CLINICAL ALERT

Severe porphyric neuropathy – importance of screening for porphyria in Guillain-Barré syndrome

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The hepatic porphyrias are a group of rare metabolic disorders, each of which is associated with a specific enzymatic alteration in the haem biosynthesis pathway. In South Africa (SA), a high incidence of variegate porphyria (VP) is seen as a result of a founder effect, but acute intermittent porphyria (AIP) is also encountered. The development of acute neurovisceral attacks is related to environmental factors, including medications, hormones and diet. A possible manifestation of a severe attack is rapidly progressing quadriparesis, which may mimic Guillain-Barré syndrome. We present four such cases, highlighting that acute porphyria should be considered in the differential diagnosis of Guillain-Barré syndrome. Three patients presented to Steve Biko Academic Hospital, Pretoria, SA, with progressive quadriparesis, and one to a private hospital with acute abdominal pain followed by rapidly progressive quadriparesis. Two patients had started antiretroviral therapy before the development of symptoms, and one had started antituberculosis therapy. All patients had marked weakness with depressed reflexes, and showed varying degrees of confusion. An initial diagnosis of Guillain-Barré syndrome led to administration of intravenous immunoglobulins in two patients. On testing for porphyria, it was found that two patients had AIP and two VP. Electrophysiological investigations revealed severe mainly motor axonal neuropathy in all. Two patients deteriorated to the point of requiring mechanical ventilation, and one of them died due to complications of critical illness. Haemin was administered to three patients, but the process of obtaining this medication was slow, which delayed the recommended early administration. The surviving patients showed minimal recovery and remained severely disabled. Porphyric neuropathy should always be considered as a differential diagnosis in a patient with an acute neuropathy, especially in SA. Absence of abdominal pain does not exclude the possibility of porphyria, and attacks may be precipitated by antiretroviral and antituberculosis medication. The outcome of our patients was not favourable; specifically, obtaining haemin was a challenge in the state hospital setting.

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The porphyrias are a group of inherited metabolic disorders that are associated with a specific enzymatic abnormality in the haem biosynthesis pathway. Porphyrias are traditionally classified as hepatic or erythropoietic according to the site of accumulation of haem precursors, but classifications reflecting the clinical presentation, such as acute and cutaneous, may be more practical.[1] The acute porphyrias that are inherited in an autosomal dominant pattern include acute intermittent porphyria (AIP), variegate porphyria (VP) and hereditary coproporphyria, while acute porphyria due to δ-aminolaevulinic acid (ALA) dehydratase deficiency is an autosomal recessively inherited condition.

AIP is estimated to occur in one in 75 000 people in Europe, except in Sweden, where the condition is seen in one in 1 000 owing to a founder effect.[1,2] Similarly, VP is estimated to occur in one of 150 000 people in Europe, but the prevalence in SA is much higher, estimated at 3/1 000 in the white population as a result of a founder mutation that was introduced from the Netherlands in 1688.[3] An acute porphyric attack may be precipitated by several factors, including starvation, certain medications and hormonal fluctuations. The typical attack begins with severe abdominal pain and autonomic hyperactivity, followed by psychiatric disturbances and possibly neuropathy. Whereas most patients recover well from acute porphyric attacks, neurological complications may develop; these include electrolyte disturbances and seizures, confusional states, autonomic dysfunction and severe quadriparesis.[1]

We describe the clinical presentation and outcome of four patients with acute porphyria who presented to a neurology unit in Pretoria, South Africa (SA), during one year, emphasising that the presentation of acute porphyric neuropathy may be similar to that of Guillain-Barré syndrome and occur in the absence of acute abdominal pain. The occurrence of AIP in the black population is highlighted and some clinically relevant points regarding treatment are detailed.

Three patients presented to Steve Biko Academic Hospital with progressive quadriparesis, and one to a private hospital with acute abdominal pain followed by rapidly progressive quadriparesis. Two patients had started antiretroviral therapy before the development of symptoms, and one had started antituberculosis therapy. All had marked weakness with depressed reflexes, and showed varying degrees of confusion in the ward.

An initial diagnosis of Guillain-Barré syndrome led to the administration of intravenous immunoglobulins in two patients.

On testing for porphyria, it was found that two patients had AIP and two VP. Electrophysiological investigations revealed features of a severe mainly motor axonal neuropathy in all (Table 1). Two patients deteriorated to the point of requiring mechanical ventilation, and one of them died due to complications of critical illness. Haemin was administered to three patients, but the process of obtaining this medication was slow, proving a challenge in the state hospital setting, so the recommended early administration was delayed. As a result, the surviving patients showed minimal recovery and remained severely disabled.

Case reports

Case 1

A 42-year-old black woman presented with an acute onset of progressive quadriparesis that had developed over 4 days. She was HIV-positive and antiretroviral therapy had been initiated 4 weeks previously; at around that time, she had also had a flu-like illness. In addition to the weakness, she experienced paraesthesiae and numbness over the extremities. In the ward, she was intermittently confused. On examination, she showed facial weakness and a global power of grade 2/5 with areflexia and loss of sensation of the 'bathing suit' type. A diagnosis of possible Guillain-Barré syndrome was made and she was treated with intravenous immunoglobulins (IVIG). It was also noted that her urine was a dark brown colour, and porphyria screening was requested. Her condition deteriorated in the ward and she required intubation and ventilation in the intensive care unit. The urinary porphobilinogen (PBG) level was 378 µmol/L (reference value <9), the faecal porphyrins were marginally elevated at 374 nmol/g dry weight (reference value <200) and the plasma emission spectrum was maximal at 619 nm. A final diagnosis of AIP was made. Lumbar puncture showed high cerebrospinal fluid (CSF) protein levels and serum biochemical investigations revealed hyponatraemia (126 mmol/L, reference range 136 - 145). Electromyography (EMG) demonstrated low compound muscle action potential (CMAP) amplitudes in all four limbs, as well as reduced sensory nerve action potentials. Unfortunately it was impossible to obtain haemin for this patient. She developed a pulmonary embolism, received intensive physiotherapy and was eventually extubated. The weakness improved marginally, but she remained severely weak and was still bedridden after 2 months.

Case 2

A 34-year-old black man was admitted with progressive quadriparesis that had developed over 3 - 4 weeks. He had had a respiratory tract infection before the onset of symptoms and had possibly received antibiotics. He also complained about a cold sensation in his limbs, as well as hoarseness and a soft voice. On examination, he appeared confused and had a bovine cough (later confirmed to be due to left-sided vocal cord paralysis), power of grade 0/5 in the arms proximally and 3/5 distally, and weakness in the legs of 4/5 proximally and 5/5 distally. The deep tendon reflexes were absent and glove-and-stocking-type sensory loss was evident. The patient was initially treated with IVIG for possible Guillain-Barré syndrome. However, investigations for porphyria revealed a urinary PBG level of >100 µmol/L, total urinary porphyrins of 2 236 nmol/L (reference value <300 nmol/L), faecal porphyrins of 333 nmol/g dry weight, and a plasma peak at 619 nm on emission spectrofluorimetry. A diagnosis of AIP was made, and it was discovered that the patient's sister had

Table 1. Motor nerve conduction studies of patients

	Median nerve			Ulnar nerve			Peroneal nerve			Tibial nerve		
Patient	DL (ms)	Amp (mV)	NCV (m/s)	DL (ms)	Amp (mV)	NCV (m/s)	DL (ms)	Amp (mV)	NCV (m/s)	DL (ms)	Amp (mV)	NCV (m/s)
Patient 1												
Right distal	4.1	1.08	51.2	3.0	2.21	64.7	4.6	1.46	41.5	4.3	4.57	47
Right proximal	8.2	0.860		7.65	1.89		12.85	1.3		12.5	3.63	
Left distal	3.55	2.12	50	2.75	2.25	72.3	8.85	0.072	64.6	4.3	4.17	48.1
Left proximal	7.75	1.36		6.0	1.48		14.5	0.06		12.2	5.47	
Patient 2												
Right distal	3.5	3.6	46.8	2.8	3.2	40.9	4.3	3.2	38.6	7.8	11.2	35.6
Right proximal	8.2	3.6		9.5	2.7		13.5	2.9		19.2	10.6	
Left distal	3.2	3.0	54.2	2.5	5.8	48.2	4.4	2.3	37.2	3.7	9.7	40
Left proximal	8.0	2.9		9.4	4.5		13.8	1.6		14.2	8.0	
Patient 3 (baseline)												
Right distal	5.1	3.3		3.3	3.7	43.1	5.8	1.5	38.1	4.7	7.5	31.4
Right proximal	10.4	0.470		10.3	2.4		16	1.2		16.8	4.6	
Left distal												
Left proximal												
Patient 3 (after 2 mo)												
Right distal							Absent					
Right proximal							Absent					
Left distal	4.9	0.101	42.2	Absent			Absent					
Left proximal	10.35	0.079					6.2	0.021				
Patient 4												
Right distal	3.1	0.100	33.8				2.5	3.3	47.9	4.1	6.5	41.8
Right proximal							11.2	2.3		13.2	5.8	
Left distal												
Left proximal												

DL = distal latency; Amp = amplitude; NCV = nerve conduction velocity; ms = milliseconds; mV = millivolts; m/s = metres per second.

also previously been diagnosed with this condition. The CSF protein level was within normal limits and hyponatraemia (128 mmol/L) was present. On EMG, the patient had low CMAP amplitudes and slowing of conduction velocity in motor and sensory nerves, while an electroencephalogram showed generalised slowing at 6 - 7 Hz. The patient received a course of haemin, which was only available 6 weeks after admission. He improved somewhat, but remained weak and quadriparetic with persistent hoarseness.

Case 3

A 69-year-old white woman presented with weakness, which had developed over a 10 - 14-day period, and complaints of numbness and paraesthesiae in the hands and feet. She was known to have VP and reported that her last acute porphyric attack some 30 years previously had been characterised by abdominal pain and an impaired level of consciousness. The current attack was probably precipitated by antituberculosis treatment that had been started for pulmonary tuberculosis. The patient's weakness quickly progressed to respiratory failure, necessitating intubation and ventilation. On examination, she showed facial weakness and a global power of only grade 2/5 with 1+ reflexes in the upper limbs and absent reflexes in the lower limbs. The urinary PBG level was elevated at 201 µmol/L, total urinary porphyrins were 1 516 nmol/L and faecal porphyrins were markedly elevated at 5 736 nmol/g dry weight. The plasma emission spectrum revealed a peak at 625 nm, consistent with a diagnosis of VP. Molecular genetic analysis confirmed the presence of the R59W mutation. Severe hyponatraemia developed with the administration of glucose solutions, and although haemin was finally administered after 3 weeks, the patient's clinical condition continued to deteriorate. She developed multiple complications related to critical care and ultimately died due to sepsis after 4 months in the intensive care unit.

Case 4

A 32-year-old white man presented with acute abdominal pain, confusion and hallucinations, followed by rapidly progressive weakness of the arms more than the legs and generalised seizures. He had taken antiretroviral therapy for post-exposure prophylaxis before this admission. On examination, he was acutely delirious, with facial weakness, proximal weakness of grade 0/5 and distal weakness of 1/5 in the arms, and proximal weakness of 2/5 and distal weakness of 4/5 in the legs. The ankle reflexes were the only reflexes that were retained. The urine was a dark brown colour and porphyria investigations revealed a positive urinary PBG screening test, total urinary porphyrins of 1 429 nmol/L and markedly elevated faecal porphyrins. The plasma emission spectrum was maximal at 625 nm, in keeping with VP. The R59W mutation was also positive. Haemin was administered after 5 days, leading to amelioration of the delirium and seizures. Although the weakness in the legs improved somewhat, the arms remained severely weak even at follow-up 4 months later.

Discussion

AIP and VP form part of the acute hepatic porphyrias, which are associated with a range of extrahepatic, gastrointestinal and neurological and psychiatric manifestations.[4] During an acute attack, haem precursors accumulate in front of the deficient enzyme, which in AIP is porphobilinogen deaminase and in VP protoporphyrinogen oxidase. The excess porphyrin metabolites are then excreted in the urine and faeces according to a characteristic pattern. In AIP urinary ALA and PBG are markedly elevated, and in VP urinary ALA, PBG and coproporphyrinogen levels are high. Protoporphyrinogen is usually markedly elevated in the faeces in VP.[4] These patterns were also observed in our patients, and genetic confirmation was available in both of our patients with VP.

Typical acute porphyria attacks begin with severe abdominal pain, which may sometimes lead to exploratory laparotomies; constipation, nausea and vomiting may be associated symptoms. The pain is usually followed by psychiatric disturbances which include confusion, delirium, hallucinations, and frank psychosis.[4,5] Autonomic instability with tachycardia and elevated blood pressure may be present and generalised tonic-clonic or partial seizures commonly occur. Mental changes may progress to coma. Only one of our patients presented with this typical clinical picture of abdominal pain followed by psychiatric disturbances and convulsions; the others showed varying degrees of intermittent confusion in the ward, but did not report any abdominal pain preceding admission.

Our patients all presented with an acute onset of progressive quadriparesis. However, the peripheral neuropathy of porphyria is reported to develop typically after the onset of abdominal pain and psychiatric disturbances. Three of our patients did not give any history of acute abdominal pain. Porphyric neuropathy may develop within 3 - 75 days after the onset of abdominal pain,[6] and 80% of patients develop the neuropathy within 1 month. A study by Hift and Meissner[7] from SA reported that a sudden cessation of abdominal pain in an acute attack may actually constitute a warning of an incipient quadriparesis. These authors considered presentation without pain as highly atypical, a view that may, as in our patients, lead to consideration of Guillain-Barré syndrome as a cause for the severe weakness. One study from the USA, however, did not find a single case of porphyria in 450 patients with Guillain-Barré syndrome who were screened for the condition.[8] Our cases emphasise that in SA specifically, clinicians should have a high index of suspicion not only for VP, which is well known to have a high incidence in the white population, but also for AIP in patients of all population groups presenting with a Guillain-Barré-like picture.

The typical electrophysiological findings in porphyric neuropathies show an axonal mainly motor neuropathy, with varying sensory involvement.[9,10] Previous reports have demonstrated that electrophysiological improvement of the neuropathy can take many months. In one patient report, not all nerve conduction studies had returned to normal even after a period of over 21 months.[11] All our patients had low CMAP amplitudes on the nerve conduction studies of motor nerves, and in one patient, electrophysiological deterioration after 2 months was documented, with absent responses of the ulnar and peroneal nerves that had previously been present. This was also the patient who did very poorly and died in the intensive care unit without regaining the ability to breathe autonomously. No specific reports were found that correlated CMAPs with prognosis in porphyric neuropathy, but studies in patients with Guillain-Barré syndrome have shown that a very low CMAP (<10% of normal) is associated with a poor outcome.[12] In our patient, a superimposed critical care neuropathy, as well as the severe hyponatraemia aggravated by the glucose solutions against which Hift and Meissner[7] have cautioned, may have contributed to the findings and poor outcome.

Information on the prognosis of porphyric neuropathy is limited. As mentioned, the degree of axonal damage probably predicts the ultimate prognosis and recovery often takes many months with some patients remaining permanently quadriparetic.[4,13] In the SA study that reported on clinical features recorded during 112 acute porphyric attacks, three patients with quadriparesis improved with rehabilitation and eventually regained the ability to walk. In the same study, several other patients with pre-existing neuropathy deteriorated markedly at the onset of a new attack, but the weakness resolved rapidly after haemin administration.[7] One patient with AIP improved even after a long period of being bedridden when a course of haemin was given,[14] and other authors similarly report a favourable outcome after haemin administration.[15] Unfortunately, the administration of haemin was delayed in most of our patients owing to local unavailability of the drug, which may have worsened

the outcome, since studies recommend early administration of haemin[7,16] to limit or reverse the toxic effects of haem precursors on the peripheral nerves.

Porphyric attacks can be precipitated by many factors, the most common being restricted caloric intake, alcohol, hormones and specific medications.[4] Interestingly, in two of our patients we believe that the attack was precipitated by antiretroviral medication – one patient was started on highly active antiretroviral therapy (HAART) before the onset of the symptoms, and the other took antiretroviral medication for post-exposure prophylaxis. In the first case, the patient received tenofovir, emtricitabine and efavirenz. Although not many reports linking acute porphyria with these medications are available, one recent report describes a patient with VP who developed an acute attack after receiving the same HAART.[17] Drugs that induce cytochrome P450 proteins (CYP), by causing haem depletion, lead to enhanced transcription of the rate-limiting enzyme of the haem biosynthetic pathway, 5-aminolaevulinate synthase.[17] Since antiretroviral drugs that induce CYP3A4 and 2C9 have the greatest porphyrinogenicity, it is likely that the efavirenz (a strong CYP3A4 inducer) in the abovementioned regimens precipitated the acute attacks.[17] Treating HIV infection in patients with porphyria is therefore challenging.

Conclusion

Our cases emphasise that acute and severe porphyric neuropathy can occur without preceding symptoms and that this condition should be considered in patients with a Guillain-Barré-like clinical presentation. It is important to note that attacks may be precipitated by antiretroviral therapy, and that in SA specifically, care should be taken when prescribing HAART and antituberculosis drugs to patients with possible porphyria. The availability of haemin proved to be problematic in our setting, and streamlining the process of obtaining this medication should be made a priority in public hospitals.

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