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Research Letter

Porphyric neuropathy in black South Africans: a case series

***A. Koufos, G. Modi**

Division of Neurology, Department of Neurosciences, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

**Corresponding author: annitakoufos@gmail.com*

Abstract:

Porphyria is a rare disorder that results from mutations in the genes important in haem biosynthesis. Several types are described. Acute attacks lead to central, autonomic and peripheral nervous system manifestations. These acute attacks typically occur in acute intermittent porphyria, and less so in variegate porphyria.

The neuropathy in this condition can mimic Guillain-Barré syndrome (GBS), and is often misdiagnosed and incorrectly treated. It is rare in general, but considered to be extremely uncommon in the black African population.

We describe five black South African patients, three of whom were diagnosed with variegate porphyria, with the presenting manifestation of a severe neuropathy. The neuropathy was atypical in nature and variable in presentation and highlight the importance of considering porphyria in such patients.

INTRODUCTION

Porphyria is a rare inborn error of metabolism that results from various enzymatic deficiencies in the biosynthesis of haem.(1,2) The diagnosis of acute intermittent porphyria (AIP From a neurological point of view, acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP), and the rare aminolevulinic acid dehydratase deficient porphyria (ALAD) are significant as they are characterised by acute attacks that may at times have life-threatening neurological complications.

Acute attacks are triggered by events that deplete the body's haem stores, including fasting, alcohol, infection, hormonal changes; and medication, predominantly those that act on the cytochrome P450 enzymes.(1–4) The neurovisceral triad of an acute porphyric attack is comprised of abdominal pain, neuropsychiatric symptoms, and neuropathy.(2–5) These occur variably, with neuropathy being an infrequent complication and of inconsistent severity. (2–5)

Porphyria is rare. The true prevalence thereof is difficult to quantify as the clinical penetrance is low.(1,6,7) AIP is the most identified porphyria worldwide.(1,3,8,9) In South Africa, VP is the most common porphyria due to the founder R59W mutation introduced by a Dutch settler in 1688. It is most prevalent in the Afrikaner population who descended directly from the original Dutch settlers. (1,3,8,10)

Porphyria in black Africans is thought to be uncommon.(11–16) Early literature illustrates the predominance of cutaneous manifestations and that acute neurological symptoms are a rare occurrence.(11–16) Individual case reports of porphyric neuropathy have been published throughout Africa, but information is still limited.(9,17–21) This report describes five black South Africans who presented with severe forms of porphyric neuropathy.

CASE STUDIES (TABLE 1)

Case 1

A 23 year old black female presented with a rapidly progressive pure motor flaccid areflexic quadriparesis that had developed over several days. This had been preceded by a month's duration of recurrent episodes of abdominal pain and constipation. At a point it was documented that her urine had become red in colour. No aetiology for her persistent gastrointestinal symptoms had been identified. A preliminary diagnosis of GBS was made and plasmapheresis was commenced. Nerve conduction studies (NCS) were normal, as was the cerebrospinal fluid (CSF) evaluation. Her weakness further progressed to involve bulbar and respiratory muscles, and she developed respiratory failure and autonomic instability, leading to cardiac arrest. She was resuscitated and intubated and commenced on intravenous immunoglobulin. NCS at this point were in keeping with a motor axonal neuropathy. Her urine porphyrin screen was positive, and she was commenced on haem arginate. She had a slow recovery and she was discharged home after 6 months, being able to mobilise with assistance.

Table 1: Clinical and biochemical profiles of cases

	Case 1	Case 2	Case 3	Case 4	Case 5
Demographics	23y black female	19y black female	36y black male	30y black female	31y black male
Clinical exam	Symmetrical quadriparesis Facial weakness Bulbar weakness Respiratory weakness	Asymmetrical quadriparesis No facial/bulbar weakness Respiratory weakness	Asymmetrical quadriparesis Facial weakness No bulbar weakness No respiratory weakness	Bibrachial weakness Subtle LLW	Symmetrical quadriparesis (asymmetrical onset) No facial/ bulbar weakness No respiratory weakness
Distribution of weakness	LL = UL Proximal > distal	LL > UL R > L Distal > proximal	LL > UL, RUL >> LUL Proximal > distal	Distal > proximal	UL > LL Proximal > distal
Reflexes	Global areflexia	Ankle reflexes present	Brisk reflexes till late, then absent	Hyporeflexic	Globally areflexic
Sensory exam	Normal	Asymmetrical 'bathing suit' sensory loss R > L; neuropathic pain	Normal	Normal	Patchy sensory fallout
Autonomic involvement	Yes: autonomic instability and cardiac arrest	Yes: persistent tachycardia and orthostatic hypotension	Possibly: supraventricular tachycardia	No	Yes: orthostatic hypotension
Abdominal pain	Yes	Yes	No	No	Yes
CNS involvement	No	No	No	No	No
Porphyria studies	UPBG neg UPOR pos BPOR neg	UPBG pos UPOR pos	UPBG neg UPOR neg BPOR neg Fluor: VP	UPBG pos UPOR: VP BPOR pos Fluor: VP	UPBG pos UPOR pos BPOR neg Fluor: VP

LL, lower limbs; *UL*, upper limbs; *UPBG*, urine porphobilinogen; *UPOR*, urine porphyrins; *BPOR*, blood porphyrins; *R*, right; *L*, left; *Fluor*, plasma fluorescence emission; *LLW*, lower limb weakness

Case 2

A 19 year old black female was referred with a history of progressive quadriparesis over a period of one month, leaving her bedridden. This was preceded by a period of abdominal pain, constipation and red urine. She was HIV positive and had been taking a tenofovir/ efavirenz/ emtricitabine combination for three years. Examination revealed an asymmetrical flaccid quadriparesis, respiratory muscle involvement, and autonomic dysfunction. Reflexes were globally absent, except for the ankle reflexes. She had an asymmetrical 'bathing trunk' distribution of sensory loss, and significant allodynia in the lower limbs. NCS demonstrated a sensorimotor axonal neuropathy. CSF evaluation was normal. The urine porphyrin screen was positive. Haem arginate was initiated, and she started to improve rapidly. She was discharged home after 2.5 weeks, being able to feed herself, sit with minimal support, and stand with assistance.

Case 3

A 36 year old black male was referred with an asymmetrical pure motor quadriparesis. This had slowly progressed over several weeks after he had been admitted with diabetic ketoacidosis. His admission had been complicated by an episode of supraventricular tachycardia that was managed with amiodarone, and numerous episodes of sepsis that were treated with various antibiotics. Eventually his face and neck flexion had also become weak. Reflexes were initially brisk, but were later all lost. Sensation remained normal. MRI of his brain and spine were normal. CSF showed a raised protein of 1.7g/L which was ascribed to his diabetes as no other reason could be identified. NCS, normal initially, revealed non-stimulable nerves after one month. Urine porphyrin studies were negative, but plasma fluorescence emission confirmed a peak in the range typical of VP. He was started on haem arginate and made a slow recovery with gradual improvement in endurance and strength. He

was discharged home after four months, being able to sit in a wheelchair but not walk independently.

Case 4

A 30 year old black female developed progressive bibrachial weakness one week after her ARV regimen was changed. Efavirenz had been replaced by a lopinavir/ ritonavir combination due to previous toxicity. Reflexes were reduced in the upper limbs. There was subtle weakness of her neck and lower limbs as well. Sensation was normal. NCS revealed a motor axonal neuropathy of her upper limbs; lower limbs were normal. CSF evaluation was normal. Blood and urine porphyrin studies were positive and were in keeping with VP. Haem arginate was initiated and her upper limb strength began to improve soon thereafter. She was discharged home after two months.

Case 5

A 31 year old black male was referred with a quadriparesis that had progressed over three weeks whilst being admitted for a hot water burn. He described recurrent episodes in the preceding years of lower limb weakness that would resolve spontaneously, often associated with vague abdominal symptoms. He had a background history of hypertension and heavy ethanol use. Examination revealed a flaccid areflexic quadriparesis with patchy sensory fallout of the limbs, and evidence of autonomic dysfunction. It was noted that the urine in his catheter bag had turned a red colour after being exposed to sunlight. NCS showed a sensorimotor axonal neuropathy. CSF was normal. Urine porphyrin studies were positive and plasma fluorescence emission was suggestive of VP. Due to numerous administrative delays, haem arginate was administered 4 months after the diagnosis was confirmed. He was left with significant disability but did show gradual improvement in strength after the haem infusion.

DISCUSSION

Porphyric neuropathy affects both autonomic, motor and sensory components of the peripheral nerves. Autonomic involvement accounts for the severe and poorly localized abdominal pain that characterizes more than 90% of acute porphyric attacks, often associated with constipation.(2–5)

Peripheral neuropathy is reported to occur in 10%–40% of acute attacks, more so in AIP.(2,3,5) It is of an acute axonal type but is classically described as primarily affecting proximal muscles and the upper limbs, and may also be asymmetrical.(2–5) A variable distribution of weakness is, however, well-documented.(22–24) Deep tendon reflexes may be retained, especially the ankle reflexes, or globally absent.(2–4)

When present, sensory symptoms may occur in the typical 'bathing-trunk' distribution with the involvement of the proximal limbs and trunk; or in a 'glove and stocking' distribution.(2–5) Significant pain may develop.(2–5,8) The cranial nerves may also be affected, usually after the onset of limb and trunk weakness, predominantly involving the facial and vagus nerves.(2–5)

In contrast to the classic presentation as described in the literature, our case series highlights the variability of the clinical presentation in porphyric neuropathy. Asymmetry of deficits and autonomic dysfunction were important features. NCS and CSF findings in these patients were in keeping with that expected in porphyria, except for case 3 whose high CSF protein was ascribed to his underlying diabetes. In two cases, biochemical workup was unfortunately incomplete, and the type of porphyria could not be discerned. In the other three cases, VP was confirmed. Of importance is that all our cases presented with severe neuropathy. This is of interest in those with VP as the neuropathy is often described to be a rare complication of the acute attack and usually mild.(6,8) None of the cases described had a family history of porphyria, or a preceding history of any skin manifestation.

Early reports from central and southern Africa describe how porphyria is not an uncommon entity in black populations.(11–16) However, the documented cases suffered predominantly from cutaneous manifestations, and acute symptoms were generally a rare finding.(11–16) In a few cases, vague abdominal discomfort, peripheral 'neuritis', and psychosis were described; but these symptoms were ascribed to the effects of ethanol that was used heavily by the studied populations.(13,15,16) The abdominal pain was not as severe as that typically seen in the acute porphyrias.(11,13,15,16) Other rare findings associated with the cutaneous manifestations included pain in the chest and limbs, and hypertension.(11,16) In retrospect, all these additional symptoms may well be explained by the variable involvement of the nervous system during an acute attack. Underlying liver dysfunction was often noted in these patients, again ascribed to chronic ethanol ingestion that was an important factor in the development of porphyria.(12,15) This type of porphyria was hence identified as a 'chronic cutaneous subgroup of the hepatic variety'.(15) It was thought of as an acquired condition that was benign in nature,(12–15) in contrast to that seen in European populations which was known to be a genetic illness with potentially severe manifestations.(12,15)

In terms of serious symptoms of the acute attack in African individuals, there are only several case reports;(25) and more so of patients with AIP (18–21) than with VP.(17) In addition, more recent South African studies illustrate how acute attacks were more prevalent and more severe in AIP compared to VP.(6,8) Hift et al (2005) report eleven of 24 patients of different ethnicities developing neuropathy during an acute attack, eight patients with AIP and three with VP.(8) In most cases the neuropathy was

mild and limited to distal weakness of the limbs i.e. wrist or foot drop; with only three cases demonstrating quadriparesis.(8) Five patients in their case series were black, but it is unclear if any of these had developed neuropathy.(8)

Although only few genetic studies in patients with VP or AIP have been performed in South Africa, these have identified novel mutations amongst black individuals and provide evidence for heterogeneity of molecular abnormalities in different populations.(7,26) Robreau-Fraolini et al (2000) performed the first porphobilinogen deaminase gene study within a black population, demonstrating that the spectrum of mutations differ compared to those found in white counterparts.(27) They identified four novel mutations and further discovered that certain single nucleotide polymorphisms existed only in black individuals and not in whites.(27) This suggested that AIP was again a heterogeneous disease within the black population.(27)

Our case series thus highlights several points:

- The index presentation of porphyria may be that of an acute neuropathy, without a preceding history of any skin manifestation.
- Porphyric neuropathy can be severe regardless of the type of porphyria.
- It may have a very variable presentation.
- Preceding abdominal pain is not always present.
- Family history is often negative.
- VP is also found in black South Africans, and not only in the Afrikaner population.
- Delays in diagnosis and definitive therapy can lead to poorer patient outcome.
- It can often, but not always, have a GBS-like presentation.

CONCLUSION

Porphyria is found across all ethnic groups. This case series emphasises its presence in black South Africans and its severe manifestations. Although still rare, the diagnosis should be considered in any patient with an atypical acute or subacute neuropathy where no other aetiology can be identified, in order to minimize complications and patient morbidity.

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