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Major Stroke in Thrombotic-Thrombocytopenic Purpura (Moschcowitz Syndrome)

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Introduction

Thrombotic-thrombocytopenic purpura (TTP) was first described by Moschcowitz in 1924 [1] and has since been regarded to be a rare disorder with an estimated incidence of 3–7/1,000,000 [2]. However, in recent years increasing numbers have been reported (several thousand new cases of idiopathic TTP annually in the USA and Canada) [3]. The reasons for this increase in incidence are unknown. The disorder consists of a heterogeneous syndrome, which manifests itself with a Coombs-negative hemolytic anemia, thrombocytopenia, petechial hemorrhages, fever and renal and neurological complications. There are two main clinical pictures: primary systemic and CNS involvement, as in TTP, and predominant involvement of the kidneys, as in hemolytic-uremic syndrome. The underlying pathological mechanism is the formation of platelet aggregates in the microcirculation, which is due to the occurrence of unprocessed large or unusually large multimers of von Willebrand factor (vWf) [3]. Neurological symptoms as well as abnormal imaging findings on CCT and MRI are often transient [4, 5]. With the use of MRI, cortical and subcortical microinfarcts have been reported [5–7]. We describe a case of parainfectious TTP with multiple cerebral large artery infarctions.

Case Report

A 46-year-old previously healthy right-handed male caught a gastroenteritis during a holiday in the Dominican Republic in August 1998. The patient reported abdominal pain, nausea and diarrhea, which were followed by petechial hemorrhages and paresthesias, mainly of the left limbs. No physician was consulted. After returning to Germany in September 1998, the patient developed fever and was finally admitted to hospital. Anemia and thrombocytopenia were diagnosed. Schistocytes were detected on blood films, and TTP was diagnosed. A positive IgG titer against *Escherichia coli* (O157:H7) was detected by ELISA in the serum of the patient, and an association of TTP and gastroenteritis by cytotoxin-producing serotypes of *E. coli* was assumed. The patient was treated with heparin and prednisolone (initially 50 mg/day), and the anemia and thrombocytopenia resolved completely. Two months after prednisolone treatment had been ended, a first relapse of the thrombocytopenia was documented. Azathioprine was prescribed but not tolerated so that prednisolone was again started. A second relapse of the thrombocytopenia occurred in December 1999. Now treatment with cyclosporin was started, under which the patient developed renal insufficiency and arterial hypertension.

A second neurological symptomatology was reported during a relapse in July 2000, when the patient developed a transient aphasia. CCT showed multiple cortical infarcts: a large infarct in the territory

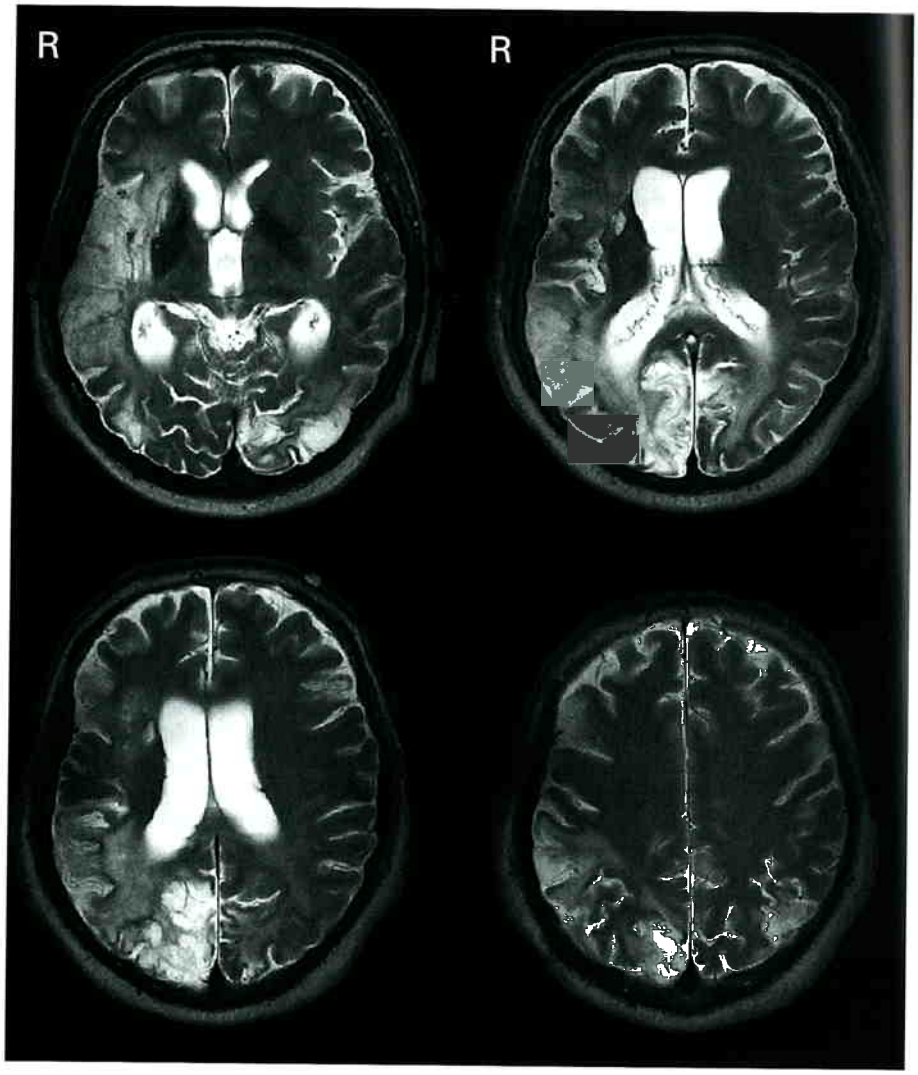

Fig. 1. MRI (December 2002; T_2-weighted axial slices at the levels of the basal ganglia, the lateral ventricles and the centrum semiovale), documenting a severe worsening of the neuroradiological findings. In comparison to CCT in July 2000 (see text), an additional extensive infarction in the territory of the right MCA is depicted.

of the right posterior cerebral artery, PCA, a smaller cortical infarct in the territory of the left PCA and small cortical infarcts in the territories of the left middle cerebral artery, MCA (temporo-occipital artery), and right MCA (parietal branches). Magnetic resonance angiography of intracranial vessels was unremarkable. Platelet count at that time was $<20 \times 10^9$/l and normalized soon after the administration of steroids. An absence of plasma vWf-cleaving metalloprotease and the presence of vWf-cleaving-metalloprotease-inhibiting IgG antibodies could be demonstrated in blood samples of the patient (laboratory Prof. U. Budde, Hamburg, Germany). Between July 2000 and September 2001, the patient was continuously treated with plasmapheresis and steroids, and multiple relapses of the thombocytopenia were documented.

In April 2002, the patient again developed mild aphasia of subacute onset. Furthermore, he complained of memory problems and gait imbalance. The neurological deterioration occurred under treatment with plasmapheresis (once every week) and prednisolone (10 mg/day). In April 2002, treatment with defibrotide (800 mg/day) was started, and prednisolone and plasmapheresis were successively stopped. Additionally, in August 2002, splenectomy was performed. Under this regimen, no further relapses of the TTP occurred. However, in July 2002 there was a first epileptic seizure, and additional anticonvulsant medication was prescribed (valproate 900 mg/day).

In December 2002, the patient was admitted to our institution. Deficits in different cognitive domains were present: dyslexia, visuospatial deficits, probably prosopagnosia and a dysexecutive syndrome. Clinical neurological examination showed a bilateral homonymous hemianopia. MRI revealed bilateral infarcts in the territories of both MCAs and PCAs (fig. 1). A diagnostic procedure to rule out concomitant stroke etiologies was completely unremarkable (blood chemistry, screening for HIV and autoantibodies, CSF lumbar puncture, extracranial Doppler sonography, electrocardiography, transesophageal echocardiography, 24-hour blood pressure monitoring).

Discussion

The patient is suffering from recurrent TTP, which was probably induced by gastroenteritis caused by cytotoxin-producing serotypes of *E. coli* (O157:H7). The diagnosis has been confirmed by recurrent

episodes of thrombocytopenia, hemolytic anemia with the occurrence of schistocytes and repeated evidence of decreased levels of plasma vWf-cleaving metalloprotease activity in the context of inhibiting autoantibodies. In contrast, chronic relapsing TTP, which is now regarded as an autosomal recessive disorder and usually begins in childhood, is characterized by the chronic absence or by chronically low levels of vWf-cleaving metalloprotease without the presence of autoantibodies [8, 9]. The association of recurrent TTP with *E. coli* gastroenteritis is an infrequent finding. More often, a single episode of hemolytic-uremic syndrome is associated with gastrointestinal infections with *E. coli* or *Shigella* species [3].

Irrespective of the distinct type of TTP, in about 90% of cases neurological symptoms are present during the course of the disease [10]. Due to the preferential involvement of the microcirculation, pathological neuroimaging findings, if present, usually consist of small cortical or subcortical infarcts, which are best visible by MRI [6, 7]. However, a few reports of major intracranial artery occlusion also exist. Rinkel et al. [11] and Wijdicks [12] reported 2 patients with PCA infarcts; Kelly et al. [13] studied 2 siblings with MCA main stem thrombosis and TTP.

In comparison with the subjects of these previous reports, our patient had multiple and bilateral large artery infarcts (fig. 1). The lingering character of the neurological abnormalities is noteworthy. The patient's history does not reveal any exact date, on which a specific infarction might have taken place. This is similar to the previous report of a silent brain infarction in TTP [12] and fits the observation of an increasing pathology when comparing CCT and MRI of our patient. Irrespective of the higher sensitivity of MRI, the latter shows an extensive infarction in the territory of the right MCA, which cannot be seen on the CCT, which was performed several months earlier. However, the neuroradiological worsening was obviously not accompanied by an acute clinical symptomatology.

The latter finding might indicate a subacute or chronic process of simultaneous intra-arterial thrombosis and thrombolysis. As has already been suggested before [11, 12], this observation might be of clinical relevance with respect to therapy. Standard treatment of recurrent TTP is plasmapheresis with or without the prescription of steroids. Experimental treatment includes the administration of interferon α or different immunosuppressive drugs and splenectomy. Early and aggressive drug treatment with antiplatelet agents could be useful in order to prevent the formation of larger platelet clots. Measurement of vWf-cleaving metalloprotease and screening for antibodies might prove to be a useful tool for the assessment of the overall risk in a specific patient. In addition to platelet count, low levels of vWf-cleaving metalloprotease might be helpful with respect to the question, when to prescribe antiplatelet agents. However, the existence of ticlopidine/clopidogrel-associated TTP as well as the increased risk of hemorrhage might hinder the use of certain or combined antiplatelet agents. To date, low-dose aspirin therapy (75 mg/day) is recommended, when the platelet count rises above 50×10^9/l [2].

Side effects of therapy (steroids and plasmapheresis) must be discussed also in the differential diagnosis of stroke etiologies in our patient. Although it cannot be excluded completely, such an association seems very unlikely. Methylprednisolone induces hypercoagulability mainly via thrombocytosis. An assumed neurological complication of steroid treatment is intracranial sinus or venous thrombosis, not arterial infarction [14]. With the exception of one case description from 1981, to our knowledge there are no reports of plasmapheresis-induced strokes in the literature [15].

Conclusion

Taken together with the few previous reports, our findings clearly demonstrate the risk of large intracranial artery thrombosis in TTP. Due to the increasing incidence of TTP possibly more major strokes will be seen in the future. Further studies are needed to clarify whether antiplatelet agents and the deoxyribonucleic acid derivative defibrotide [16] can prevent major intracranial artery occlusion in TTP.

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