for the same patient in their lifetime[1].

CASE DESCRIPTION

Here we describe the case history of a 34-year-old man with type I HAE diagnosed at the age of 10, who experienced cutaneous, abdominal, and laryngeal episodes. In the early years of his diagnosis, he suffered 2/3 attacks per month. He was given prophylactic treatment with tranexamic acid at the time which yielded no positive results. Treatment with attenuated androgens (danazol) was later prescribed but without achieving the expected clinical outcome. At the age of 28, the patient's HAE attacks became more frequent, increasing up to 8 episodes per month when receiving prophylactic treatment with antifibrinolytic agents and attenuated androgens. Given the lack of clinical response and gradual liver transaminase alteration, treatment with antifibrinolytic agents and androgens was discontinued. However, the patient continued to have 6–8 attacks per month. Moderate as well as severe attacks were treated intravenously with 1000 IU of plasma-derived C1-INH concentrate or icatibant.

When the patient was 33 years old and still experiencing the same number of HAE attacks per month without prophylactic medication, he suffered an episode of severe headache and pain in the right eye with visual loss in the ipsilateral visual field. A nuclear magnetic resonance imaging (MRI) scan of the brain and spinal cord was conducted as well as optical coherence tomography, which led to a diagnosis of multiple sclerosis (MS). After treatment with corticosteroid pulse therapy, visual function partially improved. Two months later, when receiving oral treatment with corticosteroids at a dosage of 0.5 mg/kg, he experienced paresthesia in the lower limbs with no evidence of progression on brain and spinal cord MRI. Oral treatment with teriflunomide at a dosage of 14 mg/day was prescribed, and his MS symptoms did improve.

When the patient was 34 years old, following treatment with teriflunomide, we observed a gradual and progressive reduction of his HAE attacks with complete remission of HAE symptoms 40 days after starting treatment. Six months later he was diagnosed with COVID-19 and it was decided to discontinue treatment with teriflunomide. About 21 days later, the patient started having HAE attacks at cutaneous and abdominal level on a weekly basis again. When treatment resumed, the attacks reduced again from day 30, until he was once more HAE symptom-free. The patient experienced no attacks within the last 9 months of receiving treatment with teriflunomide.

DISCUSSION

HAE clinical symptoms include episodes of angioedema caused by an increase in plasma levels of bradykinin, due to C1-INH deficiency. By binding to the B2 receptor in the vascular endothelium, bradykinin produces vasodilatation and hence edema[1]. The mechanisms that trigger attacks have not yet been fully explained. Therefore, their frequency – the number of episodes can vary depending on the individual and even throughout their life – and why the edema affects only certain areas should be further studied[1].

The prevalence of systemic and organ-specific autoimmune disease in patients with HAE is 12% in comparison with 4.5% of the general population[2]. Complement system regulation disorders are likely to be involved in the pathogenesis of this condition[2]. In MS, complement activation may lead to oligodendrocyte lysis and macrophage chemoattraction. The sensitivity of oligodendrocytes to the injury caused by the complement may be due to the lack of inhibitors in this protein cascade, a mechanism which may be facilitated in patients with HAE. On the other hand, it has not been reported that treatment of autoimmune disease in patients with HAE may modify the occurrence or frequency of angioedema attacks, except for a recent report of a patient, with similar characteristics to our patient, whose HAE attacks improved after fingolimod treatment[3]. Following infection with SARS-CoV-2, our patient's treatment with teriflunomide was interrupted and the HAE attacks resumed. Although SARS-CoV-2 may trigger attacks similar to many other viral infections, it fails to explain the sustained increase in episode frequency once the infection was resolved.

Teriflunomide is an immunomodulatory agent with anti-inflammatory properties that selectively and reversibly inhibits the mitochondrial enzyme dihydro-orotate dehydrogenase required to synthesize the de novo pyrimidine, blocking the proliferation of B and T activated lymphocytes[4]. It has also been described as preventing the formation of the immunological synapse in lymphocytes and reducing the release of IL-6, IL-8, and chemotactic protein-1 from monocytes[4]. It is a drug with widely reported usage.

Adaptive immunity has not been thoroughly analyzed in HAE pathogenesis. A few studies show alterations in T-cell profiles and/or cytokine production[5]. On the other hand, it has been observed that adaptive immune responses may be involved in the development of autoimmune disease in patients with HAE, mainly through alterations in B-cell activation and survival[3,6]. The way in which teriflunomide

acts on the contact system remains unknown, as well as its effect on vasoactive peptide generation, such as bradykinin. Similarly, it is not clear whether it has other impacts, such as a modulatory effect on adaptive immune responses. Taking into account our case report and the previously cited case of HAE and MS[3], it is essential to further study HAE physiopathology to determine all the factors involved in triggering angioedema attacks, the frequency of such attacks, and the way in which teriflunomide or other MS treatments, such as fingolimod, may prevent them.

CONCLUSION

This clinical case report shows that highly frequent HAE attacks do not appear to be related to a diagnosis of MS. The fact that the number of episodes decreases when teriflunomide is administered suggests that this drug may reduce HAE attacks, especially considering that when this immunomodulator is interrupted, the frequency of attacks increases and when re-administered, they gradually decrease and then completely disappear. Teriflunomide may be a suitable option for the prophylactic treatment of HAE attacks. It is an interesting research opportunity for a probable 'new' oral treatment, which would add another option to the existing therapies. Therefore, trials should be conducted to confirm or reject its effectiveness in HAE.

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