




## Case Report

# Hereditary thrombotic thrombocytopenic purpura: a case report



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## ARTICLE INFO

## Article history:

Received 25 July 2019

Accepted 2 August 2020

Available online 13 September 2020

## Introduction

Thrombotic microangiopathies (TMAs) are conditions characterized by the triad: generalized microvascular occlusions by platelet thrombi, thrombocytopenia, and microangiopathic hemolytic anemia (MAHA).<sup>1</sup>

Two typical phenotypic manifestations of TMAs are hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP), both serious and life threatening. HUS is characterized by three clinical signs, the classic triad, mentioned above, while TTP is characterized by a set of five manifestations, which correspond to the triad associated with fever and neurological signs. The classic description of TTP is present in only 40% of cases<sup>1,3</sup> and both diseases are clinically indistinguishable.<sup>2</sup>

We report the case of a patient admitted to the Hematology Care Service of a public pediatric hospital in Belo Horizonte, Brazil, for the investigation of a condition of non-immune hemolytic anemia and congenital thrombocytopenia with an

exacerbation of anemia and thrombocytopenia during infectious conditions, which progressed to renal dysfunction and a cerebral thrombotic event.

## Case report

Patient I.B.A.S., female, 3 years old, whose parents have a consanguinity relationship, accompanied at the Hematology Care Service of a pediatric public hospital in Belo Horizonte, due to a condition of non-immune hemolytic anemia and thrombocytopenia for 2 years. During this period, hemoglobin ranged from 4.7 to 12 mg/dl and platelet count from 14.000/mm<sup>3</sup> to 53.000/mm<sup>3</sup>, presenting partial response to corticosteroids and an exacerbation under viral conditions. The direct Coombs, anti HIV, anti HCV, VDRL and ANA testing gave negative results. The renal function showed no change. The osmotic fragility curve remained normal, 3.2% HbA2, without alfa-globin deletion.

In July 2018 she had, during hospitalization for thrombocytopenia exacerbation, a sudden condition of left upper limb paresis and left central facial paralysis. A magnetic resonance angiography was performed, which showed a subtotal luminal occlusion emerging from the middle cerebral artery.

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<https://doi.org/10.1016/j.htct.2020.08.007>

There was no previous history of comorbidities, but after the acute event, right upper limb paresis was reported in the neonatal period, at the time associated with possible childbirth trauma, without neurological propaedeutics. In her family history there is a report of a paternal uncle with a condition of anemia and thrombocytopenia, with no defined etiology.

During hospitalization she had, in addition to the described neurological condition, a change in renal function, with increased blood pressure levels and significant microangiopathic hemolytic anemia (presence of numerous schizocytes in the peripheral blood). After extensive propaedeutics and in the presence of microangiopathic hemolytic anemia, thrombocytopenia, cerebral thrombosis, and renal dysfunction, the hypothesis of TTP or atypical HUS was considered. The patient was transferred for plasmapheresis at a reference center.

There was an evolution of her condition, with a marked improvement in clinical and laboratory findings after the use of corticosteroids and plasmapheresis. An examination was performed to determine the von Willebrand factor protease activity (ADAMTS13) and search for the ADAMTS13 inhibitor by the Fluorescence Resonance Energy Transfer (FRET) method, which demonstrated an activity below 5% and the absence of the inhibitor, concluding the diagnosis of hereditary thrombotic thrombocytopenic purpura. Sample for examination was collected 4 weeks apart between plasma transfusions.

Currently, 15 months after the diagnosis of hereditary TTP, she is in an excellent overall condition, undergoing a plasma transfusion regimen, 15 ml per kilogram of body weight, every 21 days and the use of antihypertensives in decalation phase, without transfusion or infectious complications and without the need for hospitalization. She is under follow-up, having pediatric hematology, nephrology and neurology care.

## Discussion

The deficiency in the von Willebrand factor cleavage by ADAMTS13 metalloproteinase may be genetic or more commonly acquired, resulting from the production of ADAMTS13 inhibitor antibodies, causing TTP. The hereditary TTP, also known congenital TTP, familial TTP or Upshaw-Schulman syndrome (Online Mendelian Inheritance in Man number, 274150), is a rare autosomal recessive condition, caused by biallelic mutations in ADAMTS13. Patients have severe ADAMTS13 deficiency (activity <10%) without a demonstrable autoantibody inhibitor during remission on at least two 4-week intervals.<sup>4,5</sup> As for the atypical HUS, it has been shown over the past decade to be result of a deregulation of the alternative complement pathway.<sup>3</sup>

The hereditary TTP seems to be a very rare disorder. A registry of congenital TTP has estimated that there may be only 150 families worldwide, although it may be underestimated.<sup>6</sup> The Oklahoma TTP-HUS registry (which includes any patient referred with a clinical suspicion of TTP or hemolytic uremic syndrome), representing a population base of 2 million people, has identified a family every 26 years. Three daughters in this family have congenital TTP, suggesting a prevalence of 1.5 patients per 1 million people. A cross-sectional

population-based study in Norway found an unexpectedly high prevalence, with 17 individuals affected per 1 million inhabitants.<sup>7</sup>

Although considered a monogenetic disorder, the clinical presentation of congenital TTP is variable. Its symptoms develop shortly after birth in some patients, while others remain asymptomatic until the second or third decade of their lives. This phenotypic variability is believed to be related to causal mutations and to the plasma activity level of ADAMTS13.<sup>8,9,10</sup> So far, it was not possible to conduct the genetic study of the reported patient. In the newborn, hereditary TTP typically presents with jaundice and thrombocytopenia,<sup>11</sup> whereas in childhood symptomatic episodes are often associated with recurrent infections or vaccinations. Among hereditary TTP patients who present a late first episode, pregnancy is often the triggering event.<sup>12</sup> The reported patient required multiple hospitalizations due to worsening anemia and thrombocytopenia due to infectious conditions.

There are no medicines currently approved for the treatment of hereditary TTP, specifically. Acute episodes are treated with fresh frozen plasma (FFP) infusions to replace the deficient ADAMTS13 enzyme. Plasma exchange (PEX) is not required as patients do not have an ADAMTS13 inhibitor that needs to be removed. The recommended starting plasma dose according to the literature is 10 to 15 ml per kilogram of body weight, which provides an ADAMTS13 activity level of 25 to 37%, for an estimated plasma volume of 40 ml per kilogram of body weight. The treatment is continued at this dose daily until platelet counts recover to normal levels, which may require only one to three days of plasma infusion. The ADAMTS13 circulation half-life is approximately 2.5 days.<sup>13</sup>

The prophylactic plasma infusion consists of administering 10 to 15 ml per kilogram of body weight of FFP every two to three weeks to provide a significant improvement in the patient's clinical and laboratory condition and maintain adequate serum levels of ADAMTS13.<sup>13</sup> The patient has remained asymptomatic and with blood count within the normal range by receiving an infusion of 15 ml of plasma per kilogram of body weight, every 3 weeks for about 15 months.

The FFP dose and dose changes are guided by symptoms and/or platelet count, not by ADAMTS13 activity, since symptoms and platelet count are the most reliable and direct measure of disease activity.<sup>13</sup>

Two plasma-derived concentrates containing factor VIII and von Willebrand factor: antihemophilic factor (Koate-DVI) and intermediate purity factor VIII (BPL 8Y) has been shown to contain low levels of ADAMTS13 and can be used as an alternative treatment and prophylaxis in selected patient populations.<sup>14</sup>

Although treatment of TTP through plasma infusions is generally effective, the therapy is often complicated by allergic and anaphylactic reactions or volume overload. The plasma infusions also pose a risk of infection from bloodborne pathogens and as they need to be performed in hospitals or outpatient clinics are costly and time consuming. In addition, they can become stressful for younger patients. The development of a recombinant ADAMTS13 represents a new therapeutic option with potential to improve current treatment.<sup>8</sup>

A long-term follow-up of patients with congenital TTP is scarce in the literature, in part because the etiology and genetic documentation of congenital TTP is only available from 2001 onwards.<sup>15</sup>

Our patient represents one of the few cases with a medium-term follow-up, which contributes to a better understanding of the evolution of hereditary TTP in the current context.

## Conclusion

Hereditary TTP is a very rare microangiopathy. Its congenital form is associated with several mutations in the ADAMTS13 gene that lead to a severe enzyme deficiency. The course of the disease is invariably fatal if not treated quickly. The prognosis was drastically altered with the introduction of periodic transfusion of fresh frozen plasma, and an even better and safer response is expected with the development of recombinant ADAMTS13. The reported case already showed some signs and symptoms of hereditary TTP since childbirth, thus showing the importance of differential diagnosis of hemolytic anemia associated with thrombocytopenia with TTP. After an adequate treatment with regular transfusion of fresh frozen plasma was established, our patient showed a significant improvement, and has been asymptomatic for 15 months, without any transfusion complications.

## Conflicts of interest

The authors declare no conflicts of interest.

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