Unusual presentation of more common disease/injury

Coma in thrombotic thrombocytopenic purpura

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Summary

Thrombotic thrombocytopenic purpura (TTP) is characterised by a thrombotic, haemolytic microangiopathy leading to microvascular occlusion, haemolysis and ischaemic dysfunction of various organs including the brain. TTP may present with a variety of neurological symptoms, including headache, focal deficits, seizures and coma. The authors describe a 55-year-old man presenting with abdominal pain and rapidly progressive deterioration into coma without focal neurological deficits or seizures. A concomitant, transient, rapid increase in blood pressure raised the suspicion of a hypertensive crisis. Yet, our patient did not improve after vigorous treatment with antihypertensives. Brain imaging excluded a hypertensive leucoencephalopathy. Despite the absence of a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13 (ADAMTS13) deficiency, the diagnosis idiopathic TTP was made after excluding secondary causes of TTP. Upon treatment with plasma exchange, corticosteroids and vincristin our patient gradually improved. On discharge to a rehabilitation centre he was awake and alert, had minor cognitive deficits and a mild proximal tetraparesis consistent with a critical illness poly(neuro)myopathy.

BACKGROUND

Thrombotic thrombocytopenic purpura (TTP) is a rare and potentially fatal microvascular occlusive disease. Prior to the use of plasma exchange and treatment with corticosteroids, it had a case fatality rate of over 90%. Nowadays, full recovery is possible when vigorous treatment is started early in the course of the disease. However, TTP remains a diagnostic challenge; in particular, if symptoms are atypical and laboratory results are inconclusive. In over 90% of cases TTP is complicated by neurological symptoms varying from headache, focal deficits to seizures and coma.^{1,2} Coma is in most cases preceded by focal deficits or seizures. Yet, in a descriptive study by Scully *et al*, 8% of all patients presented with coma as the predominant neurological feature of TTP.³ Therefore, it is important to increase the awareness that a coma even without premonitory focal neurological deficits and seizures may be a complication of untreated TTP; in particular, because treatment delay may negatively influence clinical outcome and could be fatal.

CASE PRESENTATION

The authors present a 55-year-old Caucasian man, who had a history of hypertension, hypercholesterolaemia and diabetes mellitus—the latter being complicated by a diabetic retinopathy and peripheral neuropathy. His medication regimen included antihypertensives, a statin and oral antidiabetics, which had not changed in recent years. He was admitted to hospital by his general practitioner with a 2-day history of abdominal and lower back pain and light-headedness. Physical examination revealed several bruises, no petechiae or other abnormalities, a blood pressure of 160/80 mm Hg and no fever. Laboratory results showed a direct-antiglobulin-test negative haemolytical anaemia with red cell fragments, thrombocytopenia, decreased haptoglobin, elevated bilirubin, lactate dehydrogenase (LDH), urea and creatinin consistent with a diagnosis of TTP. Urea

and creatinin levels remained high but stable during the next days. Plasma exchange and high-dose prednisone were started. Yet, a few days later his consciousness decreased during plasma exchange. Prior to plasma exchange, our patient did not receive analgesics or sedatives. Neurological examination revealed a Glasgow Coma Score (GCS) of E4M5V3 without focal neurological deficits except for an extensor response at both sides. Because of a blood pressure of 230/130 mm Hg prior to plasma exchange, hypertensive encephalopathy was considered initially. However, despite aggressive blood pressure lowering, our patient deteriorated to GCS 3, needed to be intubated and ventilated, and was transferred to the intensive care unit (ICU). Before this deterioration the patient did not receive analgesics or anaesthesia. He only received midazolam during the next 2 days at the ICU because a non-convulsive status epilepticus was suspected, and no analgesics, such as fentanyl or morphine, only acetaminophen. Repeated EEGs showed no evidence for a non-convulsive status epilepticus. Upon further treatment with plasma exchange and prednisone he improved and 2 days later his GCS was E4M6V4. Because a hypertensive crisis was suspected to have caused the microangiopathic haemolysis, plasma exchange was stopped and his prednisone dose was lowered. Nevertheless, despite adequate control of his blood pressure, he became comatose again (GCS 3). Plasma exchange was restarted and the prednisone dosage increased upon which our patient gradually improved to E4M6V4. After a week, he was extubated and transferred to the haematology ward.

INVESTIGATIONS

Laboratory tests at hospital admission showed normal electrolytes, liver enzymes, impaired kidney function (urea 27.6 mmol/l, creatinin 246 µmol/l), decreased haemoglobin (7.8 mmol Fe/l), normal mean corpuscular volume, decreased platelet count ($24 \times 10^9/l$), elevated bilirubin (36 µmol/l) and

LDH (1981 U/l), decreased haptoglobin (<0.05 g/l), red cell fragments and a negative Coombs test consistent with a microangiopathic haemolytic anaemia. No underlying cause for the haemolysis was found: coagulation tests were normal, including a normal a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) activity (>100%) as an indicator of von Willebrand Factor (vWF) protease activity.

Our patient was extensively screened for an underlying cause of TTP, which was not found:

a CT scan of the thoracic and abdominal regions showed no evidence for a primary tumour or metastases. His prostate-specific antigen level was normal. A bone marrow specimen showed a normal trilinear haematopoiesis and no morphological abnormalities except for an increase in megakaryocytes, and no evidence for a monoclonal B cell population. Virological tests for infections with HIV, cytomegalovirus and Epstein-Barr virus were negative. In addition, no infection with *Escherichia coli* 0157:H7, which can be associated with the TTP-associated haemolytic uremic syndrome, could be detected. The antinuclear antibody test (ANA) was negative.

Other causes of coma, in particular hypertensive leucoencephalopathy, cerebral venous sinus thrombosis and ischaemia in the posterior circulation, were ruled out as CT and MRI scans of the brain both with and without contrast appeared normal. In addition, EEGs repeatedly showed no evidence for (non-convulsive) status epilepticus. A lumbar puncture showed no cerebrospinal fluid abnormalities (normal glucose corrected for serum glucose levels, normal protein, immunoglobulin G (IgG) and IgG-index, absence of pleiocytosis, negative for neurotropic viruses including herpes simplex virus 1 and 2, varicella zoster, enteroviruses and parechoviruses). Serum lupus anticoagulant and anticardiolipin antibodies were absent, as were paraneoplastic antibodies, and the ANA profile was negative, which rendered (viral) encephalitis, autoimmune or systemic diseases and vasculitis all unlikely. Since our patient did not receive any analgesics or sedatives, and urea and creatinine levels were stable (although elevated) in a 4-day period prior to the first deterioration of his GCS score, a toxic-metabolic encephalopathy is also unlikely to have caused the first coma in our patient. However, it is possible that the half-life of the midazolam our patient received during his stay at the ICU may have been prolonged given the concomitant uraemia, which may have lengthened the duration of his coma and may have (partly) caused his second relapse.

DIFFERENTIAL DIAGNOSIS

Reversible leucoencephalopathy, in particular due to a hypertensive crisis, toxic-metabolic causes of coma (in particular the use of sedatives/analgesics and uraemia) and (non-convulsive) status epilepticus.

TREATMENT

Monitoring on ICU, plasma exchange, corticosteroids and vincristin.

OUTCOME AND FOLLOW-UP

Our patient gradually improved after plasma exchange and treatment with oral corticosteroids was started. He was transferred to the department of haematology awake and

alert and with a GCS of 14 where vincristin was added to his treatment. At discharge to a rehabilitation centre he only had minor cognitive deficits and a minimal proximal tetraparesis without other focal neurological deficits—the latter being consistent with a critical illness poly(neuro) myopathy.

DISCUSSION

The authors described a case of TTP with a rapidly deteriorating coma without preceding focal neurological deficits or seizures. Coma is known as one of the neurological sequelae of TTP^{1 2} yet it has less often been described in the absence of focal neurological deficits or seizures.³ Kelly *et al* described two cases with confusion and drowsiness developing into coma who both fully recovered after plasma exchange.⁴ Frankel *et al* already in 1981 advocated vigorous and continuous treatment with plasma exchange for coma in TTP in the absence of major central nervous system structural lesions when presenting a 45-year-old woman with a 18-day long coma who fully recovered after daily treatment with plasma exchange, antiplatelet drugs, prednisone and vincristin.⁵

Since then, treatment of this rare but potentially fatal microangiopathy has remained virtually unchanged. Although an optimal plasma exchange regimen has not yet been established, daily plasma exchange with single plasma volume exchange is recommended at presentation, leaving more intensive treatment regimens for patients who do not respond within the first days of treatment or who improve but exacerbate while on treatment, which should be continued at least 2 days after remission is achieved (defined as stabilisation of clinical symptoms, normalisation of platelet count and LDH levels, with a rising haemoglobin).^{6 7} The relapse of our patient after subsiding plasma exchange indeed stresses the need for prolonged continuation of treatment after remission of laboratory findings to normal values.

The microangiopathy in TTP is characterised by platelet and vWF rich thrombi occluding the microvasculature. vWF thrombi are considered to be the result of insufficient processing of newly secreted and extremely adhesive ultra-large multimers of vWF. With the discovery of ADAMTS13, a disintegrin and metalloproteinase with thrombospondin type 1 repeats, insights in the pathophysiological mechanisms underlying TTP have dramatically improved. In the majority of patients with an acquired TTP, severe ADAMTS13 deficiency is caused by circulating anti-ADAMTS13 antibodies, which either enhance its clearance or inhibit its activity. However, ADAMTS13 deficiency is normal in approximately 10% of TTP cases.⁶ Therefore, a negative ADAMTS13 does not preclude a diagnosis of TTP and plasma exchange might be effective for this subgroup of patients.⁶ As Scully *et al* mention in their paper,³ patients with TTP may have IgG antibodies to ADAMTS13 despite negative inhibitor screens. The authors attribute the therapeutic effect of plasma exchange in these patients to the possible presence of these antibodies, although these were not defined in our patient.

Interestingly, ADAMTS13 activity has also been found to be decreased in malignant hypertension in which it has been associated with higher levels of vWF and the severity of thrombotic microangiopathy.⁸ The decreased ADAMTS13 activity appears to be irrespective of blood pressure and is likely due to release of vWF after endo-

thelium stimulation. Endothelial dysfunction in TTP or malignant hypertension may, thus, be two sides of the same coin. Endothelial dysfunction has been hypothesised to result in toxicity related blood–brain barrier dysfunction, hyperperfusion and vasogenic oedema. In addition, MR perfusion studies in TTP have shown hyperperfusion to be related to the occurrence of cerebral (micro)haemorrhages.⁹ Given the absence of an effect of blood pressure lowering and absence of posterior leucoencephalopathy or brain infarcts on MRI or seizures in our case, this may indeed be the mechanism underlying the encephalopathy and coma in our patient. Unfortunately, in our patient no MR perfusion studies were performed.

In conclusion, in prolonged coma, even in the absence of premonitory focal neurological deficits or seizures, TTP should be considered a possible cause, and plasma exchange together with oral corticosteroids should be started as soon as possible, even in patients with normal ADAMTS13 levels. Full recovery is possible after treatment with plasma exchange and treatment delay may be fatal.

Learning points

- ▶ TTP must be considered in the differential diagnosis of coma even without focal neurological deficits or seizures.
- ▶ Vigorous treatment with plasma exchange and corticosteroids is mandatory and may lead to full recovery in a patient with a prolonged coma related to TTP.
- ▶ Endothelial dysfunction rather than hypertension may be the mechanism underlying coma in TTP in the absence of a posterior leucoencephalopathy.

Competing interests None.

Patient consent Obtained.

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