Inherited ADMATS13 deficiency: When to evoke the in the newborn?

Déficit héréditaire en ADAMTS13: quand l'évoquer chez le nouveau-né?

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RÉSUMÉ

Le déficit héréditaire en ADMTS13 ou purpura thrombopénique thrombotique congénital (PTT) est associé à une déficience héréditaire récessive du facteur ADAMTS13, protéase de clivage du facteur Von Willebrand. C'est une pathologie sévère qui peut engager le pronostic vital. Elle est caractérisée par des épisodes récurrents de thrombopénie réversibles par des perfusions de plasma frais congelé, une anémie hémolytique micro angiopathique et des micro thrombi vasculaires conduisant à des lésions ischémiques de plusieurs organes d'où l'insuffisance rénale terminale, et les séquelles neurologiques en l'absence du traitement.

Chez le nouveau-né, le PTT congénital est généralement caractérisé par un ictère néonatal sévère, une thrombopénie et / ou une anémie hémolytique avec un test de Coombs négatif, et une augmentation de la créatinine.

Nous avons décrit un nouveau-né chez lequel le PTT congénital s'est présenté initialement, dès la quatrième heure de vie, dans un tableau de syndrome hémorragique rattaché à une infection materno-fœtale. Le dosage plasmatique du facteur ADAMTS13 à l'âge de 20 mois, a révélé une faible activité (<1%).

Le PTT peut aggraver et/ou être masqué par d'autres pathologies, ce qui peut entrainer un retard diagnostique et favoriser les conséquences viscérales et les séquelles neurologiques graves. Le diagnostic doit être évoqué précocement devant la discordance entre la gravité d'un syndrome hémorragique et la profondeur de la thrombopénie ; la résistance au traitement symptomatique et la correction après transfusion de plasma frais congelé.

Mots-clés

ADAMTS13, facteur von Willebrand factor, syndrome d'Upshaw–Schulman, purpura thrombotique thrombocytopenique, coagulation intravasculaire disséminée, nouveau-né

SUMMARY

Inherited ADMATS13 or Upshaw–Schulman syndrome (USS) is caused by the deficiency of the Von Willebrand factor-cleaving protease. It is characterized by recurrent episodes of thrombocytopenia reversible by fresh frozen plasma (FFP) infusions, microangiopathic hemolytic anemia, and microvascular thrombosis leading to ischemic damage of multiple organs with end stage renal failure, or neurological sequelae in the absence of appropriate treatment. The typically reported features of USS in neonates are severe jaundice with hyperbilirubinemia, thrombocytopenia and /or combs negative hemolytic anemia, and an increased creatinine.

We presented a clinical case of USS with unusual features, which delayed the diagnosis.

USS was declared at sixth hours of life with diffuse hemorrhage related to an early neonatal infection. Analysis of the plasma, at the age of 20 months, revealed low ADAMTS13 activity in the patient (<1%).

Inherited ADMATS13 deficiency manifestations may overlap with other conditions, which may delay diagnosis and lead to visceral and neurological damage. The diagnosis should be, early considered in some clinical conditions: discrepancy between the severity of a hemorrhagic syndrome and thrombocytopenia, recurrence, resistance to symptomatic treatment. The diagnosis can be suggested by the normalization of platelet count after FFP transfusions.

Key-words

ADAMTS13, von Willebrand factor, Upshaw–Schulman syndrome, thrombotic thrombocytopenic purpura, Disseminated Intravascular Coagulation, newborn, infant.

Inherited ADMATS13 or Upshaw–Schulman syndrome (USS) is caused by the deficiency of the Von Willebrand factor-cleaving protease (A Disintegrin-like And Metalloprotease with ThromboSpondin type 1 motifs-13 or ADAMTS13) due to mutations in the ADAMTS13 gene (1). ADAMTS13 is a protease involved in the regulation of Von Willebrand factor (VWF). Reduced ADAMTS13 activity results in increased unfolded forms of VWF in the circulation, leading to VWF–platelet binding and the formation of platelet thrombi in the arterioles and capillaries, characteristic of thrombotic thrombocytopenic purpura (TTP).The precise incidence of USS is still unknown; approximately 100 patients with USS have been identified in 80 families worldwide (1).

USS or Congenital TTP is a rare life-threatening recessively inherited disease characterized by thrombocytopenia, microangiopathic hemolytic anemia, microvascular thrombosis and ischemic damage of multiple organs with end stage renal failure, or neurological sequelae in the absence of appropriate treatment (2).

USS, typically results in severe neonatal jaundice with a negative coombs test and repeated childhood episodes of thrombocytopenia reversible by fresh frozen plasma (FFP) infusions (3).

USS has heterogeneous presentation and clinical course, and may be misdiagnosed in absence of some of clinical features. We presented a clinical case with unusual features leading to a delayed diagnosis.

CASE REPORT

A full term male infant was born in 2014 in Military Hospital of Tunis. He was the first offspring of non-consanguineous parents. No significant familial history was noted. Pregnancy was complicated with gestational diabetes equilibrated with diet. The delivery was natural and the infant weighted 3 kg. He was hospitalized in Neonatology Unit at birth, for monitoring newborn from diabetic mother with moderate respiratory distress.

At four hours of life, the newborn declared a status of hemorrhagic shock with a diffuse and overwhelming hemorrhage (subcutaneous, pulmonary, digestive, umbilical, and urinary) followed by convulsions (11 hours of life). Neither the initial clinical picture nor the subsequent course were associated with jaundice. The newborn was managed in Neonatal Resuscitation Unit. Initial laboratories revealed biologic signs of DIC: low platelet count of 90×10^9/l, low fibrinogen level (0.4 g/l), low Prothrombin Ratio (PR) of 35%, Cephalin-Kaolin Coagulation Time of 94 (normal 50-70). The other biologic parameters founded hemoglobin of 13g/dl, Ht of 48%, white blood cell count of 27.9×10^9/l, negative direct Coombs test, C- Reactive Protein <8mg/l, elevated serum levels of lactate dehydrogenase (LDH) (3920 UI/l), Creatine Phosphokinase of 800 IU/l, mixed acidosis (pH of 7, 29, HCO3- of 9,8 mmol/l and PCO2 of 54,3 mmHg), Serum Glutamic-Oxaloacetic Transaminase of 487 IU/l (normal <40UI/l), Serum Glutamic-Pyruvic Transaminase of 90 IU/l (normal<40UI/l). Examination of the peripheral smear showed normal size platelets without schizocytes. Blood levels of VWF, IX and WIII factors were normal. A second CRP of 66mg/l and bacteriological tests concluded to Escherichia coli maternal-fetal infection.

The patient recovered under artificial ventilation, hemodynamic support, antibiotics, plasma infusion, packed red blood cells and platelet transfusion. Ultra sonography (day 14 of life) and brain MRI (day 17 of life) showed an intra ventricular hemorrhage with quadri ventricular hydrocephalus. The patient was discharged 19 days after birth.

At the age of two months, recurrence of thrombocytopenia (62 $x10^9$/l) with anemia (hemoglobin of 7.8 g/dl) were noted. Platelet transfusion and intravenous Ig G therapy were administered with increase in platelet counts (160 x 10^9 /l). Since then, the patient developed repeated episodes of purpura with thrombocytopenia, regenerative normochromic normocytaire anemia, and elevated serum levels of LDH (800 and 1011IU/l). Repeated examination of the peripheral smear showed normal size platelets without schizocytes. Renal function remained normal during all the evolution. The recurrence interval was increasingly short with a stabilization at a level of 12 days. The lowest level of platelet count was 7000/ mm^3. Normalization of thrombocytopenia was always slow and transient after platelet transfusions and corticosteroid. Parent's platelets counts, platelet functions and the myelogram were normal. Platelet coombs test, karyotype on blood lymphocytes with chromosomal instability with Mitomycin search was negative. No deep hemangiomas were found in the CT scan examination. Hereditary TTP was suspected at the age of 20 months. Normalization of platelet was, finally obtained after three fresh frozen plasma (FFP) infusions. Analysis of the plasma, performed before FFP infusions and based on antigen enzyme-linked immunosorbent assay, revealed a severe deficiency of ADAMTS13 activity (<1% of normal activity) (normal range of laboratory is 40–130%). Anti-ADAMTS13 antibodies level was normal (11 IU/l, normal values: 0-12 IU/l). These result confirmed the clinical suspicion of hereditary thrombotic thrombocytopenic purpura (TTP). Assays of ADAMTS13 antigen were performed after written informed parent's consent. The patient has since required periodic prophylactic FFP infusions every 12 days. A ventriculo-peritoneal shunt was performed at 9 months of life. With a decline of two years, the patient developed a moderate encephalopathy with tolerated myocardial deficiency (ejection fraction of the left ventricle at 40%) at 22 months requiring medical treatment. Genetic study is under way.

DISCUSSION

In our patient, the onset of USS was, originally declared with early and diffuse hemorrhage in context of infectious DIC. Some of typical features of USS had been, never noted during all the evolution: jaundice with hyperbilirubinemia, increased creatinine, and the presence of schizocytes on the peripheral smear. Correction of all hematologic disorders after different treatments given simultaneously contributed to mislead and to delay diagnosis. Nevertheless, and posteriorly, there was a discrepancy between the severity of the neonatal hemorrhagic syndrome, the level of thrombocytopenia and the other coagulation disorders. Recurrence and/or resistance to symptomatic treatment of thrombocytopenia should evoke a constitutional origin of thrombocytopenia.

The correction of thrombocytopenia by FFP transfusions had a dual diagnostic and therapeutic interest in USS. The typically reported features of USS in neonates are jaundice with hyperbilirubinemia, thrombocytopenia and /or combs negative hemolytic anemia, and an increased creatinine (4).

After neonatal period, the USS subsequently develop different clinical courses. Patients with newborn-onset USS has been categorized as having the early-onset phenotype, and are treated throughout their lives with occasional or periodic prophylactic or therapeutic plasma infusions (5). This fact has been highlighted by the report of the two newborn-onset patients of USS with different individual's subsequent clinical courses. One of these patients required periodic prophylactic plasma infusions (every two weeks), whereas the other did not receive FFP infusions outside the neonatal period until the age of 8 years (6). Our patient developed an early onset of thrombocytopenia and has a short interval of recurrence. Genetic explication is probably underling this phenotype variability. Lotta et al suggested that type of ADAMTS13 mutations may influence the severity of clinical phenotype, probably by determining different levels of residual plasmatic activity of ADAMTS13 and they proposed a genotype-phenotype correlation in USS patient (7). Genetic analysis will clarify the severity of the clinical evolution in our patient.

Further, deficiency of plasma ADAMTS13 activity and increased plasma VWF concentrations are also associated with increased risk for myocardial infarction (8). In fact, VWF and ADAMTS13 interfere in the pathogenesis of these arterial thrombotic diseases (9). Studies in animal models proved that ADAMTS13 deficiency leads to a larger aortic atherosclerosis plaques than high-fat diet (10). This hypothesis may explain myocardial dysfunction in our patient.

CONCLUSION

Inherited ADMATS13 deficiency manifestations may overlap with other conditions such as infection as described in our report. We suggest that this diagnosis should be, early considered in some clinical conditions: discrepancy between the severity of a hemorrhagic syndrome and thrombocytopenia, recurrence, partial or total resistance of thrombocytopenia to platelet transfusion, immunoglobulin and corticosteroid. When USS is not yet, confirmed by analysis of ADAMTS13 level, diagnosis can be suggested by the normalization of platelet count after FFP transfusions, which may has a dual diagnostic and therapeutic interest. FFP remain the reference treatment for USS, until recombinant ADAMTS13 and other novel therapeutics become available.

Conflict of interest:

The authors declare that they have no conflict of interest.

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