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# TOTAL PLASMA EXCHANGE FOR THE MANAGEMENT OF THROMBOTIC THROMBOCYTOPENIC PURPURA IN A 13-YEAR-OLD FEMALE – A CASE PRESENTATION

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***Keywords:*** *total plasma exchange, thrombotic thrombocytopenic purpura, Rituximab, ADAMTS-13*

***Abstract:*** *Acquired thrombotic thrombocytopenic purpura (TTP) is a rare thrombotic microangiopathy, affecting preferentially young women in their fourth decade. Intensive care admission is often required due to organ dysfunction development risk and for specific critical care measures (Plasma Exchange-PEX). In this article, we will discuss our experience with PEX in the treatment of TTP. Case report: A previously healthy 13-year-old female presented with neurological impairment, and suspicion of stroke. The head computed tomography (CT) scan revealed absence of acute intracranian pathology, and biological evaluation displayed severe thrombocytopenia and haemolytic anemia. After 24 hours, the neurological symptoms were remitted and suspicion of thrombotic thrombocytopenic purpura was raised. The presence of ADAMTS-13 antibodies and Moschcowitz's pentad confirmed the diagnosis. Discussions: The distinctiveness of this case lies in the development of the disease in a 13-year-old person, though TTP usually occurs after the age of 40. The exact cause of ADAMTS-13 low activity could not be established. The use of a high dose of steroids and of plasma exchange is considered to be the first line therapy, with the use of monoclonal antibodies in refractory cases, as it was in our case. Conclusions: The primary end points of our management was to prevent organ damage and to achieve a platelet count greater than 150 000 /µL, as well as a normal or an almost normal lactate dehydrogenase. We achieved this by using high dose corticosteroid therapy, filtration of approximately 50 liters of plasma in 14 PEX session and by administration of monoclonal antibodies.*

## INTRODUCTION

Thrombotic microangiopathies (TMAs) are rare heterogeneous entities, which are very challenging for any clinician. They are characterized by the formation of platelet thrombi in the microvascular environment, the presence of thrombocytopenia due to platelet consumption, and anemia due to erythrocyte destruction, with consecutive organ ischemia.(1)

Two typical phenotypes of TMA are thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). TTP and HUS are acute, fulminant thrombotic microangiopathic disorders, characterized by hemolytic anemia with erythrocyte fragmentation, thrombocytopenia, and renal impairment. Although TTP and HUS are often indistinguishable, TTP is often accompanied by neurologic abnormalities (commonly resulting in mental status changes), while HUS typically involves more a severe renal dysfunction.(2)

Acquired thrombotic thrombocytopenic purpura (TTP) is affecting preferentially young women in their fourth decade.(3) Intensive care admission is often required due to the risk of organ dysfunction and for specific management (plasma exchange and organ support).

Regarding the incidence and prevalence of TTP, they are infrequent and the exact values are not clear. It is cited that the incidence of acquired TTP (acute idiopatic TTP) varies between 1 and 13 cases per million, depending on the geographic location. There has also been a peak incidence in Europe in the third decade.(4,5) The congenital form of TTP is an extremely rare condition, with about 100 patients reported around the globe.(6)

Thrombotic thrombocytopenic purpura (TTP) is caused by a severe functional deficiency in the von Willebrand factor cleaving protease (ADAMTS-13), which is documented *in vitro*, in more than 90% of the cases.(7) The uncleaved von Willebrand factor (vWF) multimers accumulate and bind to platelets which causes spontaneous microthrombi, ultimately causing microangiopathic hemolytic anemia, thrombocytopenia, and end-organ ischemia.(8) The deficiency can be hereditary in the majority of pediatric patients or acquired via autoantibodies in the majority of adult cases.(7)

ADAMTS13 is a normal enzyme in human plasma, that cleaves large parts of the von Willebrand factor coagulation protein into smaller functional subunits. The acquired form of TTP is thought to be due to an autoantibody directed against ADAMTS-13 and the inherited form is due to a genetic deficiency of ADAMTS-13. Since the role of VWT in the pathogenesis of TTP has been scrutinized, the understanding of TTP pathophysiological mechanism has deepened. The molecular mechanism of microvascular thrombus formation is caused by ADAMTS-13 deficiency and by the activation of vWF by sheer stress in the circulation, leading microvascular thrombosis.(9,10,11)

The cornerstone in the treatment of TTP is daily

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plasma exchange and high dose corticosteroids. The refractory cases call for further interventions, such as adding a monoclonal antibody targeting the CD-20 antigen on B lymphocytes (Rituximab), immunomodulating drug that inhibits T-cell activation (cyclosporine), immunosupresive therapy (cyclophosphamide and vincristine) or even splenectomy.(12)

## CASE PRESENTATION

A previously healthy 13-year-old Caucasian girl, with no history of chronic diseases, malignancies or chemotherapy, with a body mass index (BMI) of 31 and a body surface area (BSA) of approx. 2 $m^2$ is admitted in the Pediatric Hospital Emergency Department for right hemiparesis, headache, aphasia, epigastric pain and low-grade fever, with suspicion of stroke. Routine biological evaluation reveals: severe thrombocytopenia and haemolytic anemia. After 24 hours the neurological symptoms are remitted; as TTP is a presumptive clinical diagnosis, the suspicion of thrombotic thrombocytopenic purpura (TTP) is formulated on the basis of a clinical pentad: neurologic impairment, thrombocytopenia, signs of hemolysis, renal impairment and low-grade fever. The patient is being transferred to the Haematology Department of the County Clinical Emergency Hospital of Sibiu for further investigations. The patient is then transferred to the Intensive Care Department for emergency plasmapheresis, as our department is the only plasmapheresis facility in the area, but also because our team is familiar with PEX, in particular with neuroimmune disorders. The patient's medical history reveals an unspecified endocrine disorder based on obesity, hirsutism and purple abdominal stretch marks.

Upon admission in the Intensive Care Department: the patient is conscious and cooperative, with no signs or symptoms of neurological impairment, haemodynamic stable, with no respiratory distress. Neurological symptoms settled down during the two days of hospitalization in the pediatric hospital without any specific therapeutic measures. The patient's slight tendency to hypertension, is easily controlled with continuous infusion of Urapidil, with dosage depending on the patient's blood pressure. After 24 hours, the infusion is stopped because of the possible side effects of the drug, which can produce thrombocytopenia and the patient was switched on oral antihypertensive agents (methyldopa 250 mg tablets, every eight hours); upon inspection, pale skin and two petechial lesions on the oral mucosa are revealed.

Medical imaging and laboratory investigations:

- No signs of acute intracranial pathology on the head CT scan;
- Total bilirubin 40.87 mmol/L, Urea nitrogen 16,78 mmol/L, hyperglycemia 9.1 mmol/L, lactate dehydrogenase (LDH) 934 U/L, platelets 8000/µL, hemoglobin (Hb) 70 g/L, hematocrit (Ht) 24%, leukocytes 23 x $10^9$/l, schistocytes 8% and fibrin monomers +++;
- Hepatitis C virus (HCV) antibodies (qualitative) non-reactive, hepatitis B surface antigen (HBs AG) (qualitative) non-reactive, human immunodeficiency virus (HIV) (rapid test) negative;
- Nasal and pharyngeal Staphylococcus Aureus multi-sensitive;
- ADAMTS-13 antibodies = 116 U/ml (normal value - NV<12 U/ml), ADAMTS-13 = 0,06 IU/ml (Normal value = 0,41-1,41IU/ml), with very low ADAMTS-13 enzymatic activity 1,6% (Normal value 40-130%).

The Moskowitz clinical pentad (microangiopathic haemolytic anemia, transient ischemic attack, renal impairment, thrombocytopenia, low-grade fever), alongside the biochemical studies, the peripheral blood smear and ADAMTS-13 (antibodies and enzymatic activity) supports the diagnosis of TTP, previously observed just from a clinical point of view.

Due to low-grade fever and leucocytosis we considered a possible infection, which is why we continued the broad spectrum antibiotic therapy. We have only been able to isolate a multisensitive staphylococcus aureus - S.A. in the nasopharynx on the microbilogical battery of test that we have collected. The tests should have included a stool test and a lumbar punction, but the patient did not have any intestinal transit before initiation of the antibiotic treatment and a spinal puncture was absolutely contraindicated.

As the analysis revealed the presence of ADAMTS-13 antibodies, we have reached the conclusion that TTP is acquired, although this variant is likely to be found in women in their forties and the congenital variant is more likely to be observed in the neonatal period, with a high rate of relapse.

Since the diagnosis of thrombotic thrombocytopenic purpura has been confirmed, emergency plasmapheresis procedure and high dose corticosteroid therapy (pulse therapy with methylprednisolone 1 gram once daily, for five days, with progressive decrease of the dose) are instituted. A dual lumen central venous catheter is placed on the right internal jugular vein for the extracorporeal procedure and an 18 G peripheral venous catheter is inserted for hydro-electrolytic balancing and treatment administration. Other supportive care and preventive measures for purpura-associated complication are taken: oral alimentation with no salt, red blood cells transfusion (4 units in total with Hb target of 8-9 mg/dl) and anticoagulants (continuous heparin, with target activated partial tromboplastin time (APTT) 40-60 seconds).

The plasma volume of the patient was calculated (approx. 3000 ml) according to their lean body weight. In order to filter the necessary amount of plasma approx. 4500 ml should be filtered per PEX session. According to the TTP treatment protocols, the procedure is continued daily until a target platelet count of 150000/µl and a normal lactate dehydrogenase was reached.

Due to the slow resolution of the disease and the mildly unsatisfactory response with plasma exchange and steroids, it is decided together with the Haematology Department to introduce monoclonal antibody (Rituximab 375 mg/$m^2$ – 750 mg/dose) in slow infusion once a week, along with PEX.

After 14 sessions of plasmapheresis, filtration of approximately 50 liters of plasma, high-dose corticotherapy and 4 doses of monoclonal antibodies, the platelet count returned to the normal value of 268000/µl and the LDH to 216 U/L.

## DISCUSSION

The particularity of the case is the occurrence of acquired TTP in a 13-year-old girl, since TTP usually occurs after the age of 40. Moreover, the child does not present any of the common risk factors such as immunosuppression, anti-platelet therapy or contraceptive agents.

Plasma exchange removes large-molecular-weight substances such as antibodies form the plasma. It is usually carried out using an automated blood cell separator to ensure fluid balance and maintain a normal plasma volume. Typically, 1-1,5 x plasma volume is removed at each procedure and replaced with human albumin solution. Exchange with fresh frozen plasma (FFP) is reserved for the replacement of clotting factors or to replace functional enzymes, as ADAMTS-13 in thrombotic thrombocytopenic purpura.(13)

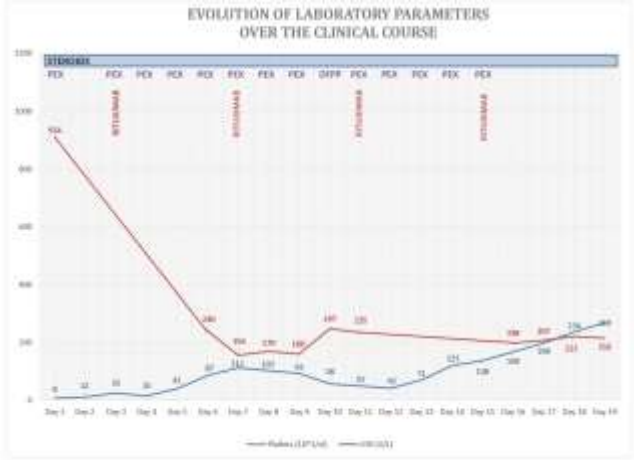
The current opinion in the management of TTP is that the beginning of PEX exclusively with FFP as substitution fluid is a first line therapeutic measure, along with the use of disease modifying drugs. Daily plasma exchange in TTP has reduced mortality from over 90% to 10-20% (14). Before introducing

plasma exchange as a cornerstone in the treatment of TTP only 10% of the patients survived. But the improvement of the survival rate has revealed the risk of relapse.(15)

In patients with TTP, daily PEX should be continued until the platelet count and the LDH are in the normal range and signs of hemolysis and organ dysfunction have resolved. In refractory cases and severe organ dysfunction, treatment intensity can be increased either by rising the exchanged plasma volume or by performing PEX twice a day, on a regular basis.(12) ADAMTS-13 antibodies are IgG and are predominantly found in the intravascular compartment (16), therefore the treatment is efficient if it is performed daily or even twice a day, because no redistribution is required.

Another particularity of this case is the relative resistance to therapy, as the majority of the cases have a favourable evolution after an average of 10 session of PEX, with the amelioration of neurologic changes in 3 days, normalization of the LDH in 5 days and of the platelet count in 10 days. This kind of typical evolution was not seen in this case. After obtaining satisfying values of the platelets and of the LDH, on day 10 the platelets started to decline and the LDH to raise.

**Figure no. 1. Evolution of laboratory parameters**




Because of the technical difficulties and of the hypercoagulability state, the target volume of plasma exchange per session was not achieved, and we filtered approximately 3500 ml per session of PEX, with good end results. Also, because of logistic factors (lack of PEX kit), on day 10 we decided to use double plasma membrane plasmapheresis as an alternative for refractory TTP.(17)

The patient is discharged with recommendations and is advised to present herself at regular follow-up and to search for pregnancy counselling when she decides to have children; because pregnancy can be a trigger for approximately 2-25% of TTP patients.(6) Also, during gestation there is the risk of a superimposed hemolysis elevated liver enzymes low platelet count (HELLP) syndrome.(18)

The primary end point of our management was to prevent end-organ-damage and to obtain a platelet count greater than 150 000 /µL and a normal or almost normal LDH.

We achieved this with the filtration of very large volumes of plasma exchange (14 plasma volumes - approximately 50 liters), by using high dose corticosteroid therapy and by administration of monoclonal antibodies.

After more than two years and a half of regular follow-up, the patient showed no symptoms or signs of recurrence and no other medical conditions.

## CONCLUSIONS

Based on this experience and on medical literature, we encourage the use of PEX in the treatment of TTP, with a strong emphasis on interdisciplinary collaboration.

As a "take-away" message, even if that acquired thrombotic thrombocytopenic purpura (TTP) affects preferentially young women in their fourth decade,(3) in rare cases it can occur at any age, as in the present case.

In conclusion, the diagnosis of thrombotic thrombocytopenic purpura should also be considered, regardless of the patient's age.

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