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CASE REPORT/*OPIS PRZYPADKU*

D-dimer elevation during tranexamic acid therapy and the debate on the therapeutic approach in hereditary angioedema type I

Zwiększenie stężenia D-dimerów podczas terapii kwasem traneksamowym i dyskusja na temat postępowania terapeutycznego w dziedzicznym obrzęku naczynioruchowym typu I

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ABSTRACT

Hereditary angioedema type 1 (HAE-1) is the most prevalent HAE type, and it results from decreased antigenic C1 inhibitor (C1-INH) levels or function. Bradykinin-mediated angioedema in the face, trunk, extremities, genitalia, gastrointestinal tract, and upper airway are the symptoms of this rare and potentially fatal disease. PD-C1-INH concentrates, recombinant C1-INH, tranexamic acid (TXA), danazol, icatibant, ecallantide, and fresh-frozen plasma (FFP) may be used for treatment. The focus of this article is to point out D-dimer elevation during TXA use. We detected d-dimer elevation incidentally in 2 patients with hereditary angioedema (HAE) type 1 during tranexamic acid (TXA) therapy, in whom elevations were normalized a week after suspended TXA. However, the TXA treatment is expected to decrease D-dimer levels in surgery and hyperfibrinolysis. On the other hand, although using TXA in long-term prophylaxis in HAE treatment is not recommended, we observed that 2 patients had significant reduction of their attack frequency for over a year.

KEY WORDS

angioedema, tranexamic acid, hereditary angioedema type I, D-dimer elevation.

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INTRODUCTION

Hereditary angioedema type 1 (HAE-1) is the most prevalent HAE type and results from decreased antigenic C1 inhibitor (C1-inh) levels [1]. Bradykinin-mediated angioedema in the face, trunk, extremities, genitalia, gastrointestinal tract, and upper airway are the symptoms of this rare and potentially fatal disease.

Angioedema is the painful swelling of the deep dermis, subcutaneous tissue, and mucous membranes. C4 is reduced in 98% of cases [2], and for almost all patients during an attack. C4 and C1-inhibitor antigenic (C1-inh) levels are generally sufficient for diagnosis of a patient with a positive family history for HAE-1 [1]. Plasma-derived C1-inhibitor (PD-C1-inh) concentrates, recombinant C1-inh, tranexamic acid (TXA), danazol, icatibant, ecallantide, and fresh-frozen plasma (FFP) may be used for treatment [3].

CASE REPORT

We documented D-dimer elevation during TXA therapy in 2 patients within the same family.

Patient 1 (P1), a 5-year-old boy, admitted to hospital for hand pain and swelling extending to the wrist. He had no erythema or pruritus. Based on family history and symptoms, after being tested for C1-inH and C4 levels, he was diagnosed with HAE-1 (Figure 1). Following PD-C1-inh, hand elevation, and cold compression, symptoms started to resolve within 30 min [4]. Hand and eyelid swelling episodes recurred twice a month, and he was treated each time with PD-C1-inh. We did not use long-term PD-C1-inh prophylaxis. Once, he experienced minimal chest oedema that resolved spontaneously. He had scrotal oedema at 7 years of age and benefited from the PD-C1-inh. He had eyelid swelling after trauma and mucosal swelling after a dental filling. Once, he experienced neck swelling and dysphagia, which resolved after PD-C1-inh. After danazol prophylaxis, he became free of attacks for 8 months. In children and adolescents, attenuated androgen use is not appropriate because of potential effects on bone development [5, 6], and the potential risk of early puberty [7, 8]. He started school at that time, which might have increased the stress and the attacks. Due to the risk of side effects and development of recurring attacks, we replaced danazol with TXA after assessment for hypercoagulability/thrombosis risk. He had a previously defined heterozygous methylenetetrahydrofolate reductase (MTHFR A1298C) [9] mutation. Plasma homocysteine level was normal. However, we added acetylsalicylic acid (100 mg/day) to therapy after consulting with the haematologist because of the risk of thromboembolism. P1 experienced only one attack during over a year under TXA. Hand swelling lasted a day and resolved spontaneously. Validation of the therapy was done by Angioedema Control Test (AECT) [10]. The score was 3 points before TXA (-3 mo), and 15 after TXA (+6 mo). We tested coagulation tests intermittently, and a D-dimer increase (3.84 mg/l) was observed incidentally in the follow-up visit. When we suspended the TXA for a week and tested the D-dimer again, the D-dimer level normalized in a week (Figure 2).

Patient 2 (P2), a 20-year-old woman, admitted hospital for the first time with hand swelling and abdominal pain. She had a family history of individuals with HAE-1 (Figure 1) and was diagnosed with HAE-1. We treated the attacks (hand or foot swelling, abdominal pain, laryngeal angioedema) each time with the PD-C1-inh. She experienced abdominal pain twice during the pregnancy; we applied the PD-C1-inh for both. Because the episode frequency increased to approximately twice a week after 5 years of intermittent PD-C1-inh therapy, we started TXA after evaluation for hypercoagulability/thrombosis.

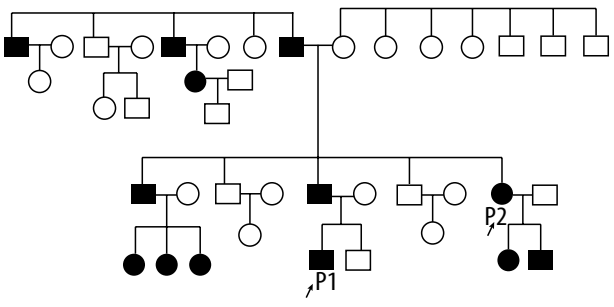

FIGURE 1. Pedigree of the family of the patients

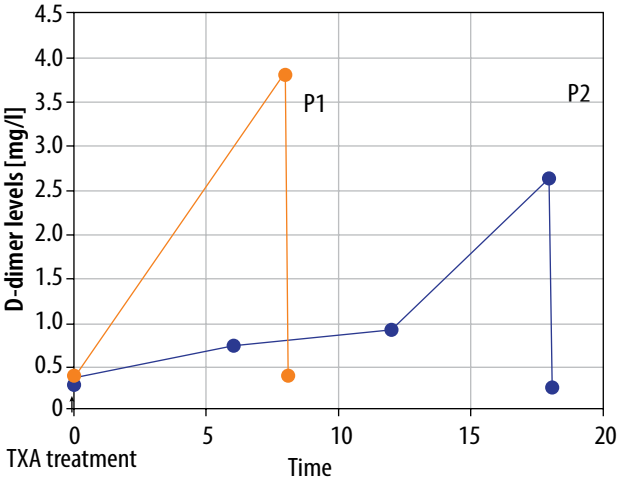

FIGURE 2. The timeline for D-dimer levels in P1 and P2 during TXA use. The baseline D-dimer levels of both P1 and P2 were normal before TXA use. P1 used TXA for 8 months. P2 used TXA for 18 months. D-Dimer levels increased with TXA use and normalized just a week after they stopped the TXA therapy

P2 had another frequently seen MTHFR variant: homozygous MTHFR(C677T) mutation [9]. The plasma homocysteine level was normal. Nonetheless, we added acetylsalicylic acid to the therapy, similarly to P1. The frequency of attacks decreased. She experienced 2 attacks in more than a year under TXA. She experienced foot swelling that resolved spontaneously. For the other episode, which was concomitant with abdominal pain and throat swelling, we used the PD-C1-inh therapy. Validation of the therapy showed that the AECT score was 3 points before (-3 mo), and 10 after TXA (+6 mo) in P2. During the period of TXA use, we tested her with coagulation tests intermittently, and D-dimer elevation was also observed incidentally in this patient during the TXA therapy (2.64 mg/l). As soon as we suspended the TXA therapy, the D-dimer levels normalized in a week (Figure 2).

DISCUSSION

HAE-1 is characterized by cutaneous and submucosal swelling attacks. Acute uncontrolled complement, contact, and kinin-system activation during trauma or stress occur.

There are many challenges both for the patients and clinicians in the road of therapy. The patients need to be alert at all times. There is a necessity for urgent parenteral medication, PD-C1-inh, ecallantide, and icatibant during the attacks. This is difficult, especially for children. The plasma half-lives of these medications are relatively short (32.7 h for PD-C1-inh [11], 0.8 to 4.5 h for ecallantide [12], and 1.5 h for icatibant [13]). The resolution phase may be prolonged, sometimes lasting for more than a day. The cost of these parenteral medications are high for patients living in low- and middle-income countries. Patients' psychological situation may also increase the attack frequency. Adult patients generally present a determinist and negligent mood, possibly due to the complementary, non-curative nature of the therapies, although they are aware of the urgent situation. That might be followed by noncompliance with parenteral regular therapy. There is a difficulty of organizing controlled studies in this rare disease. Even in the same family with the same mutation, the characteristics of the individuals may vary. There may be associating factors in each individual, such as the heterozygous and homozygous MTHFR variants, respectively, in P1 and P2. Homogenization of the therapy groups is difficult. These challenges lead clinicians to find better therapeutic alternatives and individualized therapy options. For long-term prophylaxis, WAO/EAACI 2021 guideline suggests the use of parenteral therapies, including PD-C1-inh, lanadelumab, berotralstat, and androgens [14]. TXA is not present in the long-term prophylaxis in this guideline.

We pointed out the use of TXA as a combination therapy either with PD-C1-inh concentrate or icatibant in our previous article [15]. The dose of oral TXA that controlled the symptoms was 500 mg/day in P1 and 1000 mg/day in P2. The TXA combination with PD-C1-inh or icatibant is cost-effective and could be an alternative, especially in patients with high attack frequency. Because the HAE patients are experienced about the spectrum of their disease symptoms through their life, they do not usually use parenteral therapy even in short-term prophylaxis for attacks that are frequent but not severe. So, we did not give twice-weekly PD-C1-inh therapy to them because their compliance could be bad for long-term prophylaxis. However, their compliance to oral therapies are well that we used TXA for long-term prophylaxis.

The benefit of TXA therapy was demonstrated in a randomized placebo-controlled trial with 18 HAE-1 subjects [16] and a double-blind crossover study of epsilon-amino-caproic acid (ACA) in 9 patients [17]. In another study, the average number of episodes decreased from 14 to 7 at the 6th month of TXA medication in 12 patients [18]. A systematic review included the results of 4 prophylactically given medications: TXA, epsilon -ACA, danazol, and methyltestosterone. All 4 drugs, one being TXA, reduced the frequency of HAE-1 attacks compared to a placebo [19]. However, current recommendations do not support the use of antifibrinolytics, such as tranexamic acid, for long-term prophylaxis due to insufficient data on the efficacy. However, some HAE-1 patients may benefit with TXA.

During the treatment course of TXA, the attack frequency, which was biweekly before the treatment, decreased prominently in P1-P2 when compared to courses of other treatments. However, we recorded a transient increase in D-dimer levels during the TXA therapy. Both had similar fibrinogen levels before the TXA therapy and did not use any other medication with TXA. This incidental D-dimer elevation was not detected in other family members with HAE-1, except for these 2 patients. Interestingly, we did not observe any clinical symptom and signs that could be related to diseases associated with D-dimer elevation (pulmonary embolism, deep vein thrombosis, arterial thrombosis, malignancy, infections, atrial fibrillation, stroke, arterial dissection, aneurysm, trauma, surgery, preeclampsia, and eclampsia) [20].

As far as we know, D-dimer elevation was not defined before in individuals with MTHFR gene variants unless they experience a thrombosis, and there are no reports regarding the D-dimer elevation in patients who have MTHFR variants or who are on acetyl salicylic acid therapy. D-dimer elevation is a common finding in HAE patients during attacks [21]; however, our patients did not have angioedema attacks at the same time. Cugno *et al.*

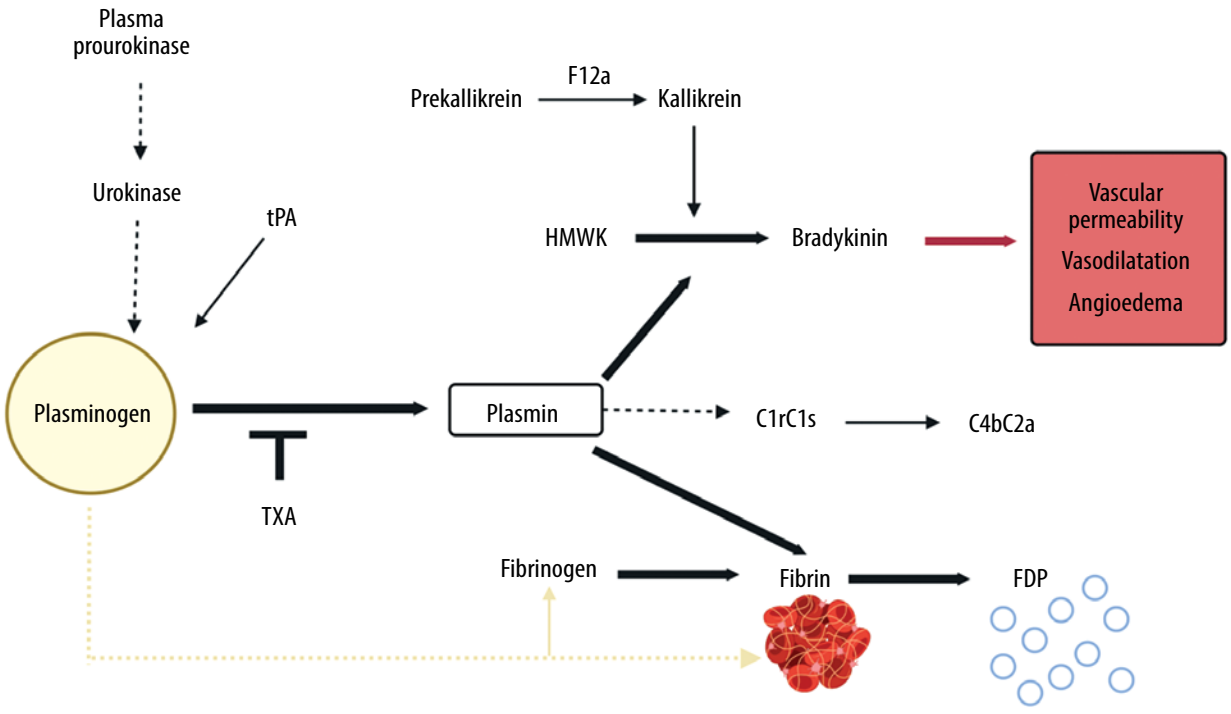

FIGURE 3. Tranexamic acid (TXA) blockage was not possible in 2 of our HAE patients in the fibrinolytic pathway that we observed D-dimer increase in the patients

demonstrated elevated D-dimer levels during remission in HAE patients [22]. However, our data show that after we stopped TXA, D-dimer levels normalized in both patients (Figure 2). Hence, further observations are needed.

During fibrinolysis, plasminogen is converted into the fibrinolytic enzyme plasmin by tissue plasminogen activator (tPA). Plasminogen and tPA bind to C-terminal lysine residues on fibrin, leading to localized plasmin formation and fibrin cleavage [23]. The plasmin is a fibrinolytic system effector protease, playing essential roles in the fibrin breakdown and clot dissolution elucidating soluble fibrin degradation products. Bradykinin production follows plasmin formation during the complement activation, which is the step responsible for bradykinin-mediated angioedema in patients [24].

TXA, an amino acid (lysine) analogue, competes with fibrin and inhibits plasmin's enzymatic breakdown [25]. TXA binds the plasminogen lysine-binding site and inhibits conversion of plasminogen to plasmin, preserving blood clots from plasmin-mediated lysis. TXA reduces bleeding by inhibiting enzymatic breakdown of fibrin blood clots [25]. Intravenous TXA administration in patients undergoing spinal surgery demonstrated reduced D-dimer formation [26]. A low attack frequency with TXA led us think that the plasmin-mediated bradykinin pathway had been adequately suppressed by TXA during the treatment in P1 and P2.

Because the D-dimer increase is a result of fibrinogen breakdown, we suggested that the fibrinolytic system, especially the plasmin, may not have been suppressed by TXA. The plasminogen may be in direct contact with fibrinogen and may have degraded independently of plasmin (Figure 3). Another suggestion is that the increase may be the result of asymptomatic episodes that came across with the D-dimer measurement. Lastly, TXA resistance may develop because of a drug-specific antibody.

Patients 1 and 2 did not experience any symptoms during therapy. D-dimer increase was a coincidental finding. However, we stopped TXA use because we do not know the exact reason for the increased D-dimer levels. As far as we know, no study has mentioned this kind of D-dimer elevation during TXA use. The limitations are that both of those elevations could be seen in remission, and so there is a need for studies or observations with more patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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