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Thrombotic thrombocytopenic purpura: prospective neurologic, neuroimaging and neurophysiologic evaluation

Giovanna Meloni, Anna Proia, Giovanni Antonini,* Carlo De Lena,* Vito Guerrisi, Saveria Capria, Silvia Maria Trisolini, Giancarlo Ferrazza, Giulio Sideri,*Franco Mandelli

Ematologia, Dipartimento di Biotecnologie Cellulari ed Ematologia, *Dipartimento di Scienze Neurologiche, University "La Sapienza", Roma, Italy

Correspondence: Giovanna Meloni, MD, Dipartimento di Biotecnologie Cellulari ed Ematologia, University "La Sapienza", via Benevento 6, 00161, Roma, Italy. Phone: international +39.06857951. Fax: international +39.06.85795293. E-mail: meloni@bce.med.uniroma1.it

Background and Objectives. Neurologic symptoms are present in 60% of patients with thrombotic thrombocytopenic purpura (TTP) on initial examination and ultimately develop in about 90% of cases during the course of the disease. Despite central nervous system involvement being frequent, abnormalities in the brain of patients with TTP are infrequent on neuroimaging (CT/MRI) and neurophysiologic (EEG) evaluation, often reversible and mainly limited to symptomatic stages of the disease. The aim of our study was to establish the value of a complete neurologic screening as part of the work up of TTP.

Design and Methods. We prospectively evaluated 16 TTP patients, performing serial neurologic, neuroimaging and EEG examinations, independently of the presence of an objective central nervous system involvement.

Results. Our study shows that a complete neurologic evaluation is of modest help in improving the diagnosis of TTP, but may be useful for the neurologic management.

Interpretation and Conclusions. Accurate neuroimaging and, especially, EEG evaluation and monitoring allowed us to identify patients who could benefit from anticonvulsive therapy, avoiding the unnecessary administration of the latter. The prognostic utility of complete neurologic screening in TTP remains to be conclusively demonstrated in larger prospective neurologic studies.

Key words: thrombotic thrombocytopenic purpura, neurologic involvement, neuroimaging, EEG.

Thrombotic thrombocytopenic purpura (TTP) is an uncommon multisystem vasculopathy with fluctuating signs and symptoms. The classic pentad of TTP - Coombs' negative microangiopathic schistocytic hemolytic anemia, consumptive thrombocytopenia causing severe hemorrhagic diathesis, fluctuating neurologic symptoms, renal impairment and fever - is recorded in only about 40% of patients, while the triad of anemia, thrombocytopenia and bizarre neurologic abnormalities can be observed in as many as 75% of patients.[1-3]

TTP is characterized by widespread platelet thrombi in arterioles and capillaries. Both endothelial-cell injury and unusually large multimers of von Willebrand factor occur in this condition. These intravascular multimers are capable of agglutinating circulating platelets under high shear stress. Non-familial TTP is due to an inhibitor of von Willebrand factor-cleaving protease, whereas the familial form seems to be caused by a constitutional deficiency of the protease.[3-6]

Prior to the systematic use of plasma infusion and plasma exchange, TTP was associated with a mortality rate of 95%. During the last two decades, various reports have documented the efficacy of plasma exchange and TTP has become a curable disease with a response rate of about 80%.[3,6,7]

Neurologic symptoms, generally attributed to altered microvascular hemodynamics and concomitant metabolic derangements, are present in 60% of patients on initial examination and ultimately develop in about 90% of patients. Focal seizures and generalized convulsions are common, while waxing and waning neurologic deficits, including encephalopathy and altered mental status, can occur in a minority of patients.[8-10]

Despite the frequent involvement of the nervous

system, abnormalities on brain computed tomography (CT) scan, magnetic resonance imaging (MRI) and electroencephalogram (EEG) are infrequent, often reversible and mainly limited to symptomatic stages of the disease.[10-12] The true usefulness of neuroimaging and neurophysiologic evaluations in the context of TTP has, to our knowledge, not been adequately investigated. In an attempt to define this problem better, a parallel neurologic, neuroimaging and electroencephalographic prospective study was performed in patients with a diagnosis of TTP.

Design and Methods

Between December 1996 and December 2000 we performed prospective neurological evaluations in a series of patients with TTP admitted to our institution. The diagnosis of TTP required a Coombs' negative microangiopathic schistocytic hemolytic anemia, consumptive thrombocytopenia and multiorgan dysfunction without other causes. To investigate the pathogenetic mechanism, an accurate serologic screening for antibody, infection and cancer markers was carried out in all cases. All patients were treated with therapeutic plasmapheresis in addition to fresh frozen plasma infusion, glucocorticoids and antiplatelet agents. Independently of the presence of central nervous system involvement, neurologic, neuroimaging and EEG evaluations were performed serially.

Clinical and neurologic examinations were carried out daily until complete remission of central nervous system involvement.

Brain CT scan or MRI was performed in all patients during the acute phase of the disease, independently of the presence of neurologic symptoms.

An EEG recording was made at admission and, if normal, was repeated weekly for 3 controls. When EEG abnormalities were detected, neurophysiologic re-evaluations were performed at different time intervals as clinically indicated, until neurologic improvement, and then weekly for 1 month. In cases requiring anticonvulsant treatment, additional EEG evaluations were performed monthly until neurophysiologic normalization.

Results

During a four-year period we observed 22 consecutive TTP patients. Sixteen (12 females and 4 males, age range 18-72 years, median 39.5) were eligible for our study because submitted, at diagnosis, to a complete neurologic evaluation (clinical, neuroimaging and neurophysiologic evaluation). In six cases, complete neurologic screening was not performed at diagnosis, so the patients were considered not eligible for the study.

Concomitant diseases were detected in 14/16 patients. In particular, two cases had a neoplastic disease, two had infections, four had an autoimmune disease and in five the presence of antiphospholipid antibodies was documented. There was one case of TTP related to pregnancy, voluntarily terminated at 7 weeks. No possible precipitating factors of TTP were found in the last 2 patients.

Neurologic assessment

Neurologic symptoms occurred in 13 out of the 16 patients (81%) during the course of the disease. In 12 patients (75%) they were present at the initial examinations. Generalized seizures were observed in 4 patients and focal seizures in another 2 cases. Focal transient neurologic deficits were observed in 4 cases: aphasia in 3 and dysarthria in 1. Two patients showed confusion, disorientation, headache and nystagmus.

One patient without neurologic symptoms at presentation had focal seizures with secondary generalization at day +16.

Neuroimaging

Thirteen patients underwent brain CT scan and 3 patients underwent MRI. Cranial CT of the brain showed normal features in the patients without central nervous system involvement. Of the 13 symptomatic subjects, 12 (92%) had normal neuroimaging (10 CT, 2 MRI) at the onset of neurologic symptoms, while an acute brain lesion (hemorrhages in the left frontotemporal and right parietooccipital region) was documented in 1 patient.

EEG study

No EEG abnormalities were recorded in nonsymptomatic subjects. Of the 13 symptomatic patients, 9 showed normal EEG features, despite the severity of clinical signs of central nervous system involvement in at least 5 of them (Table 2).

Generalized spike-and-waves and sporadic polyspike-and wave discharges were detected on the EEG in 4 patients; all presented fluctuating neurologic symptoms: focal seizures in 1 and generalized seizures in 3 cases. In all 4 cases with EEG abnormalities, neuroimaging evaluations were normal.

Anticonvulsant treatment (phenobarbital – PB – 2 mg/kg) was administered to all the above 4 patients and continued until EEG normalization in 2 of them. In the other 2 patients with persistent EEG abnormalities PB therapy was continued, despite complete remission of the TTP for more than 2 years. Intravenous diazepam was given as

Table 1. Clinical features and outcome.

Patient no.	*Age (years)/sex*	*Therapy*	*Course*	*Final diagnosis*
1	69/M	Standard therapy	CR (OT 78 months)	Sjögren's syndrome
2	31/F	Standard therapy + HD-Ig	CR (OT 78 months)	Unknown
3	23/M	Standard therapy + HD-Ig + VCR	CR (OT 77 months)	Unknown
4	39/F	Standard therapy (Splenectomy in II Relapse)	I Relapse (OT 36 months) II Relapse (OT 18 months) CR (OT 8 months)	Osteomyelitis (*Staph. aureus*)
5	34/F	Standard therapy	CR (OT 74 months)	ACA+ LAC+
6	39/F	Standard therapy	CR (OT 25 months)	Autoimmune thyroiditis
7	18/F	Standard therapy + HD-Ig (Splenectomy in I Relapse)	Relapse (OT 34 months) CR (OT 10 months)	Myastenia gravis
8	55/F	Standard therapy	Relapse (OT 54 months) CR (OT 2 months)	ACA+
9	49/F	Standard therapy	CR (OT 22 months)	ACA+
10	23/F	Standard therapy	CR (OT 10 months)	Rheumatoid arthritis
11	40/F	Standard therapy	CR (OT 10 months)	ACA+
12	40/F	Standard therapy	CR (OT 6 months)	ACA+
13	35/F	Standard therapy – VA	CR (OT 5 months)	Pregnancy (5° week) LAC+
14	59/F	Standard therapy + CHT	CR (OT 1 months)	Krukemberg ca
15	72/M	Standard therapy	Exitus	Endocarditis (*Staph. aureus*) ACA+
16	61/M	Standard therapy	Exitus	Cancer of unknown origin (Bone marrow metastasis)

Standard therapy: plasmapheresis, fresh frozen plasma, glucocorticoids, antiplatelet agents; HD-Ig: high-dose immunoglobulin; VCR: vincristine; CHT: chemotherapy; VA: voluntary abortion; CR: complete remission; ACA: anticardiolipin antibodies; LAC: lupus anticoagulant.

an immediate symptomatic measure to all patients who presented with generalized seizures.

Follow-up

All 16 patients followed the same treatment program for TTP, detailed in Table 1. Eleven patients (68%) had a prompt complete response. The median number of plasmaphereses performed in this group was 16 (range 1-18), and the median follow-up was 10 months (range 2-79) from remission. Out of 11 promptly responding patients, 2 relapsed 36 and 54 months after the first episode and both again responded to plasmapheresis; 1 of them, after 18 months, had a second relapse that finally required splenectomy.

Three (18%) of the 16 patients did not respond to plasmapheresis treatment and achieved complete remission only after administration of intravenous immunoglobulins (2 cases) or intravenous immunoglobulins and vincristine (1 case). Of these 3 patients, 1 relapsed 34 months after remission and required a splenectomy. Two patients (12%) were completely non-responsive to treatment and finally died.

The median follow-up of the 14 (87%) surviving patients was 11 months (range 2-79). No long-term neurologic sequelae were observed.

Discussion

Neurologic involvement is a prominent component of TTP. The neurologic manifestations are impaired consciousness and focal cerebral manifestations (in order of frequency: generalized and focal seizures, paresis, aphasia, dysphasia, pares-

Table 2. Neurologic, neuroimaging, and neurophysiologic evaluations.

Patient No.#	*Neurological presentation*	*Brain CT*	*Brain MRI*	*Initial EEG*	*EEG re-evaluation*	*Anticonvulsant treatment*
1	Generalized seizures	normal	not done	abnormal	abnormal	ongoing
2	Focal seizures	normal	not done	abnormal	abnormal	ongoing
3	Absent (at onset), Generalized seizures (successively)	normal	not done	abnormal	normal	stopped
4	Generalized seizures	not done	normal	normal	normal	not administered
5	Confusion, disorientation, headache, nystagmus	normal	not done	normal	normal	not administered
6	Aphasia	normal	not done	normal	normal	not administered
7	Generalized seizures	normal	not done	abnormal	normal	stopped
8	Aphasia	normal	not done	normal	normal	not administered
9	Absent	normal	not done	normal	normal	not administered
10	Focal seizures, facial hemiparesis	not done	normal	normal	normal	not administered
11	Aphasia	normal	not done	normal	normal	not administered
12	Absent	normal	not done	normal	normal	not administered
13	Absent	normal	not done	normal	normal	not administered
14	Confusion, disorientation, headache	normal	not done	normal	normal	not administered
15	Generalized seizures	normal	not done	normal	normal	not administered
16	Dysarthria	not done	abnormal (hemorrhages)	normal	normal	not administered

thesia and visual problems). Neurologic complications in TTP are attributed to a variety of vascular insults that may affect the brain, such as endothelial injury, thrombus formation, bleeding diathesis and hypertensive encephalopathy.[9]

Previous neuroimaging and neurophysiologic correlations of neurologic dysfunction in TTP are sporadic, consisting primarily of case reports or small series of patients. A CT study revealed vascular brain lesions, such as ischemic strokes or hemorrhages, in 10/20 TTP patients.[13] MRI analysis revealed a variety of brain lesions in 9/12 patients (75%) during the acute phase of TTP, while another series showed normal findings in all TTP patients during convalescence.[14] The lesions included reversible cerebral edema with MRI features of reversible posterior leukoencephalopathy syndrome, suggesting that MRI may help in the diagnosis and prognosis of central nervous system involvement in TTP.[14] Very interesting, other authors suggest that single photon emission tomography (SPET) can show lesions otherwise undetectable by CT or MRI evaluations.[14,15] All studies conclude that prompt treatment of TTP often results in neurologic recovery without long-term sequelae.

Discordant advice exists in the literature concerning neurophysiologic evaluations; in fact, some authors report that EEG in TTP can be normal, even in patients with overt neurologic dysfunction, while other authors report diffuse slowing on the EEG in patients with generalized seizures. Nevertheless, most reports suggest that EEG evaluations are of limited utility in TTP/hemolytic uremic syndrome(HUS).[16-18] This may discourage the use of EEG, particularly when neurologic signs are transient, such that these probably typical correlates of the microvasculopathy are not investigated further.[10] However, no prospective study has so far established the real value of complete neurologic screening in TTP patients.

In an attempt to clarify this problem, we prospectively evaluated 16 TTP patients, performing serial neurologic, neuroimaging and EEG examinations during the illness, independently of the presence of central nervous system involvement. In our study neurologic symptoms were observed in 75% of patients on initial examination, developing successively during the illness in 81% of cases. Neuroimaging evaluations during acute neurologic symptoms showed normal findings in 87% of subjects. These does not, therefore, seem to be any correlation between neurologic symptoms and neuroimaging, perhaps because of the widespread, but rapidly reversible microvascular occlusive changes typical of TTP. Nevertheless in our study we predominantly performed CT evaluations (13 CT and 3 MRI), while a previous report suggested that MRI is more sensitive than CT in demonstrating brain lesions in TTP).[12] In any case, caution must be exercised before drawing any firm conclusions in view of the relatively small number of patients considered.

Based on data reported in the literature and on our own experience, we think that neuroimaging, although not of significant value in improving the diagnosis of TTP, certainly may be useful in assessing prognosis: normal CT and/or MRI findings portend a favorable neurologic outcome, whereas the presence of infarctions or hemorrhages on CT and/or MRI indicates more severe disease and the possibility of long-term neurologic sequelae.[20,21]

With regard to the neurophysiologic evaluation, in our study EEG were serially performed in all patients at various phases of the disease; our experience confirms data reported in the literature that there is no certain correlation between EEG and neurologic involvement. We agree that neurophysiologic evaluations are of modest help in improving the diagnosis of TTP; nevertheless, EEG may be useful for the management of anticonvulsant therapy, which is often administered without a real need. In TTP, the microvascular occlusive changes in the brain are widespread, but generally reversible; though associated with severe neurologic symptoms, prompt aggressive treatment of the hematologic disease may induce neurologic improvement without the need of anticonvulsant therapy. On the other hand, patients with neurologic symptoms associated with damage documented by neuroimaging and EEG certainly benefit from adequate anticonvulsant treatment. Based on these observations we administered anticonvulsant therapy to only 4 of our 13 symptomatic patients, sparing a prolonged, troublesome and, above all, unnecessary treatment in the other 9 patients, despite the presence of signs and symptoms of central nervous system involvement in at least 5 of them.

Various authors have reported that a typical complication occurring in a substantial proportion of patients with TTP presenting altered mental status is non-convulsive status epilepticus (NCSE). It may be extremely difficult to diagnose NCSE clinically, since there may be subtle or no motor manifestations. NCSE is readily confirmed by EEG and is treatable. Therefore, TTP patients with persistent mental status abnormalities should undergo EEG evaluation. If NCSE is demonstrated, the patients may benefit from aggressive anticonvulsant therapy as part of their management.[9,10,21]

In our opinion, concomitant neuroimaging and neurophysiologic evaluations in the context of TTP, although of limited value in improving the diagnosis, may be very useful to allow adequate management of central nervous system involvement. The hypotheses regarding the prognostic utility of complete neurologic screening in TTP will be strengthened by larger prospective clinical-neuroimaging studies.

Contributions and Acknowledgments

MG, PA and SG supervised the study over a 4-year period; PA, CS, TSM, DLC and FG were responsible for data collection and analysis; AG, GV and SG were responsible for neurologic, neuroimaging and neurophysiologic evaluations, respectively. MF and MG chaired the study. The manuscript was prepared by MG and PA and reviewed by all the other authors.

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Potential implications for clinical practice

Complete neurologic screening, in the context of TTP, may be very useful to allow an adequate management of central system involvement.

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