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BRIEF REPORT

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ADAMTS13 and von Willebrand factor assessment in steady state and acute vaso-occlusive crisis of sickle cell disease

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Abstract

Background: Sickle cell disease (SCD) is characterized by vaso-occlusive crisis (VOC), acute chest syndrome (ACS) and multiorgan failure (MOF) complicated by thrombosis. Von Willebrand factor (VWF) is a strong marker of SCD-related endothelial injury.

Objectives: To decipher the role of VWF and its specific-cleaving metalloprotease, ADAMTS13, in the vaso-occlusive and thrombotic process of SCD.

Patients/Methods: We investigated the VWF antigen (Ag), ADAMTS13 activity, ADAMTS13 Ag and ADAMTS13 IgGs in a cohort of 65 patients with SCD prospectively enrolled in a 20-month period from three centers. Patients were divided into two groups: an asymptomatic group (n = 30) with treated or untreated SCD at steady state, and a VOC/ACS group (n = 35) with SCD with VOC/ACS requiring either medical management or intensive care management for MOF.

Results and Conclusions: VWF:Ag levels were increased (median, 167 IU/dL; interquartile range [IQR], 124 - 279), especially in patients with VOC SCD (227 IU/dL; IQR, 134-305; $P = .04$), and positively correlated with inflammatory markers ($P < .02$). Median ADAMTS13 activity was normal (70 IU/dL; IQR, 60-80), but 7 patients exhibited a partial deficiency between 25 and 45 IU/dL. ADAMTS13 activity/VWF:Ag ratio, however, did not change during VOC. Median ADAMTS13:Ag was slightly decreased (611 ng/mL; IQR, 504-703) with no significant difference between groups. Surprisingly, ADAMTS13 IgGs were detected in 33 (51%) of our patients. We conclude that, in SCD, VWF:Ag and nonrelevant ADAMTS13 IgGs may reflect the severity of the inflammatory vasculopathy enhancing vaso-occlusive and thrombotic complications.

KEYWORDS

ADAMTS13, sickle cell disease, thrombosis, vaso-occlusion, von Willebrand factor

Essentials

- Vaso-occlusive crisis (VOC) of sickle cell disease (SCD) may be worsened by thrombosis.
- The role of the von Willebrand factor (VWF) and ADAMTS13 in the VOC and thrombosis of SCD is poorly investigated.
- VWF and ADAMTS13 were investigated in 65 patients with SCD divided into steady state and VOC.
- VWF and ADAMTS13 IgG are increased in VOC-complicated SCD.

1 | INTRODUCTION

Sickle cell disease (SCD) is the most frequent monogenic disease worldwide and results from a single amino-acid mutation of the beta-globin chain of hemoglobin (HbS) leading to hemolytic anemia and vaso-occlusion complicated by vaso-occlusive crisis (VOC), acute chest syndrome (ACS), and acute multiorgan failure (MOF).[1] The complex pathophysiology of SCD is multifactorial, including inflammatory vasculopathy resulting in a state of coagulation hyperactivation[5-7] and complement activation.[2-4] VOC/ACS/MOF may be worsened by thrombotic complications including venous thromboembolism and strokes[1,2,5-7] and, more rarely, thrombotic microangiopathies (TMAs) like thrombotic thrombocytopenic purpura (TTP)-like syndrome[8,9] or even TTP,[10-15] a disease caused by the blood accumulation of the platelet-adhesive protein von Willebrand factor (VWF) secondary to a severe deficiency of its specific cleaving protease ADAMTS13. Among primary hemostasis actors, VWF was first established as a strong marker of SCD-related endothelial injury.[2,5-7] Then, in the past 15 years, only few studies involving a total of ~ 120 adult patients with SCD, have tried to decipher the role of the VWF/ADAMTS13 axis in the vaso-occlusive and thrombotic process of SCD.[16-21] Several modulators of VWF/ADAMTS13 balance—that is, cytokines,[2,5-7] free hemoglobin,[17,22] thrombospondin-1 (TSP-1),[19,23,24] neutrophil extracellular traps,[25,26] or a hyperactive form of VWF[18,21]—were highlighted to contribute to a blood accumulation of VWF responsible for an enhancement of both erythrocytes/platelets adhesion to the (sub)endothelium and platelet aggregation, leading to microvascular thrombosis (Figure 1). In France, the annual incidence of SCD is estimated at ~1 in 2000 births with a high cluster in the Paris region. In the current study, we investigated the VWF and ADAMTS13 in a cohort of 65 patients with SCD divided into two groups as a function of the severity of their disease. We showed that SCD is associated with a more important VWF antigen (VWF:Ag) in patients with VOC/ACS/MOF and a nonspecific autoimmunity against ADAMTS13.

2 | PATIENTS AND METHODS

2.1 | Patients

We prospectively enrolled adult patients with SCD (inclusion criteria, age 18-40 years and HbS/S) in a prospective multicenter (three hospitals of Assistance Publique–Hôpitaux de Paris) study from January 2013 to August 2015. Patients were divided into two groups: the asymptomatic group included treated (red blood cell transfusion or hydroxyurea) or untreated (no red blood cells transfusion nor hydroxyurea) asymptomatic steady-state patients who had no VOC in the past 6 weeks; VOC/ACS group included patients with moderate either VOC or ACS requiring hospitalization because their symptoms were not relieved by stage I and II analgesics, and patients with severe VOC or ACS with MOF requiring management in the intensive care unit. Some patients from the VOC/ACS group (n = 21/35) had a follow-up, and they were also investigated when back to steady state, 1 year after initial inclusion. Exclusion criteria were pregnancy, cancer, organ transplantation, HIV infection, left ventricular ejection fraction < 40%, creatinine clearance < 30 mL/min, international normalized ratio > 1.5, and no health insurance. Clinical and standard biology data were collected on a specific form. Written informed consent was obtained from all patients according to the Declaration of Helsinki, and the study was approved by the ethical committee of hospital Bicêtre (CPP Paris VII, France).

2.2 | Blood collection and VWF/ADAMTS13 investigation

Venous blood was collected at inclusion in a 1:10 final volume of sodium citrate, and platelet-poor plasma was stored at −80°C until tested. Plasma VWF:Ag, ADAMTS13 activity, ADAMTS13:Ag and ADAMTS13 IgGs were measured as previously described.[27] Briefly, VWF:Ag (normal range, 50-150 IU/dL) was measured using the VWF:Ag reagent (Siemens Diagnostics, Saint Denis, France) in the STARMAX automate (Diagnostica Stago, Asnières-sur-Seine, France). ADAMTS13 activity (normal range, 50-150 IU/dL) was measured using our in-house FRETS-VWF73 assay (Peptide Institute, Osaka, Japan). ADAMTS13:Ag (normal range, 630-850 ng/mL) was measured using the IMUNOBIND ADAMTS13 ELISA (Sekisui Diagnostics, Stamford, CT, USA) and ADAMTS13 IgGs (positivity threshold, 15 U/mL) were titrated using the TECHNOZYM ADAMTS-13 INH ELISA (Technoclone, Vienna, Austria).

Statistical analysis

Statistical analysis was performed using Prism version 7.00 for Windows (GraphPad Software, San Diego, CA, USA). Data were presented as medians with interquartile ranges (IQRs). Difference between the asymptomatic group and the VOC/ACS

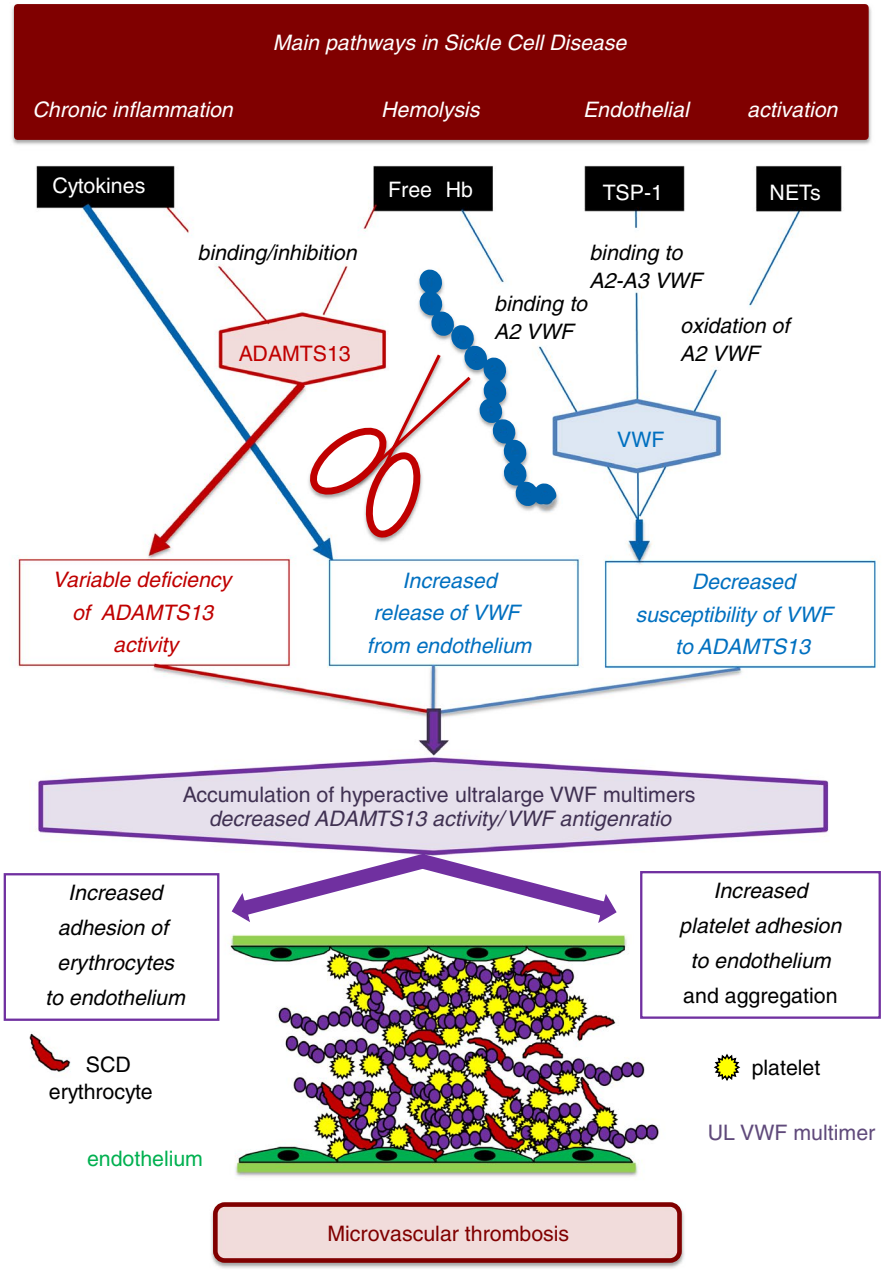

FIGURE 1 Pathophysiologic model for microvascular thrombosis involving von Willebrand factor (VWF) and ADAMTS13 in sickle cell disease (SCD). In SCD, several pathways are involved to imbalance the VWF/ADAMTS13 couple. First, *chronic inflammation* is associated with the release of cytokines that bind to ADAMTS13 and may inhibit its catalytic site[2,5-7] and induce a functional deficiency of ADAMTS13; cytokines also stimulate the release of VWF from endothelial cells. Second, cell-free hemoglobin (Hb) released during intravascular *hemolysis* can bind to both ADAMTS13 (thus inhibiting its catalytic activity) and the VWF-A2 domain (thus blocking ADAMTS13 access to the VWF cleaving site, a specific peptide bond located within its A2 domain) [17,22]. Third, *endothelial activation* leads to the secretion of thrombospondin-1 (TSP-1), which binds to the VWF-A2-A3 domains (thus blocking ADAMTS13 access to the VWF cleaving site)[19,23,24] and to the release of neutrophil extracellular traps (NETs), which induces an oxidation of the VWF cleaving site, preventing its proteolysis by ADAMTS13.[25,26]. In summary, these three pathways induce a variable deficiency of ADAMTS13 activity and an increased release of VWF from the endothelium together with a decreased susceptibility of VWF to cleavage by ADAMTS13, all three conditions promoting the blood accumulation of ultra-large hyperadhesive and hyperactive forms of VWF.[18,21]. As VWF acts as a bridge between the dysfunctional endothelium and both erythrocytes and platelets (adhesion process) as well as between platelets themselves (aggregation process), this imbalance of the VWF/ADAMTS13 couple (reflected by the decrease of the ADAMTS13 activity/VWF antigen ratio) promotes the formation of platelet-rich microthrombi in the small vessels and consequently microvascular thrombosis.[1,2,5,7]

group were compared with a Mann-Whitney test. VOC and steady state in patients of VOC/ACS group were compared with a Wilcoxon matched-pairs test. An explorative Spearman correlation analysis was used to correlate VWF and ADAMTS13 parameters with other biological parameters. *P* values <.05 were considered statistically significant.

TABLE 1 Demographic, biological, and clinical features of 65 patients with sickle cell disease at inclusion

	Asymptomatic Group (n = 30)	VOC/ACS Group (n = 35)
Age, y	29 (23-33)	26 (22-30)
Proportion of men (%)	43.3	62.9
Leukocyte count (× 10^9/L)	5.0 (4.1-7.1)[a]	8.2 (4.7-10.4)[b]
Platelet count (× 10^9/L)	403 (297-469)	384 (240-454)
Hemoglobin level (g/dL)	9.1 (8-10.1)	8.6 (7.2-9.9)
Reticulocyte count (× 10^9/L)	263 (162-337) [a]	224 (173-337)[b]
Lactate dehydrogenase (IU/mL)	551 (417-827) [b]	643 (458-906)[b]
Bilirubin (μmol/L)	48 (23-92)	35 (25-56)[a]
Prothrombin time (%)	87 (80-91)	82 (78-90)
APTT (ratio)	1.00 (0.92-1.09)	1.10 (0.94-1.18)[c]
Fibrinogen (g/L)	2.4 (2.1-2.9)	3.4 (2.7-5.2)[a]
Creatinine (μmol/L)	55 (44-66)	52 (36-64)[a]
SGOT (IU/L)	38 (30-54)	47 (33-59)[a]
SGPT (IU/L)	22 (16-29)	30 (18-47)[a]
GGTP (IU/L)	33 (17-89)	74 (24-137)[a]
Alkaline phosphatase (IU/L)	71 (58-86)	93 (63-141)[a]
Red blood cell transfusion (%)	10/30 (33.3%)	6/34 (17.6%)
Hydroxyurea (%)	9/30 (30.0%)	14/34 (41.18%)

Note: Asymptomatic group: treated or untreated asymptomatic patients; VOC/ACS Group: patients with moderate vaso-occlusive crisis (VOC) or acute chest syndrome (ACS) and patients with severe VOC or ACS with multivisceral organ failure (MOF). Continuous variables data are presented as median with interquartile ranges; categorical variables are presented as number of patients, where data were available, and percentage. APTT ratio is defined as patient's APTT to normal APTT reference value.

Abbreviations: APTT, activated partial thromboplastin time; GGTP, gamma glutamyl transpeptidase; NA, not available; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

[a]Data missing for one patient.

[b]Data missing for two patients.

[c]Data missing for three patients.

3 | RESULTS AND DISCUSSION

Sixty-five consecutive patients with SCD (53.8% of men) were enrolled with a median age of 26 years (IQR, 22-32.5 years). Thirty patients were included in the asymptomatic group, and 35 patients in the VOC/ACS group. Table 1 summarizes their demographic, biological, and clinical features. When compared to the asymptomatic group, patients with VOC/ACS exhibited both a higher proportion of men and inflammatory markers (higher white blood cell count and fibrinogen level) as well as a more important cholestasis syndrome (Table 1).

Our cohort of 65 SCD patients had an increased median VWF:Ag level of 167 IU/dL (IQR, 124-279 IU/dL) with a significantly higher level in the VOC/ACS group (227 IU/dL; IQR, 134-305 IU/dL) when compared to the asymptomatic group (P = .04) (Figure 2A). Median ADAMTS13 activity was overall normal at 70 IU/dL on the global cohort (IQR, 60 - 80 IU/dL). Seven patients with SCD showed ADAMTS13 activity partially deficient (ranging from 25 to 49 IU/dL), with no significant difference between groups (Figure 2B). Consequently, ADAMTS13 activity/VWF:Ag ratio in the VOC/ACS group was not significantly lower than in the asymptomatic group. Of note, within the VOC/ACS group, the patients with severe VOC/ACS leading to MOF had lower ADAMTS13 activity/VWF:Ag ratios than patients with moderate VOC/ACS (P = .01-.22; IQR, 0.133-0.269 vs 0.389; IQR, 0.278-0.630, Figure 2F). Interestingly, inflammatory markers C-reactive protein and fibrinogen were positively correlated with VWF:Ag levels (P = .02 and .01, respectively) (data not shown). In patients from the VOC/ACS group, comparison of VWF/ADAMTS13 parameters between VOC and steady state at 1-year follow-up showed that median VWF:Ag slightly decreased (from 175 IU/dL; IQR, 133-261 IU/dL to 163 IU/dL; IQR, 124-261 IU/dL) and median ADAMTS13 activity/VWF:Ag slightly increased (from 0.41; IQR, 0.26-0.60 to 0.49; IQR, 0.28-0.60), with, however, no statistically significant difference. As previously described in smaller cohorts of patients with SCD, our results highlight that VWF is a relevant marker of the endothelial inflammatory activation present in SCD during both steady state[16,18,21] and VOC/ACS [16,21] and that it is likely involved in the microthrombotic process. Also, in our patients with SCD, ADAMTS13 is not a major determinant of VWF as their respective plasma levels are not inversely correlated. However, as a matter of fact, the ADAMTS13 activity/VWF:Ag ratio is more frequently diminished in SCD with VOC/ACS/MOF complications, in agreement with other groups.[16,18,21]

To further document ADAMTS13, we investigated both ADAMTS13:Ag and ADAMTS13 IgGs. Median ADAMTS13:Ag was overall slightly decreased at 611 ng/mL (IQR, 504-703 ng/mL), with no significant difference between both groups, and it was also reported subnormal or normal by other studies.[16,18,21] Thirty-nine (60%) of our patients exhibited ADAMTS13:Ag levels lower than the 630 ng/mL normal range (Figure 2D). In addition, we were surprised to find moderately positive ADAMTS13 IgG titers (ranging from 16 to 43 U/mL) in 33 (51%) of our patients (Figure 2E) while ADAMTS13 IgGs screened in only one study of 27 SCD patients were found negative.[19] At first sight, these results of low ADAMTS13:Ag levels and positive ADAMTS13 IgGs do not match with the normal ADAMTS13 activity levels observed in our patients because ADAMTS13 activity would be expected to be decreased. However, further analysis of the literature may explain our results. First, in SCD, high titers of other autoantibodies like antinuclear, anticardiolipin antibodies and rheumatoid factors with no clinical relevance were reported.[28] Second, slightly positive ADAMTS13 IgGs were previously reported in 5% to 20% of patients with no ADAMTS13 deficiency but other diseases like lupus

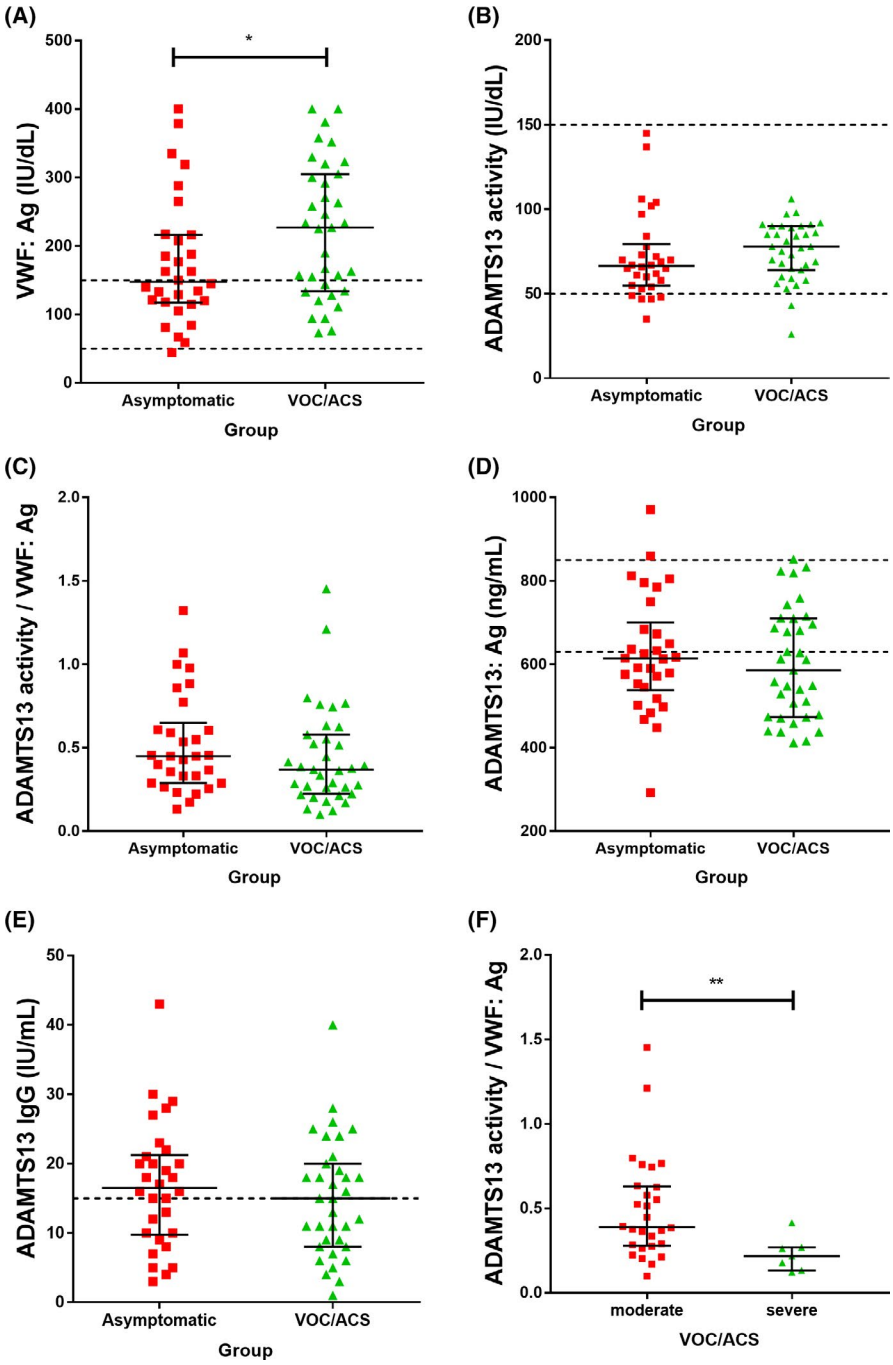

FIGURE 2 Investigation for von Willebrand factor (VWF) and ADAMTS13 in the 65 patients with sickle cell disease. (A) VWF:antigen (Ag); (B) ADAMTS13 activity; (C) and (F) ADAMTS13 activity/VWF antigen ratio; (D) ADAMTS13:antigen; (E) ADAMTS13 IgG titers. Each patient is represented by an icon; groups are indicated as asymptomatic and VOC/ACS below the abscise axis (A, B, C, D, and E) and as moderate VOC/ACS and severe VOC/ACS (F). Normal ranges (A, B, C, D, and F) and positivity threshold (E) are represented as dashed lines; median values are represented as black lines in each group. Significant differences ($P < .05$; Mann-Whitney test) are indicated with an asterisk

and antiphospholipid syndrome.[29] Third, low titers of ADAMTS13 IgGs present in some patients with TTP have been shown to sometimes induce an overestimation of ADAMTS13 activity related to a dissociation of ADAMTS13/ADAMTS13 IgGs complex.[30] Thus, in our SCD cohort, we raise the hypothesis that the discrepancy between ADAMTS13 activity and ADAMTS13:Ag might be due to a slight overestimation of ADAMTS13 activity linked to the presence of low titers of irrelevant ADAMTS13 IgGs, that is, nonspecific antibodies that do not inhibit ADAMTS13 function. In addition, although Novelli and coll.[19] found 7 patients with an ADAMTS13 activity < 10% but no evidence of TMA, in their cohort of 27 patients with SCD, we did not find any patient with a severe ADAMTS13 deficiency in our SCD cohort. This latter finding is in agreement with our personal data from the registry of the French Reference Center for TMA where only 24 patients with SCD were investigated for ADAMTS13 from 2000 to 2015 because of a TMA suspicion: only one patient exhibited a TTP with severely deficient ADAMTS13 < 10%, while 14 patients exhibited moderate partial ADAMTS13 deficiencies and 9 patients normal ADAMTS13 levels (data not shown).

As a conclusion, although we used basic biological tools for VWF and ADAMTS13 investigation, the strength of our study is to involve 65 patients with SCD divided into steady state and VOC state. We confirm that, in SCD, ADAMTS13 is not a modulator of VWF excessive levels and that VWF:Ag level is a better biomarker

than ADAMTS13 for the severity of the inflammatory endothelial vasculopathy enhancing thrombotic complications. The unexpected presence of nonrelevant ADAMTS13 IgGs in half of our patients further supports the nonspecific immune activation/dysfunction targeting the vascular endothelium in SCD possibly induced by a partial loss of the phagocytic function of the spleen. However, these results should not keep physicians from investigating ADAMTS13 in case of TMA suspicion in patients with SCD because TTP-like syndrome and TTP remain tricky differential diagnoses of SCD vaso-occlusive and thrombotic complications.[9-15] In addition, because VWF is likely not only a biomarker of SCD-associated endothelial inflammatory activation but also a pivotal actor of the microvascular thrombotic complications of SCD, anti-VWF nanobodies may be a new therapeutic perspective in the most severe grades of this hemoglobinopathy.

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AUTHOR CONTRIBUTIONS

JD wrote the manuscript; collected, analyzed, and summarized the clinical and biological data; and performed the statistical analysis. AD and FD designed the study, enrolled patients, analyzed the data, and critically reviewed the manuscript. AS, NA, LA, DR, AH, SB, SC, and PC enrolled the patients, provided blood samples and access to clinical and biological data, and critically reviewed the manuscript. AV designed and supervised the study and cowrote and critically reviewed the manuscript.

RELATIONSHIP DISCLOSURE

The authors declare no conflict of interest.

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