**Mind and Matter: The Neurological Complications of TTP**

**Rebecca J. Shaw1,2, Tina Dutt2**

1Department of Clinical Infection, Microbiology and Immunology, University of Liverpool, Liverpool, UK

2The Roald Dahl Haemostasis and Thrombosis Centre, Liverpool University Hospitals NHS Foundation Trust, Liverpool, UK

**Abstract word count:** 200

**Manuscript word count:** 3630

**Key words:** Thrombotic thrombocytopenic purpura, TTP, neurological

**Abstract**

Thrombotic thrombocytopenic purpura (TTP) is a rare and potentially fatal condition, with >90% mortality if untreated; deficiency of ADAMTS13 leads to widespread microvascular thromboses and organ injury particularly affecting organs with high shear stress, including the brain. The acute neurological complications have historically been those most feared by clinicians and synonymous with a poor prognosis. TTP, however, is no longer perceived as two extremes of acute presentation and remission, rather once diagnosed a chronic condition with the potential for a long-term symptom burden. Optimal neuroimaging timing and modality lacks consensus and as we learn more about the changes seen during the acute and chronic stages of TTP, there is scope for neuroimaging to play a greater role in guiding management and the secondary prevention of vascular disease. Reduced ADAMTS13 activity levels have been associated with increased thrombotic risk and novel therapies including caplacizumab and recombinant ADAMTS13 may offer a neuroprotective role. Given the increasing evidence of the neurocognitive and psychological disease in TTP, the importance of screening and timely intervention should not be underestimated. As more patients are surviving their initial TTP presentation, it is crucial for us to develop a greater understanding of the longer-term morbidity affecting these patients.

**Introduction**

Thrombotic thrombocytopenic purpura (TTP) is a rare, life-threatening condition driven by genetic mutation or auto-antibody driven removal of the enzyme ‘A disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13’ (ADAMTS13) giving rise to congenital (cTTP) or immune-mediated TTP (iTTP) respectively. Understanding of both the acute and long-term complications of TTP and their management has evolved dramatically over the last few decades leading to the development of targeted therapies and improved disease monitoring. The neurological manifestations of the disease have historically been the acute complication most feared by clinicians, synonymous with a poor prognosis and severe disease course1. This traditional, acute clinical phenotype has extended with time to include the now more well-recognised, long-term neurological features of the disease. Such symptoms are often most troublesome for patients and have the potential to impact significantly on quality of life. It has become evident that the spectrum of clinical disease extends beyond the two extreme states of acute disease and remission, and levels of ADAMTS13 activity persisting at the lower end of normal in remission may correlate with overt neurological sequelae at a later stage2. Undoubtedly, a deeper insight of the neurological manifestations of TTP will bear significant benefits for patients affected by this aspect of the condition.

**ADAMTS13 and neurological complications of TTP**

ADAMTS13 deficiency leading to von Willebrand factor (VWF)-dependent platelet adhesion is responsible for the cardinal features of TTP: microangiopathic haemolytic anaemia and thrombocytopenia. Under high-shear conditions, condensed VWF multimers extend in the direction of elongational blood flow unfolding a VWF-A2 domain, which is recognisable by ADAMTS133, 4 and responsible for proteolytic cleavage of the A2 domain Tyr-Met bond to release smaller VWF multimer units.

With severe ADAMTS13 deficiency, ultra-large VWF multimers accumulate in the circulation and bind platelets, creating widespread occlusion of the microvasculature leading to tissue ischaemia and organ damage5. The microthrombi consist of predominantly platelets with little fibrin6, 7 and can occur in any tissue, but appear most frequently in organs with high pressure and shear forces which promote VWF-platelet binding, including the heart, kidney and brain8.

The level of ADAMTS13 activity and associated thrombotic risk is not fully understood. Patients with inherited ADAMTS13 deficiency may remain asymptomatic until adulthood9 and around 50% of women affected develop their first acute presentation in pregnancy10. There is increasing evidence of recurring, non-overt neurological symptoms in patients with cTTP. In one study, recurrent headaches, non-hemiplegic migraine and lethargy were the most frequently reported symptoms in untreated patients, with around one quarter having experienced transient ischaemic attacks or stroke at presentation or following diagnosis. Of cTTP patients receiving regular prophylactic plasma infusions, more than 80% reported symptomatic relief with commencement of prophylaxis. Furthermore, the authors reported a significantly reduced incidence of stroke (2% vs. 17%) in this group compared to those not receiving prophylaxis11.

Patients with iTTP treated for an acute clinical episode may enter a haematological remission despite incomplete recovery of ADAMTS13 activity. Sustained ADAMTS13 deficiency appears to increase the risk of relapse and below a certain threshold, most patients will receive elective treatment with rituximab to restore the activity to within normal range12-14. For iTTP patients where the ADAMTS13 activity persists below normal, but is not considered low enough for pre-emptive treatment, the effect of prolonged low ADAMTS13 activity on the integrity of the vascular endothelium is unclear.

In mice, complete ADAMTS13 deficiency does not invariably result in stroke, but may lead to an augmented prothrombotic state15. Exploring further the role of ADAMTS13 as a risk factor for ischaemic stroke, a murine ischaemia-reperfusion model showed reduced regional blood flow after reperfusion in ADAMTS13 -/- mice and an accumulation of inflammatory cells in the brains of these mice. Here, the authors proposed a neuroprotective role of ADAMTS13 through regulation of VWF-dependent inflammation after reperfusion16. Emerging evidence from subsequent experimental studies suggest manipulation of the different conformational states of ADAMTS13 may further enhance the dose-dependent activity of wild type ADAMTS13 in murine models17.

For TTP patients who are in remission, a lower baseline ADAMTS13 activity is associated with an increased risk of stroke (13.1% TTP in remission vs. 2.6% in the general population)18. Even within the general population, a prospective study of almost 6000 volunteers >55 years of age (with no preceding history of stroke) showed that individuals with lower ADAMTS13 activities had a higher risk of ischaemic stroke versus those with normal levels. These findings were independent of age, sex and traditional cardiovascular risk factors19. This could be due to the reduced clearance of high molecular weight VWF multimers, leading to a pro-thrombotic state and localised thrombus formation. ADAMTS13 deficiency may also be a risk factor through accelerated consumption in response to acutely elevated VWF19, 20.

Further characterisation of ADAMTS13 activity and its role in acute and chronic TTP states will inform its potential as a neuroprotective agent. This is of particular relevance in the context of ongoing clinical trials studying recombinant ADAMTS13 therapy in both congenital and iTTP21, 22.

**Neurological complications in acute TTP**

The diversity of neurological manifestations may be explained by the development of multiple, microthrombi plus the location of thrombotic burden in a major vessel with an available collateral blood supply. Partially occlusive thrombus or transient occlusion of blood vessels typically manifests as the intermittent or fleeting neurological signs observed clinically23. Fluctuating neurological signs at presentation is well-described and reported in the very first case studies of TTP24.

More than half of all patients with TTP experience neurological complications at presentation or throughout the course of their illness25-27. Most frequently reported acute symptoms include impaired conscious level, seizures, headaches, confusion and focal cerebral manifestations, such as paresis, dysphasia, paraesthesia and visual disturbance (Table 1)1, 23, 25, 28. The Oklahoma TTP-HUS registry described 53% of patients (n=41) experiencing severe neurological abnormalities during their initial presentation with TTP, namely coma, stroke, generalised seizures, and transient focal signs (motor/sensory abnormalities, diplopia, and aphasia). The most common of these severe abnormalities was a transient focal deficit which occurred in 40% of patients (n=30)25. Scully et al found 10% of TTP patients with neurological complications were admitted to hospital in a coma and required mechanical ventilation; and this in turn conveyed a poor prognosis1. Intubation in severely ill TTP patients is not uncommon; a recent report, described one quarter of patients with TTP requiring intubation acutely, prompted by neurological compromise in 100% of cases (n=22)29. Around a third of patients experience less severe neurological symptoms which can be much more difficult to detect clinically, such as headaches, blurred vision, mild ataxia and subtle mental status changes1, 25. Bugarin-Estrada et al summarised studies of over 1000 patients from eight different countries across the developing world; here, the percentage of TTP cases (based on clinical diagnosis) with neurological symptoms ranged from 61 – 91.7%28. This highlights the value of astute interpretation of clinical symptoms when considering TTP as a differential diagnosis, especially in areas where there may be limited access to testing of ADAMTS13 activity.

The UK TTP registry compared patients with iTTP and secondary TTP (defined as TTP with a specified precipitating event) and described 78% of all patients having neurological features at clinical presentation. Although the incidence of neurological symptoms was similar between the two groups, those with iTTP presented with more severe neurological symptoms compared to the secondary TTP group1. For patients in the acute phase of iTTP, it has also been demonstrated that neurological symptoms are more common and severe in those patients with lower VWF:collagen binding ratios, reflecting loss of VWF high molecular weight multimers. This was attributed by the authors to the sequestration of these multimers within microthrombi in the circulation30.

Signs of ischaemic stroke may be the initial manifestation of iTTP; in one case series, 41% of strokes were multi-focal, consistent with multiple microvascular thrombi, however, both large and small vessel artery strokes were also observed indicating occlusions were not wholly restricted to the microvasculature31. Most of the patients were under 50 years old and thus a diagnosis of iTTP should remain a consideration in young patients presenting with otherwise unexplained ischaemic stroke.

Around one third of patients with cTTP present with neurological symptoms acutely, which is less when compared to iTTP. In the cohort of cTTP presenting in pregnancy, the neurological symptoms experienced are similar to those of iTTP and include headache, migraine, blurred vision and transient ischaemic attacks10.

Neurological symptoms are heterogenous in acute TTP, and the frequency appears highest in iTTP compared to cTTP or secondary TTP. Neurological symptoms are less frequent and less severe on subsequent relapse of disease25, as a result of increased symptom awareness, long-term monitoring and early intervention with immunosuppressive therapies such as rituximab12, 32, 33.

**Neuroimaging in TTP**

Due to the high frequency of neurological symptoms, brain imaging is often sought during an acute clinical episode of TTP. Computed tomography (CT) and magnetic resonance imaging (MRI) are the most common choices amongst clinicians. Not all patients with acute TTP undergo neuroimaging during their hospital admission and there is inconsistency in the timing. There is a lack of prospective randomised controlled trials determining both the most informative modality and the optimal timing of imaging for patients with TTP (Table 2).

Early neuroimaging studies in TTP from 1995-2001 consisted of small case series. These early reports showed that CT brain imaging was reported as normal in almost all cases, regardless of the presence of neurological symptoms acutely34, 35. CT appears to have a lower sensitivity for detecting the multiple widespread but rapidly reversible microvascular thromboses sustained in TTP34. Conversely, MRI appears more likely to detect intracranial abnormalities associated with TTP and has been shown to detect lesions including posterior reversible encephalopathy syndrome (PRES) in cases which had not been previously identified on CT35, 36.

More recently, Alwan et al reported the largest study of cerebral MRI findings from 131 patients with TTP who either presented with neurological symptoms or reported persistent headache after platelet count recovery; overall 56% had abnormal MRI imaging, and abnormal imaging was significantly more likely in those with neurological symptoms compared to headaches alone (80% versus 18%, p<0.0001)37.

Neuroimaging findings have also been studied for TTP patients in remission; earlier studies reported the majority of cases had resolution of the previously abnormal scan findings by 12 weeks after acute presentation35, 38. However, Cataland et al reported diffusion-weighted MRI being superior for TTP patients in remission and revealed evidence of ischemia in 39% of patients (n=9/23)39. Therefore, MRI may be able to detect clinically latent although permanent brain damage, which could be contributing to long-term neurocognitive effects of TTP. There was no significant difference noted in the presence of abnormalities on MRI between patients who were within 1 year of last acute episode compared to those who were greater than 1 year since last acute episode. Perhaps paradoxically, it appeared that patients with a single acute episode of TTP were more likely to have MRI abnormalities than those with greater than one acute episode (62 vs. 13%, p=0.017)39.

There are very limited data on the use of other forms of imaging including single-photon emission computed tomography (SPECT) scanning in TTP. SPECT scanning uses radio-labelled compounds to assess cerebral blood flow40; it is most often used in the UK to investigate seizures and dementia, but is currently not widely available. In one study, two cases of TTP underwent SPECT scanning during acute presentation; the SPECT scans were both abnormal showing evidence of hypoperfusion and reduced cerebral blood flow acutely, which resolved when scans were repeated following clinical recovery. Further evidence is needed to assess the benefits of SPECT scans in TTP, however practically this imaging modality is likely to be impeded by availability.

The neuroimaging findings of patients with TTP are diverse; most commonly reported abnormalities include reversible bilateral cerebral oedema, ischaemic infarcts and haemorrhage35, 36, 41. Other less frequently reported findings include multiple haemorrhagic infarcts42, reversible stenosis of major cerebral arteries43 as well as progressive cerebral microbleeds44, 45. As is the case with rare disease, observations are often limited to small case numbers, but there is some suggestion that patients with findings of cerebral oedema alone have a more favourable outcome compared to those with either infarction or haemorrhage36.

Reversible bilateral cerebral oedema seen in TTP patients is similar in nature to PRES. PRES is a reversible clinico-radiological syndrome presenting with headache, altered mental functioning, seizures and visual disturbance; neuroimaging shows white matter oedema in the posterior cerebral hemispheres46. Unlike adult patients, PRES is uncommon in the paediatric setting; however, when present with a diagnosis of TTP, it appears to confer a worse prognosis. Bhat et al reported n=4/7 paediatric TTP cases with PRES who died, however alternative contributory factors could not be excluded in this report47.The mechanism for PRES in TTP is unclear; but may be the result of cerebrovascular hypoperfusion leading to endothelial damage and leakage at the blood-brain barrier, as can occur with systemic inflammation36, 44. This may also explain the pathophysiology of cerebral micro-haemorrhages.

**Long-term neurological complications of TTP**

There is a growing literature describing the long-term symptom burden of TTP. Importantly, patients who survive beyond their 1st episode experience worse overall survival than age and sex-matched controls, and have higher rates of comorbidities including hypertension and obesity18, 48.

Feedback from TTP patient support groups set up through the Oklahoma TTP-HUS registry in 199649 provided the first recognition that patients were experiencing persistent problems beyond acute episodes, in particular with memory, concentration and endurance48. Patients are now known to demonstrate a significantly reduced health-related quality of life as well as increased neurocognitive impairment when compared to the general population50, 51. Health-related quality of life scores have been compared between iTTP versus other types of thrombotic microangiopathy (including following stem cell transplantation, pregnancy/postpartum, drug induced or bloody diarrhoea prodrome) with no significant difference found between these groups50. Interestingly, there were no differences observed in long-term neurological symptoms detected in patients with high versus low ADAMTS13 activities during remission from TTP50, 52.

The underlying pathophysiology of the long-term neurological complications is not clearly understood, or whether the presence of neurological symptoms at diagnosis has a bearing on the likelihood of long-term neurocognitive impairment50, 52, 53. It is hypothesised that thrombotic microangiopathy leads to chronic small vessel ischaemia resulting in subtle but persistent neurocognitive and psychological disturbances. These neurological symptoms can easily go unrecognised by both patient and clinician, whilst potentially having a significant impact on physical and mental health. Characterisation of the long-term complications to improve management and quality of life is now acknowledged to be of comparable importance to the more acute management strategies.

**Neurocognitive complications of TTP**

There have been a steady number of primarily observational studies performed describing long-term neurocognitive deficits in TTP patients spanning the last decade (Table 3). Studies have in general reviewed a single time point in follow up and comparisons have been made with healthy cohorts. Consistent findings from retrospective studies have conferred that TTP patients suffer from significant neurocognitive morbidity including poor long and short-term memory, reduced concentration and fatigue37, 50, 54, often with persistent symptomatology despite remission status48. Interestingly, neurocognitive deficit does not appear to correlate with number or severity of episodes of TTP and evidence is conflicting regarding the influence of acute neurological symptoms on long-term cognitive status48, 50, 51. We are not aware of any studies comparing TTP patients with patients demonstrating a comparable clinical phenotype, however the inherent limitations associated with rare disease and small patient numbers may make comparisons challenging.

A range of assessment tools have been used across studies, for example the Montreal Cognitive Assessment tool (MoCA) as a rapid screening tool, followed by more focused questionnaires such as the Repeatable Battery for Assessment of Neuropsychological Status (RBANS)55 or Short Form-36 (SF-36), a validated, widely used health-related quality of life questionnaire tool39, 50. Han et al reported that TTP patients demonstrated significantly lower RBANS scores than the population norm (P <0.05), and there was a significant association between MoCA scores and RBANS suggesting the use of the simpler faster screening tool in identifying patients who may benefit from support55.

Studies by both Lewis and Cataland et al employed the SF-36 and assessed a number of patients at more than one time point. Despite patients having apparently recovered completely with no additional health problems, their physical and mental health scores were significantly worse than those of the US population norms39.

More recently, Alwan et al correlated changes in cerebral white matter with neurocognitive function. Hyperintense white matter lesions were found predominantly in the frontal lobe of those TTP patients with marked intellectual impairment compared to those without impairment (67% vs 19%, p=0.002) and abnormal MRI imaging was associated with a lower median verbal and performance IQ (85 vs 99, p=0.02; 83 vs 100, p=0.02)37.

**Neuropsychological complications of TTP**

Neurocognitive deficits and neuropsychological symptoms often co-exist. Several studies report the strong correlation between these two long-term complications suggesting that self-estimated cognitive impairment may be related to the presence of depression and/or anxiety51, 52.

A high incidence of low mood and depression in TTP is reported in multiple studies; almost a third of TTP patients scored as suffering from severe depression using the Beck Depression Inventory II (BDI-II)55, and at least 80.8% of patients (n=236) scored as at least mild depression using online surveys (PCL-5 PTSD checklist and BDI-II) at a single time point (compared to 10.5% of the general population). Such statistics have been linked to higher rates of unemployment as a consequence56. Interestingly, the Oklahoma group did not find any correlation in the severity of the acute TTP episode with those suffering from depression versus those who were not48. This implies vigilance for such complications should be a part of follow-up for all patients.

For those exhibiting more severe symptoms, post-traumatic stress disorder (PTSD) is not uncommon and formal psychological support should be considered here. In one study, 35.1% of TTP patients had a positive screening test for PTSD from three to 11 years following their first episode (compared to 3.5% of the general primary care population)56.

Other mental health disorders are prevalent in patients diagnosed with TTP, including anxiety, in over 50% of patients2, 37, 52. Both depression and anxiety have been found to be more common in iTTP compared to cTTP37.

Given the significant neurological symptom burden in patients with TTP, it would seem prudent that routine screening and psychological support should be built into the long-term follow-up and care for these patients.

**Therapies for acute and long-term neurological complications of TTP**

There are no prospective clinical trials to date to determine which patients may be more at risk of developing long-term neurocognitive and/or neuropsychological complications; equally, there is currently no data to support the best management of TTP survivors with a reduced quality of life secondary to their neurological morbidity.

Caplacizumab, a humanised immunoglobulin fragment targeting the A1 domain of VWF to prevent interaction with the glycoprotein Ib-IX-V receptor on platelets, was approved for the treatment of iTTP by the Food and Drug Administration in 2018. Phase 2 and Phase 3 clinical trials demonstrated a reduction in time to platelet count normalisation compared with placebo57, 58 and early administration may reduce ischaemic tissue injury. With novel therapies such as caplacizumab, the thrombotic risk of cerebral TTP may reduce, whilst the potential risk of intracranial haemorrhage requires consideration29, 59-61.

For cTTP patients, the mainstay of treatment is regular prophylactic plasma infusions; cTTP patients who do not receive maintenance plasma therapy have a higher risk of cerebrovascular events in later life11, however, the long-term neurovascular risk for this subset of TTP patients may be influenced by the introduction of recombinant ADAMTS13 therapy.

Despite the high prevalence of depression reported in patients with TTP37, 48, 51, 52, 56, it is suggested that depression is sub-optimally treated. Falter et al. highlighted that of their patient population, only 7% of patients were receiving any form of treatment including medication or psychological therapy51. TTP patients with a history of pharmacologically treated depression appeared to view medication favourably, with the most significant reported barrier to taking medication being the side effect of emotional blunting. A qualitative study reported that TTP patients (both those who received pharmacological and non-pharmacological therapy for depression) expressed counselling was a beneficial treatment for depression. In this study, black TTP patients were more likely to state cultural barriers to pharmacological treatment, and those patients who had not tried medication raised concerns over potential side effects and addiction62.

Further research is required to improve the management of long-term neurological sequelae in TTP survivors to ensure this component of care is not overlooked, but provided in a timely fashion to meet patient need.

**Conclusions and future perspectives**

The neurological manifestations and consequences of TTP have an impact on patients from the point of diagnosis until many years later. Their presentation is common but variable, and an astute awareness of the more subtle neurological signs and symptoms, alongside those which may indicate impending deterioration, is paramount for long-term health and survival outcomes.

In an era of precision medicine, more work is needed to explore the role of ADAMTS13, in particular for patients in remission who demonstrate chronically low ADAMTS13 activity levels with potentially increased risk of stroke18. Prospective studies are needed to determine optimal neuroimaging, timing and frequency and inform secondary prevention of cerebrovascular events.

As TTP services grow and evolve, education and empowerment of patients in managing neurological disease is of prime importance. The value of formal psychological support has been recognised in funding for integrated psychology services in the UK and there are now studies observing serial measurements of neurological function over time to encourage more responsive care in a dynamic spectrum of disease63. Well-designed research studies addressing neurological disease in TTP will continue to inform how the needs of patients can be better served, both at presentation and life-long.

**Author contributions**

RJS and TD both wrote and critically reviewed the manuscript.

**Disclosures**

Both authors have completed ICJME conflict of interest disclosures form. RJS has received speaker fees from Sanofi. TD has received speaker fees from Alexion and Sanofi.

**References**

1. Scully M, Yarranton H, Liesner R, Cavenagh J, Hunt B, Benjamin S, et al. Regional UK TTP Registry: correlation with laboratory ADAMTS 13 analysis and clinical features. *British Journal of Haematology* 2008;142(5):819-26.

2. Chaturvedi S, Abbas H, McCrae K. *Increased Morbidity During Long Term Follow Up of Survivors of Thrombotic Thrombocytopenic Purpura*, 2014.

3. Schneider SW, Nuschele S, Wixforth A, Gorzelanny C, Alexander-Katz A, Netz RR, et al. Shear-induced unfolding triggers adhesion of von Willebrand factor fibers. *Proc Natl Acad Sci U S A* 2007;104(19):7899-903.

4. Auton M, Cruz MA, Moake J. Conformational stability and domain unfolding of the Von Willebrand factor A domains. *J Mol Biol* 2007;366(3):986-1000.

5. Zheng X, Chung D, Takayama TK, Majerus EM, Sadler JE, Fujikawa K. Structure of von Willebrand factor-cleaving protease (ADAMTS13), a metalloprotease involved in thrombotic thrombocytopenic purpura. *J Biol Chem* 2001;276(44):41059-63.

6. Hosler GA, Cusumano AM, Hutchins GM. Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome are distinct pathologic entities. A review of 56 autopsy cases. *Arch Pathol Lab Med* 2003;127(7):834-9.

7. Feys HB, Roodt J, Vandeputte N, Pareyn I, Lamprecht S, van Rensburg WJ, et al. Thrombotic thrombocytopenic purpura directly linked with ADAMTS13 inhibition in the baboon (<em>Papio ursinus</em>). *Blood* 2010;116(12):2005-10.

8. Sadler JE. Pathophysiology of thrombotic thrombocytopenic purpura. *Blood* 2017;130(10):1181-8.

9. Mansouri Taleghani M, von Krogh AS, Fujimura Y, George JN, Hrachovinová I, Knöbl PN, et al. Hereditary thrombotic thrombocytopenic purpura and the hereditary TTP registry. *Hamostaseologie* 2013;33(2):138-43.

10. Scully M, Thomas M, Underwood M, Watson H, Langley K, Camilleri RS, et al. Thrombotic thrombocytopenic purpura and pregnancy: presentation, management, and subsequent pregnancy outcomes. *Blood* 2014;124(2):211-9.

11. Alwan F, Vendramin C, Liesner R, Clark A, Lester W, Dutt T, et al. Characterization and treatment of congenital thrombotic thrombocytopenic purpura. *Blood* 2019;133(15):1644-51.

12. Bresin E, Gastoldi S, Daina E, Belotti D, Pogliani E, Perseghin P, et al. Rituximab as pre-emptive treatment in patients with thrombotic thrombocytopenic purpura and evidence of anti-ADAMTS13 autoantibodies. *Thromb Haemost* 2009;101(2):233-8.

13. Westwood J-P, Webster H, McGuckin S, McDonald V, Machin SJ, Scully M. Rituximab for thrombotic thrombocytopenic purpura: benefit of early administration during acute episodes and use of prophylaxis to prevent relapse. *Journal of Thrombosis and Haemostasis* 2013;11(3):481-90.

14. Zheng XL, Vesely SK, Cataland SR, Coppo P, Geldziler B, Iorio A, et al. ISTH guidelines for treatment of thrombotic thrombocytopenic purpura. *Journal of Thrombosis and Haemostasis* 2020;18(10):2496-502.

15. Banno F, Kokame K, Okuda T, Honda S, Miyata S, Kato H, et al. Complete deficiency in ADAMTS13 is prothrombotic, but it alone is not sufficient to cause thrombotic thrombocytopenic purpura. *Blood* 2006;107(8):3161-6.

16. Fujioka M, Hayakawa K, Mishima K, Kunizawa A, Irie K, Higuchi S, et al. ADAMTS13 gene deletion aggravates ischemic brain damage: A possible neuroprotective role of ADAMTS13 by ameliorating postischemic hypoperfusion. *Blood* 2009;115:1650-3.

17. South K, Denorme F, Salles-Crawley II, De Meyer SF, Lane DA. Enhanced activity of an ADAMTS-13 variant (R568K/F592Y/R660K/Y661F/Y665F) against platelet agglutination in vitro and in a murine model of acute ischemic stroke. *Journal of Thrombosis and Haemostasis* 2018;16(11):2289-99.

18. Upreti H, Kasmani J, Dane K, Braunstein EM, Streiff MB, Shanbhag S, et al. Reduced ADAMTS13 activity during TTP remission is associated with stroke in TTP survivors. *Blood* 2019.

19. Sonneveld MAH, de Maat MPM, Portegies MLP, Kavousi M, Hofman A, Turecek PL, et al. Low ADAMTS13 activity is associated with an increased risk of ischemic stroke. *Blood* 2015;126(25):2739-46.

20. McCabe DJH, Murphy SJX, Starke R, Harrison P, Brown MM, Sidhu PS, et al. Relationship between ADAMTS13 activity, von Willebrand factor antigen levels and platelet function in the early and late phases after TIA or ischaemic stroke. *Journal of the Neurological Sciences* 2015;348(1):35-40.

21. Tersteeg C, Schiviz A, De Meyer SF, Plaimauer B, Scheiflinger F, Rottensteiner H, et al. Potential for Recombinant ADAMTS13 as an Effective Therapy for Acquired Thrombotic Thrombocytopenic Purpura. *Arterioscler Thromb Vasc Biol* 2015;35(11):2336-42.

22. Scully M, Knöbl P, Kentouche K, Rice L, Windyga J, Schneppenheim R, et al. Recombinant ADAMTS-13: first-in-human pharmacokinetics and safety in congenital thrombotic thrombocytopenic purpura. *Blood* 2017;130(19):2055-63.

23. Silverstein A. Thrombotic Thrombocytopenic Purpura: The Initial Neurologic Manifestations. *JAMA Neurology* 1968;18(4):358-62.

24. Moschcowitz E. An acute febrile pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries: An undescribed disease. *The American Journal of Medicine* 1952;13(5):567-9.

25. Page EE, Kremer Hovinga JA, Terrell DR, Vesely SK, George JN. Thrombotic thrombocytopenic purpura: diagnostic criteria, clinical features, and long-term outcomes from 1995 through 2015. *Blood advances* 2017;1(10):590-600.

26. George JN. Thrombotic Thrombocytopenic Purpura. *N Engl J Med* 2006;354(18):1927-35.

27. Vesely SK, George JN, Lämmle B, Studt J-D, Alberio L, El-Harake MA, et al. ADAMTS13 activity in thrombotic thrombocytopenic purpura–hemolytic uremic syndrome: relation to presenting features and clinical outcomes in a prospective cohort of 142 patients. *Blood* 2003;102(1):60-8.

28. Bugarin-Estrada E, Gómez-De León A, López-García YK, Díaz-Chuc EA, Priesca-Marín JM, Ruiz-Argüelles GJ, et al. Clinical presentation in thrombotic thrombocytopenic purpura: Real-world data from two Mexican institutions. *Journal of Clinical Apheresis* 2018;33(6):645-53.

29. Dutt T, Shaw RJ, Stubbs MJ, Yong J, Bailiff B, Cranfield T, et al. Real-World Evidence of Caplacizumab Use in the Management of Acute TTP. *Blood* 2020.

30. Béranger N, Benghezal S, Savigny S, Capdenat S, Joly BS, Coppo P, et al. Loss of von Willebrand factor high-molecular-weight multimers at acute phase is associated with detectable anti-ADAMTS13 IgG and neurological symptoms in acquired thrombotic thrombocytopenic purpura. *Thrombosis Research* 2019;181:29-35.

31. Tomich C, Debruxelles S, Delmas Y, Sagnier S, Poli M, Olindo S, et al. Immune-Thrombotic Thrombocytopenic Purpura is a Rare Cause of Ischemic Stroke in Young Adults: Case Reports and Literature Review. *Journal of Stroke and Cerebrovascular Diseases* 2018;27(11):3163-71.

32. Scully M, Cohen H, Cavenagh J, Benjamin S, Starke R, Killick S, et al. Remission in acute refractory and relapsing thrombotic thrombocytopenic purpura following rituximab is associated with a reduction in IgG antibodies to ADAMTS-13. *British Journal of Haematology* 2007;136(3):451-61.

33. Fakhouri F, Vernant J-P, Veyradier A, Wolf M, Kaplanski G, Binaut R, et al. Efficiency of curative and prophylactic treatment with rituximab in ADAMTS13-deficient thrombotic thrombocytopenic purpura: a study of 11 cases. *Blood* 2005;106(6):1932-7.

34. Meloni G, Proia A, Antonini G, de Lena C, Guerrisi V, Capria S, et al. *Thrombotic thrombocytopenic purpura: Prospective neurologic, neuroimaging and neurophysiologic evaluation*, 2001.

35. Bakshi R, Shaikh ZA, Bates VE, Kinkel PR. Thrombotic thrombocytopenic purpura: Brain CT and MRI findings in 12 patients. *Neurology* 1999;52(6):1285-.

36. Burrus TM, Wijdicks EFM, Rabinstein AA. Brain lesions are most often reversible in acute thrombotic thrombocytopenic purpura. *Neurology* 2009;73(1):66-70.

37. Alwan F, Mahdi D, Tayabali S, Cipolotti L, Lakey G, Hyare H, et al. Cerebral MRI findings predict the risk of cognitive impairment in thrombotic thrombocytopenic purpura. *British Journal of Haematology* 2020;191(5):868-74.

38. Fiorani L, Vianelli N, Gugliotta L, Vignatelli L, Corbelli C, D'Alessandro R. Brain MRI and SPET in thrombotic thrombocytopenic purpura. *The Italian Journal of Neurological Sciences* 1995;16(3):149-51.

39. Cataland SR, Scully MA, Paskavitz J, Maruff P, Witkoff L, Jin M, et al. Evidence of persistent neurologic injury following thrombotic thrombocytopenic purpura. *American Journal of Hematology* 2011;86(1):87-9.

40. Yeo JM, Lim X, Khan Z, Pal S. Systematic review of the diagnostic utility of SPECT imaging in dementia. *Eur Arch Psychiatry Clin Neurosci* 2013;263(7):539-52.

41. Kay AC, Solberg LA, Nichols DA, Petitt RM. Prognostic Significance of Computed Tomography of the Brain in Thrombotic Thrombocytopenic Purpura. *Mayo Clinic Proceedings* 1991;66(6):602-7.

42. Gruber O, Wittig I, Wiggins CJ, von Cramon DY. Thrombotic thrombocytopenic purpura: MRI demonstration of persistent small cerebral infarcts after clinical recovery. *Neuroradiology* 2000;42(8):616-8.

43. Kondo K, Yamawaki T, Nagatsuka K, Miyashita K, Naritomi H. Reversible stenosis ofmajor cerebral arteriesdemonstrated by MRA inthrombotic thrombocytopenicpurpura. *Journal of Neurology* 2003;250(8):995-7.

44. Noorbakhsh-Sabet N, Zand R. Thrombotic Thrombocytopenic Purpura with Concomitant Progressive Cerebral Microbleeds. *Journal of Stroke and Cerebrovascular Diseases* 2016;25(11):e214-e5.

45. Yu WL, Leung T, Soo Y, Lee J, Wong KS. Thrombotic thrombocytopenic purpura with concomitant small- and large-vessel thrombosis, atypical posterior reversible encephalopathy syndrome and cerebral microbleeds. *Oxford medical case reports* 2015;2015(2):179-82.

46. Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, et al. A Reversible Posterior Leukoencephalopathy Syndrome. *New England Journal of Medicine* 1996;334(8):494-500.

47. Bhat RA, Wani Z, Baasit S, Khan I. Clinical course, laboratory parameters and outcome of TTP pediatric patients presenting with posterior reversible encephalopathy syndrome. *Renal Failure* 2015;37(6):974-9.

48. Deford CC, Reese JA, Schwartz LH, Perdue JJ, Kremer Hovinga JA, Lämmle B, et al. Multiple major morbidities and increased mortality during long-term follow-up after recovery from thrombotic thrombocytopenic purpura. *Blood* 2013;122(12):2023-9.

49. Howard MA, Duvall D, Terrell DR, Christopher AT, Thomas I, Holloway N, et al. A support group for patients who have recovered from thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS): The six-year experience of the Oklahoma TTP-HUS Study Group. *J Clin Apher* 2003;18(1):16-20.

50. Lewis QF, Lanneau MS, Mathias SD, Terrell DR, Vesely SK, George JN. Long-term deficits in health-related quality of life after recovery from thrombotic thrombocytopenic purpura. *Transfusion* 2009;49(1):118-24.

51. Falter T, Schmitt V, Herold S, Weyer V, von Auer C, Wagner S, et al. Depression and cognitive deficits as long-term consequences of thrombotic thrombocytopenic purpura. *Transfusion* 2017;57(5):1152-62.

52. Riva S, Mancini I, Maino A, Ferrari B, Artoni A, Agosti P, et al. Long-term neuropsychological sequelae, emotional wellbeing and quality of life in patients with acquired thrombotic thrombocytopenic purpura. *Haematologica* 2020;105(7):1957-62.

53. Kennedy AS, Lewis QF, Scott JG, Kremer Hovinga JA, Lämmle B, Terrell DR, et al. Cognitive deficits after recovery from thrombotic thrombocytopenic purpura. *Transfusion* 2009;49(6):1092-101.

54. George JN. The thrombotic thrombocytopenic purpura and hemolytic uremic syndromes: evaluation, management, and long-term outcomes experience of the Oklahoma TTP-HUS Registry, 1989-2007. *Kidney Int Suppl* 2009(112):S52-4.

55. Han B, Page EE, Stewart LM, Deford CC, Scott JG, Schwartz LH, et al. Depression and cognitive impairment following recovery from thrombotic thrombocytopenic purpura. *American Journal of Hematology* 2015;90(8):709-14.

56. Chaturvedi S, Oluwole O, Cataland S, McCrae KR. Post-traumatic stress disorder and depression in survivors of thrombotic thrombocytopenic purpura. *Thrombosis Research* 2017;151:51-6.

57. Scully M, Cataland SR, Peyvandi F, Coppo P, Knöbl P, Kremer Hovinga JA, et al. Caplacizumab Treatment for Acquired Thrombotic Thrombocytopenic Purpura. *New England Journal of Medicine* 2019;380(4):335-46.

58. Peyvandi F, Scully M, Kremer Hovinga JA, Cataland S, Knöbl P, Wu H, et al. Caplacizumab for Acquired Thrombotic Thrombocytopenic Purpura. *New England Journal of Medicine* 2016;374(6):511-22.

59. Völker LA, Kaufeld J, Miesbach W, Brähler S, Reinhardt M, Kühne L, et al. Real-world data confirm the effectiveness of caplacizumab in acquired thrombotic thrombocytopenic purpura. *Blood Advances* 2020;4(13):3085-92.

60. Coppo P, Bubenheim M, Azoulay E, Galicier L, Malot S, Bigé N, et al. A regimen with caplacizumab, immunosuppression, and plasma exchange prevents unfavorable outcomes in immune-mediated TTP. *Blood* 2021;137(6):733-42.

61. Schofield J, Shaw RJ, Lester W, Thomas W, Toh C-H, Dutt T. Intracranial hemorrhage in immune thrombotic thrombocytopenic purpura treated with caplacizumab. *Journal of Thrombosis and Haemostasis* 2021;19(8):1922-5.

62. Terrell DR, Tolma EL, Stewart LM, Shirley EA. Thrombotic thrombocytopenic purpura patients' attitudes toward depression management: A qualitative study. *Health Science Reports* 2019;2(11):e136.

63. The ConNeCT Study: Neurological Complications of TTP. [Internet] 2021 July, [cited 02 February 2022]. Available from: <https://clinicaltrials.gov/ct2/show/NCT04981028>. . 2021.

**Table 1. Studies of acute neurological complications in immune-mediated TTP**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study Information | | | | Neurological symptoms reported at 1st presentation of iTTP, number (%) | | | | | |
| Authors | Year of publication/country | Study design | Study population | Minor neurological symptoms\* | Coma | Seizures | Focal neurological symptoms | Stroke | TIA |
| Page EE et al | 2017/USA | Retrospective | 78 | 21 (27) | 6 (8) | 12 (15) | 31 (40) | 9 (12) | - |
| Scully M et al | 2008/UK | Retrospective | 121 | 25 (21) | 12 (10) | 8 (7) | - | 10 (8) | 18 (15) |
| Bugarin-Estrada E et al | 2018/Mexico | Retrospective | 20 | 13 (65) | 12 (60) | 3 (15) | 10 (50) | - | - |
| Vesely SK et al | 2003/USA | Retrospective | 18 | 4 (22) | 5 (28)† | - | - | - | - |

**Table 1 Legend**

Where number/% is not provided, these symptoms were not reported in the study

Scully 2008 - % is of all cases with neurological symptoms

\*including headache, blurred vision, mild ataxia, and minor mental status changes such as confusion

†this study reported severe neurological presentation overall combining coma, seizure, focal neurological signs and stroke together

**Table 2. Studies of neuroimaging in TTP**

|  |  |  |  |
| --- | --- | --- | --- |
| Author,  year of publication | Study population & sample size | Imaging modality | Summary of findings |
| Alwan F et al,  2020 | Acute TTP with neurology at presentation or severe headache after recovery, n=131 (cTTP n=12; iTTP n=119) | MRI (n=131) | * 56% abnormal MRI, main finding - hyperintense white matter lesions * Imaging significantly more likely to be abnormal with neurological symptoms vs. headaches alone (80% versus 18%, p<0.001) * Abnormal MRI associated with lower median verbal IQ (85 vs. 99, p=0·02) & performance IQ (83 vs. 100, p=0·02) |
| Bhat RA et al,  2020 | Children with acute TTP and PRES, n=7 | MRI | * Posterior reversible encephalopathy lesions (PRES) uncommon in children with TTP * PRES with TTP appears to confer worse prognosis in children 🡪 4/7 did not survive |
| Cataland SR et al, 2011 | iTTP in remission, n=27 | MRI (n=23) | * Diffusion-weighted MRI superior - evidence of ischemia in 39% (9/23) after recovery from TTP * 7/23 small vessel ischaemic changes – majority multiple subcortical white matter lesions; 2/7 large vessel infarctions in addition to microvascular abnormalities * No significant difference in MRI abnormalities between patients within 1 year of last acute episode vs. >1 year since last acute episode * Patients with 1 acute episode of TTP more likely to have MRI abnormalities vs. those with >1 acute episode (62 vs. 13%, p=0.017) |
| Burrus TM et al, 2009 | Episodes of acute TTP, n=47 | CT (n=40)  MRI (n=33) | * Retrospective study from 1997 - 2007 * Abnormalities seen in 25% of CT & 82% of MRI brain scans. MRI brain more sensitive - PRES in 42% of cases, not previously identified on CT * PRES most commonly occurring brain lesion, accounting for ~50% abnormalities seen on CT & MRI brain * Acute cerebral ischaemia & haemorrhage uncommon * Radiological lesions not associated with worse functional outcome |
| Meloni G et al,  2001 | Acute TTP, n=16 | CT (n=13)  MRI (n=3)  Serial imaging | * CT brain normal in patient presenting without neurological features * 13/16 had neurological symptoms at presentation, brain imaging normal in 92% (CT brain, n=10; MRI brain, n=2) |
| Bakshi R et al, 1999 | Acute iTTP, n=12 | CT (n=15)  MRI (n=12)  Serial imaging\* | * 9/12 acute brain lesions at presentation * 3 lesion types: reversible bilateral cerebral oedema (n=7), ischemic stroke (n=3), frank hematoma (n=1) * Patients with infarction or haematoma had unfavourable outcomes * MRI more likely to demonstrate abnormalities - lesions present in 88% acute TTP patients vs. abnormal CT findings in 45% * Serial imaging - 5/6 complete resolution of previously abnormal scan findings, 1/6 partial resolution |
| Fiorani L et al, 1995 | Acute TTP and TTP in remission, n=5 | MRI (n=5)  SPECT† scan (n=2) | * All patients presented with neurological symptoms * 3/5 MRI scans within 7-15 days of recovery, 2/5 MRI 2 & 9 years after recovery: all scans normal * 2/5 patients SPECT scans showed reduced cerebral blood flow in acute phase of disease |

**Table 2 Legend**

Where TTP is not defined as cTTP or iTTP, this information was not provided in the study

\*Up to 12 weeks after acute imaging performed

†SPECT: single-photon emission computed tomography

**Table 3. Studies of long-term neurological complications of TTP**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Authors | Study population & sample size | Study design | Assessment tools | Summary of conclusions |
| Lewis QF  et al, 2008 | TTP with no relapse within 1 year, no other major medical disorder, n=118 | Observational, telephone and self-administered questionnaires | SF-36 | * For the eight domains of physical and mental health, TTP patients found to be significantly worse than US population, suggesting patients with TTP have worse functioning and well‐being * Some improved scores among patients with initial assessments later after recovery * No significant improvement for any domains when serial assessments on individual patients >5 years after recovery analysed |
| Kennedy AS et al, 2009 | TTP, ADAMTS13 activity <10% at diagnosis, n=24 | Observational | .. | * TTP patients performed significantly worse on 4 of 11 cognitive domains, including complex attention and concentration skills, information processing speed, rapid language generation, and rote memorization, compared to US norm (p < 0.05). |
| Cataland S et al, 2010 | iTTP, n=27 | Observational | Groton maze learning test,  SF-36 | * 17/27 (63%) patients demonstrated neurocognitive impairment, particularly in tests of visual learning, attention and psychomotor function * Health‐related quality of life scores significantly lower than age and gender matched US norms for both mental and physical component score |
| Deford CC et al, 2013 | TTP - ADAMTS13 activity <10% at diagnosis, n=49 | Observational, Oklahoma TTP-HUS registry | PHQ-8 | * 37/46 surviving patients evaluated * 19% scores suggested major depression, significantly greater than expected value (6%; P = 0.005) * No significant difference in severity of TTP for 7 patients with scores suggesting major depression versus other 30 patients |
| Han B  et al, 2015 | TTP – ADAMTS13 activity <10% at diagnosis, n=52 | Observational, Oklahoma TTP-HUS registry | BDI-II +/- psychiatric interview,  MoCA, RBANS | * Cognitive ability evaluated in 33 patients by MoCA and RBANS: Both tests detected significant cognitive impairment in TTP patients * 59% patients screened positive for depression at least once; in 15 (29%), results suggestive of severe depression |
| Falter T  et al, 2017 | TTP, n=104 | Observational cohort study | IDS-SR,  FLei | * 71 (68%) TTP patients suffered from depression * Cognitive performance significantly worse for TTP patients compared to healthy cohorts * No correlation found between prevalence of depression and cognitive deficits and number/severity of acute episodes * Impairment of mental performance correlated with severity of depression (R=0.779) |
| Chaturvedi S et al, 2017 | TTP, n=236 | Cross-sectional, online survey tool | PCL-5, BDI-II | * BDI-II scores indicated at least mild depressive symptoms in 80.8% patients (15.8%, 28.2%, and 36.8% with mild, moderate and severe symptoms, respectively) * 35.1% positive screen for PTSD (PCL-5 score ≥ 38) |
| Riva S  et al, 2020 | iTTP – at least 3 months after acute event, n=35 | Cross-sectional | Psychologist assessment, HAM-A, HAM-D, SF-36 | * TTP patients demonstrated lower scores than Italian general population for direct, indirect and deferred memory * Anxiety and depression found in 20% and 43% of TTP patients, respectively * Health-related quality of life lower than the general population, mental domains impacted more than physical domains (mean difference 58.43, 95% confidence interval: 71.49–45.37) |
| Alwan F  et al, 2020 | TTP, n=131 completed neuropsychological assessments | Observational, UK TTP Registry | NART, WAIS-II Verbal/Performance Scale IQ, Hospital Anxiety and Depression Scale, PHQ-9, 7-item Generalized Anxiety Disorder Scale | * 35/131 (35%) reported persistent cognitive symptoms in remission * 65% (n=19/29) TTP patients reported depression, 55% (n=16/29) reported anxiety regardless of neurological involvement at diagnosis; both conditions more common in iTTP compared to cTTP (58% vs 8%, p=0.003 and 48% vs 8% respectively) * Impairment of executive function most common finding in TTP remission, as well as memory and intellectual impairment |