

## Congenital Thrombotic Thrombocytopenic Purpura (Upshaw-Schulman Syndrome). Case Report and Review of the Literature

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### RESUMEN

La púrpura trombocitopénica trombótica se debe a la ausencia o inhibición de la actividad de una proteasa (ADAMTS-13) encargada de cortar los multímeros del factor de Von Willebrand sintetizados por el endotelio. La deficiencia congénita de esta proteasa es la causa del síndrome de Upshaw-Schulman, descrito por primera vez en 1960. El síndrome hemolítico urémico se debe a la deficiencia adquirida de la proteasa durante una infección gastrointestinal por *Escherichia coli* O157:H7 y otras formas adquiridas son autoinmunes, por anticuerpos contra la proteasa. Se han descrito más de 100 casos de deficiencia congénita de ADAMTS 13, con más de 87 mutaciones distintas del gen que la codifica. Ninguno de estos casos procede de bibliografía mexicana o latinoamericana.

**Caso clínico:** paciente femenina de 10 años de edad, hija única, con antecedentes de trombocitopenia episódica de cinco años de evolución, resistente a diversos tratamientos. La trombocitopenia episódica se acompañaba, en ocasiones, de incremento importante de las DHL, dolor abdominal, hematuria y fiebre. Cuando iba a realizársele la esplenectomía se sospechó deficiencia de ADAMTS-13. La actividad de ADAMTS-13 fue de 0% y los anticuerpos IgG anti-ADAMTS-13 fueron negativos. Los niveles de actividad de ADAMTS-13 en los padres fueron normales. Cuando la niña padecía trombocitopenia se le administraba plasma fresco congelado con resultados favorables inmediatos; se documentaron tres brotes de anemia hemolítica, trombocitopenia, incremento grave de DHL y cifras inconmensurables de ADAMTS-13.

La cantidad de informes en la bibliografía de deficiencia congénita de ADAMTS-13 sigue incrementándose; sin embargo, en nuestro medio permanece como un padecimiento subdiagnosticado. Es necesario tener en cuenta este padecimiento en el diagnóstico diferencial de las trombocitopenias crónicas resistentes y recurrentes en niños.

**Palabras clave:** púrpura trombocitopénica trombótica, factor de Von Willebrand, deficiencia congénita de ADAMTS-13.

### ABSTRACT

Thrombotic thrombocytopenic purpura (TTP) is caused by the absence or inhibition of a protease (ADAMTS-13) that cleaves the von Willebrand factor (vWf) multimers, synthesized by the endothelial cells. In 1960 was described, for the first time, a congenital deficiency of this protease and named Upshaw-Schulman syndrome. The presence of antibodies against the protease is noted in acquired forms of TTP and hemolytic uremic syndrome (HUS); the latter is due to a gastrointestinal infection of *Escherichia coli* O157:H7. Until today, it has been described more than 100 cases of Upshaw-Schulman syndrome, and around 87 different mutations of the encoding gene. None of these cases comes from Mexican or Latin American literature.

**Case description:** 10 year old female, only child, with intermittent episodes of refractory thrombocytopenia for the last five years. Besides the thrombocytopenia, she also presented a significant increase in lactic dehydrogenase levels (LDH), hematuria, abdominal pain and fever. In order to control the platelet consumption, splenectomy was considered, along with the suspicion of an ADAMTS-13 deficiency. IgG antibodies against ADAMTS-13 were negative, and the protease activity was of 0%.

The activity levels of ADAMTS-13 in both parents were normal. Fresh frozen plasma is given to the girl any time she develops thrombocytopenia, with immediate favorable results. Until now it have been documented three outbreaks of hemolytic anemia, thrombocytopenia, and severe increase in LDH and immeasurable count of ADAMTS-13.

Despite the number of reports about the congenital deficiency of ADAMTS-13 in the literature still growing, in our environment it remains as an underdiagnosed entity. It is necessary to have this disease in mind when we approach a pediatric patient who has a chronic and recurrent thrombocytopenia.

**Key words:** Congenital Thrombotic Thrombocytopenic Purpura, Von Willebrand factor, congenital deficiency of ADAMTS13.

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Over the past years thrombotic thrombocytopenic purpura (TTP) was described as a classical pentad of symptoms that included microangiopathic hemolytic anemia, thrombocytopenia, fluctuating central nervous system abnormalities, fever and renal impairment. However, it now appears that the classical pentad is infrequently present in the early stages of disease. Only after there is widespread formation of microthrombi and a resultant impact on various organ systems does the full pentad express.<sup>1</sup>

TTP was first described by Moschkowitz in 1924 in a 16-year old girl with malaise, upper extremity weakness, fever, petechiae, anemia, and microscopic hematuria leading to death.<sup>2</sup> Postmortem examination revealed hyaline thrombi in the terminal arterioles and capillaries of multiple organs. Despite numerous case reports of TTP in the literature, this disease is rare and has an estimated incidence of up to 1 per million;<sup>3,4</sup> fewer than 10% of all cases occur in the pediatric age group.<sup>3,5</sup>

Its pathogenesis has been related to an inhibition or decrease of the von Willebrand factor cleaving protease (VWF-CP), known as ADAMTS-13 (the thirteenth member of the family of A Disintegrin And Metalloprotease with Thrombo-Spondin1), a protease that cleaves the unusually large multimers of VWF that are initially synthesized in endothelial cells and released into the circulation.<sup>6-8</sup>

Evaluation of ADAMTS-13 in plasma is now being used more frequently to support the acute diagnosis of TTP, although this is usually primarily a clinical diagnosis.<sup>9</sup> The deficiency of ADAMTS-13 activity could be of an inherited or an acquired etiology.<sup>10</sup> Congenital TTP, an autosomal recessive disorder, often described as the Upshaw-Schulman syndrome,<sup>11</sup> was first known from case reports in 1960, when Schulman et al, reported an 8-year-old female who had had episodes of thrombocytopenia and hemolytic anemia since birth that responded to plasma infusions.<sup>12</sup>

But TTP is rarely diagnosed in young children. Much more common is the clinically and pathologically similar disorder, hemolytic-uremic syndrome (HUS), defined by thrombocytopenia, microangiopathic hemolytic anemia, and renal failure and typically preceded by diarrhea caused by *Escherichia coli* O157:H7.<sup>13</sup>

The spectrum of clinical phenotype in congenital TTP is wide, encompassing neonatal-onset disease and adult onset disease, forms with a single disease episode and

chronic-relapsing forms. To date, 87 mutations of ADAMTS-13 gene are reported in the literature, and account for 106 cases.<sup>14,15</sup>

None of these cases were taken from Mexican or Latin-American sources, hence the importance to report a case of this etiology in our community.

## CLINICAL CASE

A 10 years old female was referred to the Centro de Hematología y Medicina Interna, because of thrombocytopenia, lower limbs ecchymosis, abdominal pain, occasional emesis, headache, palpitations and fever, for the past 5 years. She had only received prednisone and IV Gammaglobulin as treatment.

On admission, the parents were questioned, and they detailed previous diagnosis of intraocular hypertension (left globe), moderate effort dyspnea, hear loss and occasional oral ulcers without hemorrhagic episodes, they denied epistaxis, gingival bleeding, hematuria or other type of macroscopic bleeding.

The physical examination revealed ecchymosis on both lower limbs. The rest of the physical exam was unremarkable. Laboratory analyses were performed (Table 1). The thrombocytopenia was confirmed, besides hematuria and elevation of the reticulocyte count. We also noted a very significant increase in lactic dehydrogenase level (LDH).

**Table 1.**

| Lab test                      | Result   |
|-------------------------------|----------|
| Anti ADAMTS-13 Antibody (IgG) | 7 U/L    |
| ADAMTS-13 Activity            | 0%       |
| Anti platelets antibody       | NEGATIVE |
| LDH                           | 239U/L   |

The patient was treated with prednisone, folic acid and fresh frozen plasma exchange without needing hospitalization. Because of the symptoms and the platelet count, an alteration or deficiency of ADAM-TS-13 was considered, so a functional panel was requested by this time (Table 1).

The laboratory results clearly showed a total absent of the metalloprotease ADAMTS-13, which leads to the diagnosis of congenital Thrombotic Thrombocytopenic Purpura (TTP) known as Upshaw-Schulman syndrome. The enzyme activity was analyzed in both parents, and

it was normal. These results made us suspect that one or both parents may be heterozygous for any of the known mutations to ADAMTS-13. Both parents of the patient were also studied for the ADAMTS-13 activity and were normal. The patient is under continuous monitoring of the platelet count (Table 2) and signs of thrombotic events.

**Table 2.** Clinical and laboratory manifestations of TTP-HUS

- Microangiopathic hemolytic anemia
- Thrombocytopenia, often with purpura but not usually severe bleeding
- Renal function may be normal, but acute renal insufficiency may be present, associated with anuria and may require acute dialysis
- Neurologic abnormalities, usually fluctuating, are common, but patients may have no neurologic abnormalities
- Fever is rare; high fever with chills suggests sepsis rather than TTP-HU

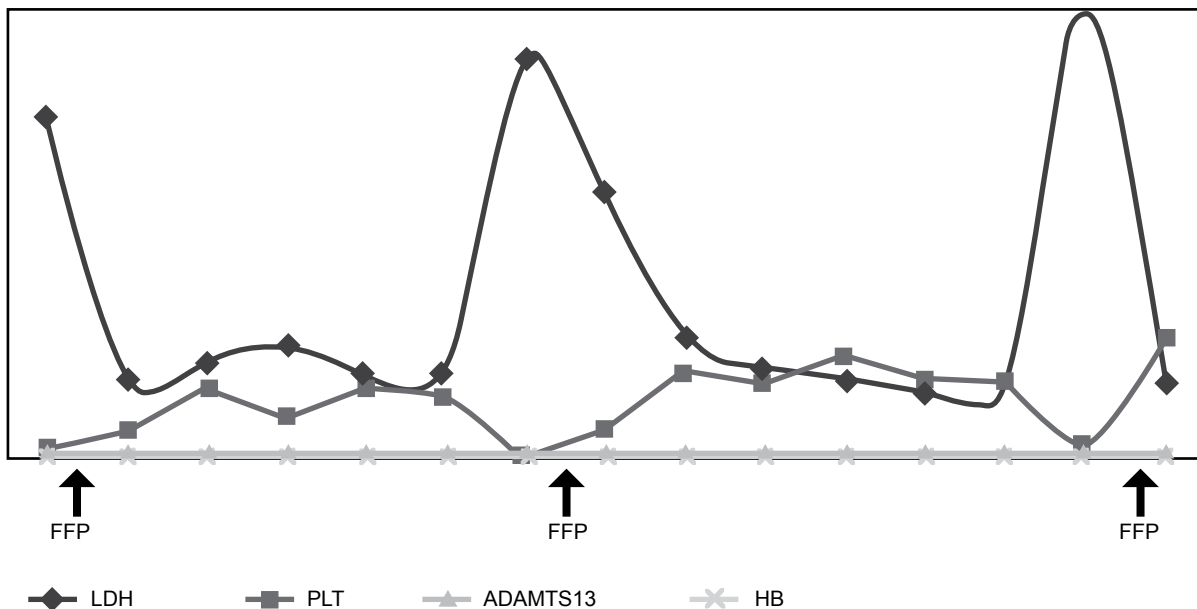
Until now three outbreaks of hemolytic anemia, thrombocytopenia, and severe increase in LDH and immeasurable count of ADAMTS-13 have been documented. Every time she develops thrombocytopenia, a therapy based on fresh frozen plasma exchange is administered, with immediate and favorable results (Figure 1).

## DISCUSSION

In 2001, Levy et al demonstrated the presence in plasma of a metalloproteinase called ADAMTS-13 (A Disintegrin And Metalloprotease with Thrombo Spondin Type 1 repeats, 13), responsible for the cleavage of the von Willebrand's factor (vWf) multimers, once these were secreted by the endothelial cells. The vWf multimers promote the platelet adhesion and aggregation at sites of vascular injury.<sup>11</sup> Absence or mutation of this enzyme, as well as an activity inhibition by a specific antibody, results in the generation of platelet thrombi in small vessels, event known as thrombotic microangiopathy (TM), which is the main pathological finding in more than one disease (examples include HELLP syndrome in pregnant women, hemolytic uremic syndrome, and thrombotic thrombocytopenic purpura). Clinical manifestations depend on the affected organ, being the most common the kidneys, the brain and the heart, among others.<sup>16</sup>

Both diagnoses, thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS) are based on almost the same clinical and laboratory tests (Table 2):

In HUS, the stimulation of the endothelial cells by the Shiga toxin (produce by *E. coli* O157:H7) results in the



LDH: Lactic Dehydrogenase PLT: Platelet count. HB: Hemoglobin FFP: Fresh Frozen Plasma Exchange

**Figure 1.**

production of abnormally large vWf multimers. Thus even with a normal activity of ADAMTS-13 the cleavage capacity is overrated, concluding in the previously mentioned platelet adhesion and aggregation. The highest incidence of this entity is observed in pediatric population.<sup>17</sup>

The clinical differentiation between HUS and TTP represents a challenge, especially in the pediatric population, and in most cases a definitive diagnosis cannot be established, and classified as an “idiopathic” thrombocytopenia. If we associate this fact to the high frequency of gastrointestinal infections in our country, it could be suspected that these patients may have HUS, without the apparent need for definitive laboratory confirmatory test.

As we mentioned above, there is an increase in the reports of a congenital deficiency of ADAMTS-13 (Upshaw-Schulman Syndrome). The suspicion of this entity must lead the efforts to ascertain the enzyme activity level, and rule out the presence of an inhibitor (such as a specific antibody) or other causes for TM.

In 2012 George et al published a review of the Oklahoma registry, which is a data base from 1995 to 2011, and it included all the patients (301) treated as a TTP-HUS, and in this series of cases they report a frequency of 23% (70 patients) with severe deficiency (< 10%) of ADAMTS-13 activity.<sup>18</sup>

Also it has been described that relapse is the most apparent risk after recovery and is almost totally restricted to patients with severe ADAMTS-13 deficiency, among whom the estimated risk at 7.5 years is 43%. Most relapses occurred within the first 2 years after the initial episode, but could occur more than 10 years after the initial episode.<sup>19,20</sup> This is an important issue, because, the presence of HUS, if it's treated rapidly, could have a definitive resolution, and do not have recurrence.

Treating a patient with an inherited deficiency of ADAMTS-13 has its own particularities, because the etiology relies in the fact that there is no enzyme to cleave the vWf multimers.

Much has been said about patients in whom TTP has an autoimmune etiology, because, along the use of plasma exchange (PEX), corticoids or other immunomodulating drugs (such as rituximab) shown a delay in the presentation of the relapse episodes, and avoid the complications related with PEX.<sup>21</sup> In the congenital form the replacement of the enzyme, using fresh frozen plasma or plasma exchange, has a positive effect on the course of the disease, but it does not delay the frequency of relapses.

In this article we have presented a case of a 10-year-old girl, who despite having a congenital deficiency of ADAMTS-13, was treated for over 5 years because of an “idiopathic” thrombocytopenia. The evolution of the patient was not favorable due to the erroneous diagnosis and treatment at the beginning of the disease.

At first the patient disease was treated as an autoimmune disease, but after 5 years with no response, she was referred to our center to investigate the cause of her thrombocytopenia. The initial clinical and laboratory approach did not showed us anything new that in the history of the patient wasn't mentioned, but came to our attention the markedly respond to fresh frozen plasma.

This is a very important matter, because since the publication of the randomized clinical trial by the Canadian Apheresis Group in 1991,<sup>22</sup> most of the reports about TTP-HUS and other pathologies with TM are emphatic in the use of PEX or FFPE as essential and urgent treatment, increasing the survival of patients from 10% to 78%, especially in those with a severe deficiency (acquired or congenital) of ADAMTS-13.<sup>19</sup>

Our patient was suspected for a congenital form of TTP (Upshaw-Schulman syndrome), and confirmed using a chromogenic ELISA (Enzyme-Linked Immuno Sorbent Assay) technique.

This case reveals that the Upshaw-Schulman syndrome can be found in our community. The clinical and typical laboratory abnormalities in a patient with persistent thrombocytopenia, as well as the respond to FFPE made us suspect this rare disease, in which the correct diagnosis and prompt treatment needs to be established.

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