CASE REPORT

A diagnosis of haemolytic-uraemic syndrome blurred by alcohol abuse

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SUMMARY

A 60-year-old man with a history of alcohol abuse was admitted to the intensive care unit (ICU) for status epilepticus. At first, laboratory and imagery findings were almost normal, and the symptoms were attributed to severe alcohol withdrawal due to a history of gastroenteritis reported by his family. But, during the following days, haemolytic anaemia, thrombocytopenia, acute renal failure, and ischaemic and haemorrhagic lesions seen on a cerebral CT scan led to the diagnosis of haemolytic-uraemic syndrome (HUS). Despite these severe complications, the patient made a good recovery following ICU and plasma exchange with fresh frozen plasma (FFP), but cognitive deficit still existed after 1 month. It is important to know that neurological manifestations can precede typical biological and radiological signs in HUS, and to not be misled in the diagnosis process, especially when a more common differential diagnosis is possible.

BACKGROUND

Alcohol abuse is a public health concern leading to various potential acute or chronic complications clinicians need to be aware of because of their frequency and severity. However, detoxification in a patient with a history of alcohol abuse must be followed closely due to the risk of alcohol withdrawal syndrome, culminating in withdrawal seizures.

The incidence of acute symptomatic seizures is 29–39 per 100 000 per year,^{1 2} and among these cases alcohol withdrawal is one of the commonest causes.^{3 4} Alcohol abuse can also frequently lead to gastrointestinal symptoms (such as diarrhoea, vomiting, etc) and metabolic disorders (such as hypoglycaemia or dysnatraemia), which can themselves cause seizures.

Assuming our patient had one of these common conditions that can lead to seizures and which are related to alcohol abuse or its withdrawal, we misdiagnosed this case, despite the progressive appearance of biological symptoms pointing at a differential diagnosis.

Haemolytic-uraemic syndrome (HUS) is a rare and life-threatening^{5–7} disease included in the thrombotic microangiopathy group, and is characterised by two main biological symptoms: microangiopathic haemolytic anaemia and low platelet count.

Thrombotic microangiopathies have various aetiologies (bacterial toxins, genetic or acquired complement dysregulations, genetic or acquired ADAMTS13 deficiencies, drugs, systemic disorders, etc) and potential target organs (mainly the kidney, brain and gut).

Infectious causes are the most common for HUS in America, Western Europe, Japan, Africa and Australia.^{8 9} Among them, Shiga-toxin-producing *Escherichia coli* O157:H7 is the more represented strain,¹⁰ but there are also other bacteria with digestive tropism that can cause HUS and that are not easily identified, which was the case in our patient. A history of digestive symptoms must alert the clinician, but the problem with infectious HUS is that, at onset, it may resemble any other benign gastroenteritis, especially when typical biological signs are absent. And sometimes, mostly in adults, the existence of other conditions to explain the symptoms can produce a misdiagnosis. In our case, these misleading symptoms were present and, also, seizures started prior to classic biological abnormalities.

CASE PRESENTATION

A 60-year-old man with a history of alcohol abuse, depression and hydrocephaly with normal pressure, had a generalised seizure at home and was sent to the ER for further examination, after spontaneous resolution of the crisis.

In the ER, he presented with fever, had repetitive seizures, with periods of unconsciousness, and had to be treated for status epilepticus. Since antiepileptic drugs (clonazepam and fosphenytoin) had no effect, he had to be intubated, sedated with thiopental and admitted to the intensive care unit (ICU). His family revealed that he had non-bloody diarrhoea, was vomiting and confused for a few days before admission.

Neurological investigations were considered normal, and the patient was extubated after 2 days and back to his regular level of consciousness.

Further investigations were made, and despite initial neurological improvement (with antiepileptic drugs: levetiracetam, clobazam) the patient's haematological and renal conditions worsened during his stay, and he finally had to be intubated again a few days later because of status epilepticus recurrence.

INVESTIGATIONS

Laboratory results on admission indicated acute kidney failure with a creatinine level of up to 170 µmol/L. There was slight abnormal clotting (international normalised ratio 1.35, prothrombin ratio 65%), elevated total bilirubin up to 50.5 mmol/L, with conjugated bilirubin levels up to 10 mmol/L and the other liver function tests (aspartate aminotransferase, alanine transaminase, alkaline phosphatase, γ-glutamyl transferase) were at the upper limit of normal range. The first CT in the ER revealed no relevant cerebral abnormality and lumbar puncture showed no sign of meningitis.

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Figure 1 (A) Day 0: No cerebral lesion except for the known hydrocephaly and leukoaraiosis; (B) Day +7: Bilateral subarachnoid haemorrhage prominent in the bilateral occipitoparietal regions; (C) Day +11: Appearance of an ischaemic lesion in the left occipitoparietal region.

The next day, the patient's haemoglobin fell from 15.9 to 11.6 g/dL, platelet count from 92 to 22×10^9 /L and creatinine increased to 223 μ mol/L despite rehydration. Mean corpuscular volume was normal, lactate dehydrogenase (LDH) was up to 1433 iu/L, haptoglobin <0.08 g/L and blood film demonstrated fragmented red blood cells (schistocytes). Upper gastrointestinal endoscopy showed inflammation of the lower end of the oesophagus with a small ulceration (without active bleeding).

Cerebral imaging (figure 1) was repeated after status epilepticus recurrence, showing subarachnoid haemorrhage and, 1 week later, the appearance of an ischaemic lesion in the left occipitoparietal region.

Stool cultures were negative for *E. coli* O157:H7 strains and *Shigella* spp. Shiga toxin was not detected. Immunological studies for antinuclear and antineutrophil cytoplasmic antibodies were negative. C3 0.72 g/L (range 0.79–1.52) and C4 0.13 g/L (range 0.16–0.38) were low with normal CH50 39 (range 33–73). ADAMTS13 activity was slightly lowered (44%) with no real deficiency and no ADAMTS13 inhibitor activity was detected. Serology for HIV and viral hepatitis B/C were negative.

DIFFERENTIAL DIAGNOSIS

Initially, before the presence of classical thrombotic microangiopathy signs, the patient's neurological symptoms and biological abnormalities were attributed to an association of more common conditions. We assumed his acute renal failure was owing to dehydration caused by the gastroenteritis, which was responsible for alcohol withdrawal, and that status epilepticus was a consequence of this last element. As for low platelet count, hepatic and coagulation abnormalities, they were presumed to be consequences of the history of alcohol abuse and its toxicity. Even when his haemoglobin fell to 11.6 g/dL, we had to exclude a digestive haemorrhage, which is a more frequent condition than HUS, especially with alcohol abuse.

Finally, the platelet count fell from 92 to 22×10^9 /L in 1 day, increase in creatinine levels up to 223 μ mol/L in spite of rehydration measures and the lack of bleeding of the upper gastrointestinal tract to explain the anaemia, made us look for another aetiology. Hepatorenal syndrome was mentioned among our team, but the lack of cirrhosis or fulminant liver failure in our patient made it impossible.

Finally, LDH and haptoglobin levels associated with schistocytes presence on the blood film made HUS the only possible diagnosis.

TREATMENT

The patient was treated with 5 days of plasma exchange with fresh frozen plasma (FFP) for HUS and levetiracetam associated with sedation (propofol and thiopental) for status epilepticus.

OUTCOME AND FOLLOW-UP

The patient was intubated for 2 weeks because of the persistence of electrical infraclonic seizures on the EEG, until the addition of clonazepam. The status epilepticus was difficult to treat, possibly because of the presence of subarachnoid haemorrhage in addition to HUS itself, but it eventually ceased and sedation was stopped.

LDH, haemoglobin, platelet count, haptoglobin and creatinine improved soon after the first plasma exchanges with FFP, and the schistocytes disappeared after 5 days of treatment. The patient did not require dialysis.

Two weeks after successful extubation, renal and haematological conditions were back to normal, neurological deficits improved but phasic and cognitive impairments still existed, and the patient was admitted to the hospital rehabilitation service.

DISCUSSION

The association of acute kidney failure, thrombocytopenia, microangiopathic haemolytic anaemia and neurological abnormalities is highly evocative of thrombotic thrombocytopenic purpura (TTP) or HUS, but the diagnosis is often uncertain because initial symptoms are variable, not specific, and may not be severe. Even diagnostic laboratory criteria are not specific. The whole set of criteria can be missing at the very beginning, as in our patient, who had no microangiopathic haemolysis, making the diagnosis even more difficult.

Once TTP or HUS diagnosis is suspected, plasma exchange therapy must be quickly discussed because, for adults, it is the only treatment with firm data on its effectiveness.¹¹ The distinction between TTP and HUS is not really important at this point, since plasma exchange treatment has documented efficacy in patients with either condition and at all levels of ADAMTS13 activity.^{11 12}

In our case, the lack of ADAMTS13 deficiency and absence of ADAMTS13 inhibitor activity made the diagnosis of TTP highly improbable. Because of the initial diarrhoea, we concluded that the condition was typical HUS, despite the negativity of stool cultures and Shiga toxin research, which can be explained by the fact that diarrhoea was no longer present when HUS diagnosis was finally made and samples sent to the laboratory.

The differential diagnosis of atypical HUS, which is a rare form of thrombotic microangiopathy frequently associated with genetic or acquired disorders leading to dysregulation of the alternative pathway of complement, was considered, but normal C3 and factor B levels, our patient's age and the absence of relapse after a 6-month follow-up made it less probable. In case of recurrence of the disease in the future, further investigations will be made.

Renal biopsy (figure 2) was performed on the 3rd day of plasma exchange (platelet count was $>150 \times 10^9$ /L), which

Figure 2 Specimens obtained after renal biopsy. (A) Periodic acid-Schiff stain showing osmotic nephrosis and a slightly abnormal glomerulus and (B) glomerular capillary wall thickening with double contours (arrowheads) revealed by silver impregnation and few fragmented red blood cells.

showed endothelial wall thickening with typical double contours and tubular injuries, but no major arterial involvement usually associated with good renal prognosis,^{6 13} which was confirmed in our case. On the contrary, the association between severe central nervous system symptoms and worse renal prognosis⁶ was not confirmed here.

A study of the largest cohort of adult patients with HUS published to date comprised of 217 Shiga toxin-producing *E. coli*-associated HUS.¹⁴ Among those patients, 104 (48%) developed neurological symptoms and only 3 of them developed neurological symptoms prior to the onset of HUS biological manifestations, as in our patient. It is a rare presentation of a rare disease, but recognising it can save time in the diagnosis process and treatment of this life-threatening condition.

Of the 104 adult patients with neurological complications, the initial phase of the disease tended to be particularly severe with almost 1 patient of 3 (n=34) having to be intubated and ventilated, but finally the long-term neurological outcome was remarkably good with only 3% of sequelae (among the 98 surviving patients). These results highlight the necessity of full treatment, no matter the severity of the case.

The pathophysiology of neurological involvement in HUS is multifactorial.¹⁵ Cerebral thrombotic microangiopathy is only found in a minority of patients with HUS on autopsy, thereby emphasising that it may not be the major process leading to neurological symptoms and partially explaining why central nervous system dysfunction is often reversible. Direct effects of Shiga toxin on the endothelial and neuronal cells of the central nervous system, in combination with toxic and metabolic disturbances during uraemia, seem to be more likely the primary causes of neurological involvement during HUS. It has been described that in addition to inflicting severe microvascular damage, Shiga toxin on its own evokes a strong neuronal

membrane depolarisation, calcium accumulation and thalamic apoptosis. In our case, the persistence of neurological sequelae (dysphasia, cognitive impairment) could be explained by the probable presence of thrombotic microangiopathy lesions, in view of the CT findings.

Contributors MK collected the data, performed the literature search, wrote the case and is the guarantor. NBT drafted and revised the paper. NM provided the kidney specimen pictures and drafted and revised the paper. BT had the idea for the article, contributed to the literature search and drafted and revised the paper. MK, NBT, NM and BT managed the case at different times.

Competing interests None.

Patient consent Obtained.

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Learning points

- ▶ Typical haemolytic-uraemic syndrome is a rare disease with initial unspecific digestive symptoms, but the appearance of anaemia and thrombocytopenia must alert the clinician to it in order to achieve a good prognosis for his patient.
- ▶ During the diagnostic process, clinicians must think in terms of pathology frequency, but it is also important for them to take account of the condition's potential severity, even though it is a rare disease.
- ▶ Cases have been described where neurological symptoms can precede some of the classic biological abnormalities, which makes the diagnosis more difficult to make.

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