

Acute variegate porphyria presenting with reversible cerebral vasoconstriction

Alastair JS Webb DPhil*, Harshal Ingale †, Sarosh R Irani DPhil*, Michele Hu ____

Affiliations:

*Department of Clinical Neurosciences, University of Oxford, Oxford, UK

†Department of Neurosurgery, John Radcliffe Hospital, Oxford, UK

Authors

Dr Alastair Webb, Neurology Specialty Registrar / Associate Clinical Fellow*

Harshal Ingale, Neurosurgical Specialty Registrar

Sarosh Irani, Wellcome Trust Intermediate Clinical Fellow / Honorary Consultant Neurologist

Michele Hu, _____, Honorary Consultant Neurologist

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Correspondence to:

Dr Alastair Webb,

Department of Clinical Neuroscience

Level 6, West Wing

University of Oxford

John Radcliffe Hospital

Headington

Oxford OX3 9DU

United Kingdom

TEL: (44) 1865 231610

E-mail: alastair.webb@ndcn.ox.ac.uk

Author Contributions:

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Conflicts of interest

Drs Webb, Ingale, Irani and Hu declare that we have no conflicts of interest.

Clinical Note

A 49 year old teacher presented to her local hospital with a collapse and acute confusion. Three weeks before this, she had a febrile illness characterised by myalgias, shivering without rigors, fatigue and severe nausea and vomiting, without headache or other neurological symptoms. After 1 week, her nausea and vomiting improved, she tolerated fluids and began to eat small volume meals. Around the time of this improvement, she developed a cough productive of green phlegm and central colicky? abdominal pain, and was treated with trimethoprim for a presumed urinary tract infection.

Subsequently, her abdominal pain and vomiting improved, but after 4 days, she became increasingly lethargic and developed brief episodes of visual distortion. The next day, she slept throughout the day and on arising in the evening was confused as to the time of day and recent events. Whilst standing, she had a brief syncopal episode with rapid return of consciousness and an ambulance was called. On arrival at the local hospital, she was speaking in confused sentences and was mildly drowsy without focal neurology.

She had a history of mild iron deficiency anaemia and had again been treated 2 months previously for a urinary tract infection with trimethoprim but was currently only taking iron supplements. She didn't smoke and drank minimal alcohol. There was no significant family history.

On admission she had a serum sodium of 117 mmol/L, osmolality of 250 and urine osmolality of 491. Routine blood tests and a CT head were normal. She was treated with intravenous saline, resulting in an initial fall in her sodium to 109, potassium to 2.3 and magnesium to 0.58, before a gradual improvement in all electrolytes, with concurrent improvement in her confusion. A lumbar puncture was attempted multiple times, and only successfully performed the next day. Her CSF contained 0 white cells, 19 red cells, 0.57g/L of protein and 5.3 glucose of 5.3mmol/l. Both bilirubin and oxyhaemoglobin were detected and she was transferred to the regional neurosurgical centre for further investigation.

Upon arrival, she was orientated in time, place and person. She had a subjective band? of numbness across her lower abdomen but had no objective abnormalities on examination. A CT-angiogram (figure) demonstrated wide-spread vasospasm. Blood tests demonstrated no evidence of a vasculitis but her urinary porphyrins were markedly elevated with a porphobilinogen:creatinine ratio of 34.5 and a porphyrin:creatinine ratio of 385 (Figure 1C). Spectrophotometry demonstrated an emission peak at 628nm and an elevated urinary coproporphyrin III:I ratio of 3.2, confirming a diagnosis of acute variegate porphyria.

Discussion

Acute intermittent porphyria, coproporphyria III and variegate porphyria are associated with acute crises characterised by abdominal pain, neuropathy, encephalopathy with prominent psychiatric disturbance, and serum hyponatraemia. Most commonly AIP is associated with these neurological features, and amongst neurologists other forms of porphyria are rarely considered. Despite their rarity, the biochemical and genetic basis of these conditions is well-defined, all sharing an acute elevation of serum and urinary of porphyrin precursors. The subgroup of porphyria is identifiable by specific biochemical abnormalities, depending on which enzyme in the heme synthesis pathway is affected. Variegate porphyria is defined by an excessive accumulation of coproporphyrin III and a

plasma fluorescence emission peak at 626nm \pm 2nm.¹ However, the pathophysiological relationship between the accumulated porphyrins and the clinical manifestations is unclear.

Vasospasm has been hypothesised to be the underlying cause of the cerebral manifestations of porphyria for greater than 40 years², with well-defined cases of acute intermittent porphyria showing reversible cerebral vasoconstriction³ or posterior reversible encephalopathy,⁴ and one case report of cerebral vasospasm in coproporphyria III.⁵

The abdominal symptoms have also been hypothesised to be due to vasospasm in both acute intermittent porphyria⁶ and in variegate porphyria.⁷ However, this is the first case report demonstrating cerebral vasospasm in variegate porphyria, showing that cerebral vasoconstriction can occur in all major forms of acute porphyria with encephalopathy.

This is an unusual presentation of a rare disease, but it is possible that this clinical scenario is more common. The limited recognition of cerebral vasospasm in porphyria may reflect a lack of vascular imaging and the difficulties in making the diagnosis of porphyria in patients presenting with idiopathic reversible cerebral vasoconstriction. We therefore suggest testing for urinary porphyrins in patients presenting with idiopathic cerebral vasospasm and other features seen in our patient. Systematic assessment of the cerebral circulation in research cohorts of acute porphyria may define the frequency of this association.

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Figure 1. Angiography demonstrating reversible cerebral vasoconstriction in the context of acute variegate porphyria. Panel A shows the acute CT angiogram during the acute attack, with diffuse vasospasm evident in distal vessels. In addition, there is evidence of dysplasia at the right MCA bifurcation and basilar tip. Panel B shows an MRA from 3 months later where there is no evidence of ongoing vasospasm, although there is persistent dysplasia. I'd suggest making this a composite figure with the biochemical pathway as 1C showing accumulation of metabolites and site of block.

