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Long-term neuropsychological sequelae, emotional wellbeing and quality of life in patients with acquired thrombotic thrombocytopenic purpura

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ABSTRACT

Neurological symptoms related to microthrombosis are the hallmark of acute manifestations of acquired thrombotic thrombocytopenic purpura. Despite the achievement of hematological remission, patients may report persisting neurological impairment that affects their quality of life. To assess the long-term neuropsychological consequences of acute thrombotic thrombocytopenic purpura, we recruited 35 acquired thrombotic thrombocytopenic purpura patients (77% females, median age at onset 41 years, interquartile range 35-48) regularly followed at our out-patient clinic of thrombotic microangiopathies in Milan (Italy) from December 2015 to October 2016. Patients underwent a psychological evaluation of memory and attentional functions, emotional wellbeing and health-related quality of life at least 3 months after their last acute thrombotic thrombocytopenic purpura event (median 36 months, interquartile range 17-54). During the psychological consultation, 17 patients (49%) referred persisting subjective neurological impairment in the frame of a remission phase, with at least one symptom as disorientation, loss of concentration, dizziness, lack of balance, headache and diplopia. Neuropsychological assessment revealed lower scores than the Italian general population pertaining to direct, indirect and deferred memory. A higher degree of impairment of memory domains was found in patients with neurological involvement at the time of presentation of the first acute thrombotic thrombocytopenic purpura episode. Anxiety and depression were detected in 7 (20%) and 15 (43%) patients, respectively. Health-related quality of life was lower than the Italian general population, with mental domains more impacted than physical domains (mean difference 58.43, 95% confidence interval [-71.49, -45.37]). Our study demonstrates compromised memory and attention functions, persisting anxiety/depression symptoms and a generally reduced quality of life in patients surviving from acute acquired thrombotic thrombocytopenic purpura. New clinical strategies should be considered to improve these symptoms.

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a rare multisystem microangiopathy with fluctuating signs and symptoms. Its mortality rate could reach 90% when patients were left untreated, but it is reduced to 10% if patients are properly treated in the first 24 hours after diagnosis. Recovery is usually complete, but with a risk of relapse and the uncommon occurrence of persistent neurologic, cardiac and renal abnormalities.[1] After recovery, despite of normal physical examination and laboratory data, many patients complain difficulties with memory, headache, loss of concentration and endurance, as expressed at patient support group meetings. Some attempts to quantify those neurological deficits in acquired TTP patients have been made in the context of small observational studies, but without taking into account a whole assessment of cognitive, emotional and health-related quality of life (HrQoL) dimensions.[2-3] Cognitive domains required for complex attention, concentration skills and high level memory functions may be involved in patients with TTP due to diffuse microvascular subcortical lesions, similarly to neurologically normal individuals with untreated hypertension, sickle cell disease and multi-infarct dementia. Two widely accepted measures to evaluate HrQoL are the Short-Form 36 (SF-36)[4] and the EuroQol 5D (EQ-5D).[5] They are self-reported scales providing a numerical score to identify the level of perceived health status. For their generic nature, the SF-36 and the EQ-5D are frequently used in chronic conditions (e.g., haemophilia) and are applicable to many diseases.

With this background and gaps of knowledge, we set up a study in order to investigate persistent cognitive abnormalities, emotional wellbeing and quality of life in patients who had recovered from an acute episode of acquired TTP. We also analyzed whether or not the presence of neurological involvement during the acute phase of TTP or severe ADAMTS13 deficiency during disease remission were related to persistent neurocognitive defects. Finally, we investigated whether there was an association between the emotional status of the patients and their quality of life.

METHODS

Patients

We performed a cross-sectional study of 35 patients with acquired TTP regularly followed at our out-patient clinic of thrombotic microangiopathies in Milan (Italy). Patients were enrolled at least three months after their last acute TTP event (median time of 36 months, interquartile range 17-54) from December 2015 to October 2016, when they underwent a comprehensive neuropsychological evaluation including memory and attentional functions, emotional wellbeing and HrQoL. Demographic and clinical variables were recorded, including age, sex, ethnicity, job status, level of education, clinical and biochemical data at the time of acute TTP (neurological involvement, platelet count and haemoglobin level at presentation, number of plasma exchange procedures required to attain remission), and plasma ADAMTS13 activity levels at the time of the neuropsychological assessment (± 3 months). Enrolment criteria are described in the Online Supplementary Appendix (Supplementary Table S1).

Written informed consent was obtained from all subjects with approval of the Ethics Committee of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, in accordance with the Declaration of Helsinki.

Neurocognitive, emotional and HrQoL assessments

Neurocognitive and psychological assessments were administered by a board-certified psychologist in standardized fashion in the frame of a single assessment session, which required approximately 1 hour to be completed, and included a test battery measuring two major cognitive domains, memory and attention[6-8], the Hamilton Depression (HAM-D)[9] and Anxiety (HAM-A)[10] rating scales for emotional wellbeing, and the Short-Form (SF) 36[4] form for HrQoL (Online Supplementary Appendix, Supplementary Table S2).

Statistical analysis

Descriptive statistics were used for demographic, clinical and laboratory characteristics. Categorical variables were expressed as counts and percentages, continuous variables as means or medians with standard deviation (SD) or interquartile ranges (IQR). With regards to neuropsychological and HrQoL analyses, each subject's raw score on each test was converted to a standardized score based on normative data generated from the value of the normal population according to the subject's age and education level, as appropriate.[11-15] Standardized scores of TTP patients were then compared with norm-referenced data from the Italian population[11-15] by calculating the difference of means with 95% confidence intervals (CI) using unpaired and paired t-tests. Similarly, difference of means with 95%CI from unpaired and paired t-tests were used to compare neurocognitive assessment results in acquired TTP patients with and without neurological manifestations during the first acute episode of TTP, and with and without reduced ADAMTS13 activity during disease remission, close to the neuropsychological evaluation. For this analysis, an ADAMTS13 activity cut-off of 45% was used (i.e., the lower limit of the normality range in our ADAMTS13 activity assays). With regards to HrQoL, a standardized score of 50 was considered the cut-off for an acceptable quality of life.[15-16] Finally, non-parametric correlation analyses were performed to evaluate the relationship between the results of emotional wellbeing tests and those of neurocognitive assessments or aggregated HrQoL scales.

Statistical analyses were performed by SPSS, release 25.0 (IBM Corp., Armonk, NY, USA), and GraphPad Prism, version 7.03 (GraphPad Software, La Jolla California USA).

RESULTS

Between December 2015 and October 2016, forty-one acquired TTP patients were approached for participating in the study during a follow-up visit at our out-patient clinic of thrombotic microangiopathy. Of them, one patient refused to participate and one patient was excluded owing to a pre-existing psychiatric disease. Four were not constantly attended at our center, and therefore they were excluded from the study. Thus, 35 patients were included in the study and underwent psychological tests and neurocognitive examinations (Supplementary File Online). Patient characteristics are reported in Table 1. All but one patient were Caucasian, with a female to male ratio of about 3:1 and a median age at TTP onset of 41 years (IQR 35-48). At the time of neuropsychological evaluation, 10 (29%) of 35 patients had suffered from recurrent TTP bouts. Twenty-two patients (63%) presented with neurological signs and symptoms at presentation of the first acute TTP episode (including coma [n=2], focal neurological signs [n=12], personality changes [n=2], transient ischemic attack [n=4], seizures [n=1], stroke [n=3]). During the psychological consultation, 17 (49%) patients reported persisting subjective neurological impairment in the remission phase, with at least one symptom as disorientation, loss of concentration, dizziness, lack of balance (unable to control and maintain the body position all the time) headache, and diplopia.

Results of neurocognitive assessment

At the digit span test, 25 (71%) and 23 (66%) patients had a scoring lower than the mean of the general population in direct (mean difference -1.26, 95%CI [-1.64, -0.87]) and backward (mean difference -1.49, 95%CI [-2.02, -0.96]) memory, respectively (Table 2). Similarly, lower scores in TTP patients were observed in the Rey List tests for both direct (mean difference -5.87, 95%CI [-8.57, -3.17]) and deferred memory (mean difference -1.67, 95%CI [-2.32, -1.02]).

With regards to the attention domain, TTP patients were slower in performing the trail making B test (sustained and divided attention) in comparison with the general population (mean difference 65.09 seconds, 95%CI [47.23, 82.94]). Conversely, patients were slightly faster in performing the trail making A test, which measures focused attention (mean difference -10.63 seconds, 95%CI [-15.81, -5.44]).

When we analyzed scores of neurocognitive assessments in patients with and without neurological signs and symptoms at presentation of the first acute TTP episode, we observed a higher degree of impairment in the memory domains of the first group of patients in 3 out of 4 memory tests (Digit span [direct]: mean difference -0.78, 95%CI [-1.54, -0.02]; Digit span [backward]: mean difference -0.90, 95%CI [-1.96, 0.17]; Rey word list [deferred]: mean difference -1.39, 95%CI [-2.65, -0.13] (Table 3).

No differences in neuropsychological assessments were found between patients with ADAMTS13 activity levels during remission below and above 45% (Table 4).

Results of emotional assessment

TTP patients presented a mean level of anxiety with the HAM-A of 9.6 (SD=8.1) and a mean level of depression with the HAM-D of 7.4 (SD=5.7). The presence of clinical anxiety (HAM-A score > 13) was detected in 7 (20%) of interviewed patients, while the presence of clinical depression (HAM-D score > 7) was present in 15 (43%) of them. All 7 patients with clinical anxiety presented concomitant clinical depression. Five (14%) patients showed a severe anxiety (HAM-A score > 24) and five (14%) a medium level of depression (HAM-D score > 18). No patients presented severe levels of depression (HAM-D score > 24).

Among the type of disturbances, we found that the most impaired domains in HAM-D were “work activities” (N=10, 77%), “depressed mood” (N=8, 60%) and “early insomnia” (N=4, 27%) while in HAM-A there were “intellectual symptoms” (i.e., difficulty in concentration and poor memory) (N=6 82%) and “tension” (N=4, 54%).

At correlation analysis, better wellbeing was associated with better memory function (the sign of the correlation coefficient is negative because of the opposite interpretation scale of the two measurements): HAM-A test versus: digit span direct Spearman rho -0.472, p-value 0.004; digit span backward Spearman rho -0.597, p-value <0.001, Rey list direct Spearman rho 0.310, p-value 0.075; Rey list recall: Spearman rho -0.432, p-value 0.011; HAM-D test versus: digit span direct Spearman rho -0.474, p-value 0.004; digit span backward Spearman rho -0.594, p-value <0.001,

Rey list direct Spearman rho 0.357, p-value 0.038; Rey list recall: Spearman rho -0.499, p-value 0.003.

Results of HrQoL assessment

Table 5 displays the mean scores of the SF-36 assessments for each of the eight domains (by physical and mental components: physical activity (PA), role physically (RP), bodily pain (BP), general health (GH), vitality (VI), social functioning (SF), role emotional (ER) and mental health (MH). Acquired TTP patients showed lower normalized scores than the Italian reference sample[14] in all scales but physical activity. With regard to the physical components, the most impacted area was the physical role, with a mean score of 57 (median 55, range 40-85) and 11 patients (31%) with scores below 50. With regard to the mental components, emotional role was the most compromised, with a mean score of 43 (median 43, range 30-56) and 22 patients (63%) with scores below 50. Overall, the mental dimension was more affected than the physical dimension, with the mental component score MCS-36 (equivalent to the sum of MH, ER, SF and VI scores) lower than the physical component score PCS-36 (equivalent to the sum of PA, RP, BP and GH scores) by almost 60 points (mean difference -58.43, 95% CI [-71.49, -45.37]) and 15 (43% of patients pertaining to the MCS-36) versus 4 (11% of patients pertaining to the PCS-36) patients with scores below 50, the commonly accepted cut-off for an acceptable quality of life.[15,16]

Finally, at correlation analysis, the better was the mental component score of the HrQoL survey, the better were the results of emotional wellbeing assessments, especially the anxiety evaluation (MCS-36 versus Hamilton Anxiety test: Spearman rho -0.358, p-value 0.035; MCS-36 versus Hamilton Depression test: Spearman rho -0.316, p-value 0.064).

DISCUSSION

Neurological signs and symptoms of acute TTP are mainly transient, brief and resolve with remission of the acute phase. Our study demonstrates persisting neurological, neuropsychological, emotional and HrQoL impairments in TTP patients even years after the acute phase.

During the remission phase, TTP patients showed a significant impairment in memory domains (direct, backward and deferred memory) when compared with the general population. This memory impairment was positively associated with the presence of neurological symptoms during the acute phase of the disease, as shown by the comparison between patients with and without neurological involvement during the first acute TTP event. Attention domains were also affected, but they were unrelated to neurological involvement during the acute phase. Our results are in line with previous findings by Kennedy et al. in 24 acquired TTP patients from the Oklahoma Registry, who performed significantly worse than the US reference population in both attention and memory functions.[3,17] Conversely, at variance with our results, previous studies did not report an association of neurocognitive impairment with the occurrence of neurological manifestations at the time of the acute TTP event,[3,18] although a trend towards a worse mental performance was detected in German patients with neurological symptoms compared with patients with no neurological symptoms (median of FLei mental performance score [IQR]: 45 [IQR 15-65] versus 31 [IQR 13-40], Mann-Whitney U test p-value 0.193).[18] It is worth-noticing that the prevalence of relapsing TTP cases were higher in patients with than without neurological symptoms during the first acute event (41% versus 8%). Unfortunately, the low sample size did not allow us to discriminate the effects of these two factors.

Beside cognitive problems, we detected clinical anxiety and depression in 20% and 43% of interviewed patients. An even higher prevalence of depression symptoms in acquired TTP patients was reported in two US and one German cohorts (59%,[17] 81%,[19] and 73%,[18] respectively), which included also cases of major depression (29%,[18] 37%,[19] and 14%[18]). However, a pre-existing diagnosis of depressive disorder was not an exclusion criterion in these studies, which may partly explain the differences in the observed prevalence. In our study, the results of anxiety and depression tests were negatively correlated with scores of neurocognitive assessments, indicating

that patients with symptoms of psychologic distress also had more pronounced cognitive defects. This is consistent with the findings of Falter and colleagues[18], who reported a strong correlation between an impaired mental performance and the severity of depression in 84 TTP patients.

It is interesting to compare our results with other cardiovascular and neurovascular diseases. High percentage of cognitive impairment were also found in patients after acute coronary syndrome (16% of patients)[20], stroke (one-third of the sample examined),[21] and after TIA (more than a third of patients).[22] After TIA, also depressive symptoms were found as prevalent as 34%.[23] However, there are important differences between these studies and ours. First, the evaluation of cognitive decline and depression were generally made during the acute phase and in patients older than ours.[23] Second, the literature mainly highlights a major deterioration at the level of functional abilities in daily life activities, especially in stroke patients. Finally, different tests were performed and different cognitive domains (e.g., language) evaluated, making any comparison difficult. We also found an overall impaired quality of life compared with the general population. In the HrQoL domains, mental components were more impaired than physical components, suggesting that the condition determines a considerable emotional burden, probably related to its course of intermittent relapse and remission phases. Indeed, the HrQoL mental domain was negatively affected by the presence of clinical anxiety and depression in our patients. Our findings are consistent with those of Lewis et al.[2] and Cataland et al.[24] although they reported a greater impact of acquired TTP on the physical component of the HrQoL,[2] and on both the mental and the physical component.[24]

We believe that our findings have clinical relevance for the management of TTP patients. Clinicians should be aware of the association between neurological manifestations during the acute TTP episodes and long-term impaired neuropsychological abilities. They should put attention on signs and symptoms of neurological impairment during the remission phase and consider early signs of anxiety and depression in order to improve the quality of life of TTP patients.

Our study has limitations. First, the neurocognitive and emotional status of the patients and their quality of life before their first episode of TTP was not objectively evaluated. However, patients did perceive and referred at the time of the psychological consultation a worsening of their conditions after TTP diagnosis. Second, the evaluation of neurological and cognitive functions abnormalities

observed in TTP patients in the remission phase and far from the clinical manifestations of acute TTP were not supported by instrumental neuro-functional analysis such as functional magnetic resonance imaging, which might be needed to assess the aforementioned alterations at the organic level. Third, we included patients with a history of a single acute TTP event but also patients with relapsing TTP, rendering our study population heterogeneous (in order to exclude potential comorbidities only primary TTP patients should be evaluated). However, the occurrence of multiple TTP episodes was never found to be associated with neurocognitive, emotional or HrQoL assessments in any previous study.[3,17,18,24] Fourth, the tests performed to evaluate clinical anxiety and depression, despite being well-validated tools, can only be suggestive of a psychiatric diagnosis, which indeed can only be confirmed by a proper psychiatric interview. Fifth, despite the relatively large sample size for a rare disease, numbers in some analyses are small, leading to statistical uncertainty and wide confidence intervals. This is a problem of any study in the field of rare diseases, and stimulate more efforts to promote collaboration between centers. Finally, the design of our study is cross-sectional and, thus cannot provide risk estimates and data about predictive factors. On the other hand, as far as we know, our study is the most comprehensive investigation on TTP patients, including clinical, cognitive, emotional and HrQoL assessment.

In conclusion, we demonstrated that, despite successful treatment with plasma exchange and immunosuppressive therapy in the acute stage of the disease, patients with TTP suffer from long-term neurological sequelae even years after the acute phase. TTP patients with neurological involvement at the first acute episode seem to be at higher risk of developing memory dysfunction. Furthermore, TTP patients have increased levels of anxiety and depression, which negatively affect their quality of life. A faster improvement of the acute state of the disease by novel drugs might have a role in this process and further studies are required to solve this question.

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TABLES

Table 1. Demographic and clinical characteristics of 35 TTP patients included in the study.

Clinical and laboratory data pertain the first acute TTP episode.

Characteristics	TTP patients (n=35)
Demographic data	
Male, n (%)	8 (23)
Caucasian, n (%)	34 (97)
Age at TTP onset, years, median (IQR)	41 (35-48)
Age at neuropsychological evaluation, years, median (IQR)*	45 (39-55)
Mean school level, years	13
Job status – workers, n (%)	30 (77)
Clinical characteristics at the first acute TTP episode	
Neurological involvement, n (%)	22 (63)
Platelet count, x 109/l, median (IQR)†	13 (8-27)
Hemoglobin, g/dl, median (IQR)†	7.8 (6.8-10.0)
Number of PEX to attain remission, median (IQR)†	11 (6-20)
Laboratory parameters close to the neuropsychological evaluation†	
Platelet count, x 10^9/l, median (IQR)	251 (212-297)
Hemoglobin, g/dl, median (IQR)	13.4 (12.8-14.3)
ADAMTS13 activity close to neuropsychological evaluation†	
Normal (45-138%), n (%)	16 (47)
Moderately reduced (10-45%), n (%)	12 (35)
Severely reduced (<10%), n (%)	6 (18)

At the time of neuropsychological evaluation, 10 (29%) of 35 patients had suffered from recurrent TTP bouts.*Neuropsychological evaluation was performed at a median time of 36 months (IQR 17-54) from the last acute TTP event.

†Available in 33 (platelet count, hemoglobin and number of PEX to remission at first acute TTP episode), 34 (ADAMTS13 activity close to neuropsychological evaluation) and 31 subjects (platelet count and hemoglobin close to the neuropsychological evaluation).

Abbreviations: IQR, interquartile range; PEX, plasma exchange; TTP, thrombotic thrombocytopenic purpura.

Table 2. Descriptive statistics of neuropsychological tests in acquired TTP patients and mean values of the Italian general population.

	Test	TTP patients Mean (SD)	General population Mean	Mean difference (95%CI)
Memory				
	Digit span (direct)	5.74 (1.12)	7.00	-1.26 (-1.64, -0.87)
	Digit span (backword)	4.51 (1.54)	6.00	-1.49 (-2.02, -0.96)
	Rey word list (direct)*	26.37 (7.74)	32.20	-5.87 (-8.57, -3.17)
	Rey word list (deferred)*	4.03 (1.86)	5.70	-1.67 (-2.32, -1.02)
Attention				
	Trail making A, seconds	34.37 (15.1)	45.00	-10.63 (-15.81, -5.44)
	Trail making B, seconds	214.09 (51.99)	149.00	65.09 (47.23, 82.94)

In memory tests a higher score indicates a better performance, in attention tests a lower score indicates a better performance.

At the time of neuropsychological evaluation, 10 (29%) of 35 patients had suffered from recurrent TTP bouts.*Available in 34 TTP patients.

Abbreviations: CI, confidence interval; SD, standard deviation; TTP, thrombotic thrombocytopenic purpura.

Table 3. Descriptive statistics of neuropsychological tests in acquired TTP patients with and without neurological manifestations at onset of the first acute TTP event.

Test		Neurological involvement at first acute TTP event		Mean difference (95%CI)
		Present (n=22)	Absent (n=13)	
Memory, mean (SD)				
	Digit span (direct)	5.45 (1.14)	6.23 (0.93)	-0.78 (-1.54, -0.02)
	Digit span (backword)	4.18 (1.59)	5.08 (1.32)	-0.90 (-1.96, 0.17)
	Rey word list (direct)*	25.36 (7.73)	27.89 (7.80)	-2.54 (-8.11, 3.04)
	Rey word list (deferred)*	3.50 (1.92)	4.89 (1.44)	-1.39 (-2.65, -0.13)
Attention, mean (SD)				
	Trail making A, seconds	37.18 (16.26)	29.62 (12.00)	7.57 (-3.01, 18.14)
	Trail making B, seconds	207.82 (49.91)	224.69 (55.71)	-16.87 (-53.95, 20.20)

In memory tests a lower score indicates a worse performance, in attention tests a higher score indicates a better performance.

At the time of neuropsychological evaluation, 9 out of 22 (41%) and 1 out of 13 (8%) patients with and without neurological involvement at the first acute TTP event had suffered from recurrent TTP bouts, respectively.

*Available in 34 TTP patients.

Abbreviations: CI, confidence interval; SD, standard deviation; TTP, thrombotic thrombocytopenic purpura.

Table 4. Descriptive statistics of neuropsychological tests in acquired TTP patients with and without ADAMTS13 deficiency next to the psychological evaluation.

Test		ADAMTS13 activity during remission		Mean difference (95%CI)
		<45% (n=18)	≥45% (n=16)	
Memory, mean (SD)				
	Digit span (direct)	6.06 (1.00)	5.50 (1.16)	0.56 (-0.20, 1.31)
	Digit span (backward)	4.61 (1.79)	4.50 (1.27)	0.11 (-0.98, 1.21)
	Rey word list (direct)*	27.22 (7.72)	26.09 (7.65)	1.13 (-4.33, 6.59)
	Rey word list (deferred)*	4.44 (1.67)	3.73 (2.02)	0.72 (-0.59, 2.02)
Attention, mean (SD)				
	Trail making A, seconds	32.06 (13.39)	36.94 (17.32)	-4.88 (-15.62, 5.87)
	Trail making B, seconds	209.89 (58.93)	220.94 (45.19)	-11.05 (-48.09, 26.00)

In memory tests a lower score indicates a worse performance, in attention tests a higher score indicates a better performance.

At the time of neuropsychological evaluation, 5 out of 18 (28%) and 5 out of 16 (31%) patients with and without ADAMTS13 deficiency next to the visit had suffered from recurrent TTP bouts, respectively.

*Available in 34 TTP patients.

Abbreviations: CI, confidence interval; SD, standard deviation.

Table 5. Descriptive statistics of HRQoL components in acquired TTP patients and in Italian reference individuals.

Test		TTP patients (n=35)		General population (n=203
		mean (SD)	N with score<50 (%)	mean (SD)
Physical domain				
	Physical activity	81.40 (15.37)	2 (6)	84.46 (23.18)
	Limitation physical role	56.77 (13.04)	11 (31)	78.21 (35.93)
	Pain	62.20 (13.92)	5 (14)	73.67 (27.65)
	General health	59.91 (11.54)	5 (14)	65.22 (22.18)
	PCS-36	260.29 (44.63)	4 (11)*	NA
Mental domain				
	Vitality	52.46 (12.85)	13 (37)	61.89 (20.69)
	Social activity	54.26 (8.60)	7 (20)	77.43 (23.34)
	Limitation emotional role	42.69 (8.76)	22 (63)	76.16 (37.25)
	Mental health	52.46 (5.45)	4 (11)	66.59 (20.89)
	MCS-36	201.86 (23.84)	15 (43)*	NA

At the time of neuropsychological evaluation, 10 (29%) of 35 patients had suffered from recurrent TTP bouts.

*Being PCS-36 and MCS-36 the weighted sum of the original scales of the SF-36, this number indicates patients with a score below 200.

Abbreviations: CI, confidence interval; NA, not available; SD, standard deviation; MCS-36, mental component summary (MCS) of the Short Form (36) Health Status Questionnaire (SF36); PCS-36, physical

component summary (PCS) of the Short Form (36) Health Status Questionnaire (SF36); TTP, thrombotic thrombocytopenic purpura.

APPENDIX

Long-term neuropsychological sequelae, emotional wellbeing and quality of life in patients with acquired thrombotic thrombocytopenic purpura

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SUPPLEMENTARY DATA

Table S1. Enrolment criteria.

	Patient characteristics
Inclusion criteria	(a) diagnosis of acquired TTP*
	(b) 18 years of age or older at the time of enrolment

	(c) adequate Italian language for the purpose of a valid psychometric testing
Exclusion criteria	(a) presence of severe neurological or psychiatric diseases before the onset of TTP
	(b) drug or alcohol-abuse possibly impacting on quality of life and neuropsychological tests

* Acquired TTP was defined by at least one episode of thrombocytopenia and microangiopathic hemolytic anemia, with exclusion of alternative explanations,[1] and by evidence of severe ADAMTS13 deficiency (i.e., < 10% activity) in at least one plasma sample collected during the acute episode or disease remission, and/or by normalization of ADAMTS13 activity levels in the remission phase. ADAMTS13 activity was measured using a modified FRETS-VWF73 or CBA assay.[2]

Table S2. Psychological measures.

Assessment	Goal	Test name	Administration	Scoring
Cognitive measure	Short memory, direct memory	Digit span[3]	List of numbers that one has to repeat in correct order immediately after presentation.	Cognitive tests are standardized measures with population-based normative data that allow the examiner to evaluate a patient's performance with an appropriate group of reference (e.g., those of the same age group). Normative data are generally gathered on typically healthy subjects who are free from diagnosed cognitive dysfunctions, mental illness, disability or neurological disorders that could affect cognitive performance (all these variables cannot be controlled using a generic control group). Data are typically gathered on samples that reflect the broad demographic characteristics of the country of reference including factors such as age, and educational status.[6]
	Short memory; backward memory	Digit span backward[3]	List of numbers that one has to repeat in reverse order immediately after presentation.	
	Immediate memory; deferred memory	Word Rey List (direct and indirect)[4]	Word-list memory task in which 15 unrelated words are presented orally over three consecutive learning trials: the participant is asked to recall as many words as possible, after each presentation (direct score) and after 15 minutes (recall score).	
	Sustained attention, focused attention	Trail Making Test A[5]	Patient is instructed to connect a set of 25 dots of numbers as fast as possible while still maintaining accuracy.	Each subject's raw score on each test was converted to a standardized score based on normative data generated from the value of the normal population according to the subject's age and education level, as appropriate. Standardized scores of TTP patients were then compared with norm referenced data from the Italian
	Sustained attention, divided	Trail Making Test B[5]	Patient is instructed to connect a set of numbers and letters as fast as possible while still maintaining	
Emotional wellbeing	Anxiety	Hamilton Anxiety Rating Scale[10]	Psychologist-driven interview consisting of 14 items, each defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety).	Each item is scored on a scale of 0 (not present) to 4 (severe), where ≤ 13 indicates absence of the disorder, 14-17 mild severity, 18-24 moderate severity and ≥ 25 severe anxiety.[10]
	Depression	Hamilton Depression Rating Scale[11]	Psychologist-driven interview consisting of 17 items, each defined by a series of symptoms, and measures associated with depression (e.g. insomnia, hyperphagia).	The score varies from ≤ 7 (absence of depression), 8-17 (mild depression), 18-24 (medium depression) and ≥ 25 (severe depression).[11]
Health-related quality of life (HrQoL)	HrQoL	SF-36[12,13]	Self-report scale evaluating 8 dimensions: physical activity (PA), role physically (RP), bodily pain (BP), general health (GH), vitality (VI), social functioning (SF), role emotional (ER) and mental health (MH).	Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight (min-max: 0-100). To aid interpretation, norm-based scoring has been introduced for the SF-36, setting the general mean at 50 and the standard deviation (SD) at 10 for all scales, with higher scores indicating better health (i.e., a score of zero is equivalent to maximum disability and a score of 100 is equivalent to the best health status perceived).[14] Each subject's raw score on each test was converted to a standardized score based on normative data generated from the value of the normal population according to the subject's age and education level, as appropriate.[14, 15] Standardized scores of TTP patients were compared with norm referenced data from the Italian population.[15]

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