Inherited Thrombotic Thrombocytopenic Purpura Revealed by Recurrent Strokes in a Male Adult: Case Report and Literature Review

Diane Beauvais, MD,*,# Laura Venditti, MD,*,# Olivier Chassin, MD,* Bérangère Joly, MD,† Alain Ameri, MD,‡ Pierre Boisseau, MD,† Olivier Lambotte, MD, PhD,§ Paul Coppo, MD, PhD,‖ Agnès Veyradier, MD, PhD,† and Christian Denier, MD, PhD*

Thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy related to a severe deficiency of *ADAMTS13* (a disintegrin and metalloprotease with thrombospondin type 1 repeats, member 13). In this article, we describe the first case of a young male adult suffering from a hereditary TTP revealed by recurrent strokes, relapsing despite antiplatelet and anticoagulant therapy. Because of the persistent moderate thrombocytopenia, plasmatic *ADAMTS13* activity was investigated and was found lower than 5% in the absence of anti-*ADAMTS13* IgG. Direct sequencing of *ADAMTS13* gene led to the diagnosis of Upschaw-Schulman syndrome (USS). Inherited TTP or USS is a rare autosomal recessive inherited disease leading to a severe deficiency of *ADAMTS13* mostly beginning in childhood or in young female adult during pregnancy. Our patient was treated with fresh frozen plasma every 2 weeks. One year after diagnosis, he was free of neurological symptoms. Around 12 cases of inherited TTP diagnosed in adults (outside pregnancy) are described in literature. Only 4 of them exhibited a stroke. This case is the first late onset genetic TTP revealed by recurrent strokes, moderate thrombocytopenia without anemia.

Key Words: Stroke—thrombocytopenia ADAMTS13—thrombotic thrombocytopenic purpura—neurogenetic

Observation

A 33-year-old Caucasian without any family history presented to the emergency department because of an acute left-side weakness that spontaneously recovered after 30 minutes. Cerebral magnetic resonance imaging revealed an acute right parietal ischemic stroke. Neck and intracranial arteries explored were normal. Twenty-hour electrocardiogram monitoring excluded arrhythmia. Body tomodensitometry revealed both renal and spleen infarcts. Transesophageal echography and hematologic parameters (bone marrow smear and biopsy, screening for mutations of myeloproliferative syndromes) were normal. The patient was treated with aspirin.

Recurrence occurred 1 month later with right-side weakness revealing a new cerebral infarct in the superficial left parietal lobe on magnetic resonance imaging. Biological examinations were still negative except a moderate thrombocytopenia (100×10^9/L) without signs of

From the *Department of Neurology, Bicêtre Hospital, AP-HP, University Paris Sud Saclay, Le Kremlin-Bicêtre, France; †Haematology biology department, Lariboisière Hospital, AP-HP and EA3518, University Paris Diderot, Paris, France; ‡Neurology, Meaux Hospital, Bicêtre Hospital, AP-HP, University Paris Sud Saclay, Le Kremlin-Bicêtre, France; §Internal medicine, Bicêtre Hospital, AP-HP, University Paris Sud Saclay, Le Kremlin-Bicêtre, France; and ‖Haematology department, Saint Antoine Hospital, AP-HP, University Pierre et Marie Curie, Paris, France.

Received September 18, 2018; revision received February 24, 2019; accepted March 2, 2019.

Address correspondence to Laura Venditti MD, Department of Neurology, Hôpital de Bicêtre, 78 rue du Général Leclerc, 94275 Le Kremlin-Bicêtre, France. E-mail: laura.venditti gzl@gmail.com.

#Both authors contributed equally to this work.

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.03.011

Table 1. *Review of previously reported late onset inherited TTP with stroke*

Reference	Sex, age at diagnosis, origin	Medical history before diagnosis	Symptoms at diagnosis	Stroke	Triggering factor	Treatment	Biological results	*ADAMTS13* activity	Mutations of *ADAMTS13* gene	Evolution
Meyer et al[5]	Male, 20, Tunisian	17 years old: petechial bleeding and epistaxis with thrombocytopenia and anemia without signs of hemolysis. Diagnosis of idiopathic thrombocytopenic purpura, treated by corticosteroids	Ischemic *stroke* with generalized seizures	Lacunar *strokes*	0	Polyvalent intravenous immune-globulins and sessions of plasmapheresis. FFP after diagnosis of inherited TTP.	Platelets: 13×10^9/L Hemolytic anemia (Hb 77 g/L; total bilirubin 107 μmol/L; and LDH 1,095 IU, normal range 91-180 IU). Schistocytes: only detected at the third crisis.	< 5% (diagnosis at 21 years old, on third hemolytic crisis)	Homozygous for a missense mutation: p.Ser119Phe in the metalloprotease domain of *ADAMTS13*	Follow-up of 2.5 years: sustained remission (platelet count $>100 \times 10^9$/L) with persistent mild renal insufficiency (serum creatinine 150 μmol/L), however, without neurological sequelae.
Antoine et al[6]	Male, 21, "white" "patient A1 born in 1964"	0	Ictere, renal failure, somnolence, abdominal pain. Relapses: renal failure, *strokes* and seizures	25 years old: ischemic *stroke* in the right medium cerebral artery territory	First relapse following febrile illness and acetylsalicylic acid intake. Other episodes preceded by infection or surgery.	Hemodialysis, FFP. After the 10^{th} bout of TTP, prophylactic plasmapheresis sessions every 4 months were instituted.	Platelets:15×10^9/L. Hb: 108g/L at diagnosis and chronic low-grade microangiopathic hemolysis on follow-up. Schistocytes: present at every bout	<3%	Compound heterozygote with 2 mutations:, p. Arg732Val (exon 18) and p. Arg1336Trp (exon 28)	More than 10 years' follow-up, with 10 bouts including 1 occurring during the prophylactic treatment with FFP every 4 months
Fattah et al[7]	Female, 48, Caucasian	32 years old: *stroke* involving multiple territories. Thrombocytopenia, hemolytic anemia. Treated with 3 days of plasma exchange for suspected TTP. She developed progressive chronic kidney disease that was presumed secondary to hypertension.	Kidney transplantation for renal end-stage disease	32 years old: *strokes* in multiple vascular territories	Kidney transplantation	FFP	Her hemoglobin (Hb) concentration decreased from 10 to 8 g/dL	< 5%	Compound heterozygote: p. Arg916Cys (exon 22) and at Exon 29 (c4143insA) results in a frame shift of the protein sequence starting with glutamic acid at Codon 1382 (p. Glu1382fs)	No relapse
Hyla-Klekot et al[8]	Male, 52, Polish	He experienced a few episodes of ischemic *stroke* with ongoing neurological deficiency and developed chronic kidney disease.	NA	*Ischemic strokes* without more precision	NA	NA	NA	NA	Compound heterozygote: missense mutation p. Gly761Ser (exon 19) and mutation of exon 29 (4143_4144insA)	NA

Abbreviations: FFP, fresh frozen plasma, NA, not available.

hemolysis. Patient was administered anticoagulation therapy (apixaban).

A third episode occurred 2 months later. Lumbar puncture and X-rays cerebral arteriography were normal. Because of the thrombocytopenia, *ADAMTS13* (a disintegrin and metalloprotease with thrombospondin type 1 repeats, member 13) activity (measured using the FRETS-VWF73 assay as previously described)[1] was investigated and was found lower than 5%, in the absence of anti-*ADAMTS13* IgG. Direct sequencing of *ADAMTS13* gene showed 2 heterozygous mutations in exon 24 consisting in 1 missense mutation p.Arg1060Trp and 1 truncating mutation p.Trp1067Serfs*47. Also, several single nucleotide polymorphisms were identified either at the homozygous state (p.Arg7Trp) or at the heterozygous state (p.Gln448Glu, p.Pro618Ala and p.Ala1033Thr). This result led to the diagnosis of congenital thrombotic thrombocytopenic purpura (TTP). The patient was treated with fresh frozen plasma. One year after diagnosis, the patient did not relapse.

Discussion

TTP is a thrombotic microangiopathy related to a severe deficiency of *ADAMTS13*[2,3] leading to a spontaneous formation of platelet thrombi responsible for a mechanical hemolytic anemia, a thrombocytopenia and a multivisceral ischemia with often brain involvement (stroke, seizure, or confusion). Indeed, *ADAMTS13* plays a key role in the control of platelet adhesion and aggregation by cleaving the von Willebrand factor (vWF) multimers. In almost 90% of cases, TTP is acquired.[1] In the other cases, TTP is inherited via biallelic autosomal recessive mutations of *ADAMTS13* gene (Upschaw-Schulman syndrome).[4] Clinical presentation of Upschaw-Schulman syndrome is variable, mostly beginning in childhood or in young female adult during pregnancy. Around 12 cases diagnosed in adults (outside pregnancy) are described in literature. Only 4 of them (Table 1)[5-8] exhibited a stroke. All these cases had severe thrombocytopenia and microangiopathic hemolytic anemia.

Conclusion

This case is the first late onset genetic TTP revealed by recurrent strokes, moderate thrombocytopenia without anemia. A stroke with thrombocytopenia, even moderate, needs to discuss a TTP and *ADAMTS13* activity should be tested. The absence of anemia or schistocytes should not call into question the diagnosis of TTP. In perspective, impact of acquired or genetically inherited low ADAMTS13 activity to promote strokes will remains to be explored in future large studies.[9]

Disclosure

None.

References

1. Mariotte E, Azoulay E, Galicier L, et al. Epidemiology and pathophysiology of adulthood-onset thrombotic microangiopathy with severe ADAMTS13 deficiency (thrombotic thrombocytopenic purpura): a cross-sectional analysis of the French national registry for thrombotic microangiopathy. Lancet Haematol 2016;3:e237-e245.
2. Levy GG, Nichols WC, Lian EC, et al. Mutations in a member of the ADAMTS gene family cause thrombotic thrombocytopenic purpura. Nature 2001;413:488-494.
3. Pérez-Rodríguez A, Lourés E, Rodríguez-Trillo Á, et al. Inherited ADAMTS13 deficiency (Upshaw-Schulman syndrome): a short review. Thromb Res. déc 2014;134:1171-1175.
4. Joly BS, Coppo P, Veyradier A. Thrombotic thrombocytopenic purpura. Blood 2017;129:28362846.
5. Meyer SC, Jeddi R, Meddeb B, et al. A first case of congenital TTP on the African continent due to a new homozygous mutation in the catalytic domain of ADAMTS13. Ann Hematol 2008;87:663-666.
6. Antoine G, Zimmermann K, Plaimauer B, et al. ADAMTS13 gene defects in two brothers with constitutional thrombotic thrombocytopenic purpura and normalization of von Willebrand factor-cleaving protease activity by recombinant human ADAMTS13. Br J Haematol 2003;120:821-824.
7. Fattah H, Kumar D, George JN, et al. Successful kidney transplantation in a patient with congenital thrombotic thrombocytopenic purpura (Upshaw-Schulman syndrome). Transfusion 2017;57:3058-3062.
8. Hyla-Klekot L, Kucharska G, Słonka K. [Variety of thrombotic thrombocytopenic purpura clinical course in Polish family members with ADAMTS 13 gene mutation]. Pol Merkur Lekarski 2013;34:161164.
9. Lambers M, Goldenberg NA, Kenet G, et al. Role of reduced ADAMTS13 in arterial ischemic stroke: a pediatric cohort study. Ann Neurol 2013;73:58-64.