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Clinical Study

Neurological complications of porphyria

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Abstract

The aim of this study was to evaluate and describe the importance of neurological complications in patients with a confirmed diagnosis of porphyria. Clinical details are presented for a cohort of 14 patients who presented with one of four categories of symptoms: seizures, polyneuropathy, transient sensory-motor symptoms and cognitive or behavioural abnormalities. Ascertainment of porphyria was often incidental and in many patients neurological complications preceded the definitive biochemical diagnosis. Porphyria is a group of diseases whose clinical picture is often complex and heterogeneous, but neurological complications are not uncommon. When indicated, differential diagnosis of neurological signs and symptoms should include porphyria, as the incidence of the disease is probably underestimated. Part of the clinical picture can be transient and it is often initially disregarded. A family history and recurrence of otherwise unexplained neurological symptoms should alert the clinician to a possible diagnosis of porphyria for patients with neurological presentations.

Keywords: Porphyria; Neurological complications; Seizures; Neuropathy; Antiepileptic drugs

1. Introduction

Porphyria is a heterogeneous group of diseases that is caused by alterations of porphyrin metabolism.[1]

Increased blood levels of porphyrins are detectable in most patients affected by porphyria. Excessive accumulation of porphyrins is deemed to be responsible for the clinical and pathological picture observed in several organs, including the central nervous system (CNS). Epidemiological data vary according to geography.[2–4]

The clinical picture is characterised by systemic involvement, comprising gastrointestinal symptoms and, rarely, chronic liver failure, cardiovascular involvement, or a diffuse erythematous reaction and subsequent vesicles. Sideroblastic anaemia is the most common haematological complication.

Several commonly used medications may induce or aggravate porphyric attacks. In neurological practice, these include antiepileptic, psychotropic and illicit drugs as well as excessive alcohol consumption. Infections, pregnancy and menstrual irregularities are also considered potential triggering factors.

Neurological manifestations can affect both the central and peripheral nervous system. Peripheral neuropathy is the most common neurological manifestation, affecting predominantly motor nerves, with a rapid onset of symmetrical weakness affecting all limbs, Cranial nerve involvement, sensory disturbances, consistent pain and asymmetrical patterns of weakness occur, spreading to the trunk and legs. Tachycardia and hypotension may be present in the acute phase.

Epilepsy is not infrequent in porphyric patients, sometimes associated with electroencephalogram (EEG) abnormalities.[5–9] The aetiology of seizures is multifactorial, attributable to hyponatraemia, consequent on vomiting

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or diarrhoea, brain structural pathology, or supposed neurotoxic and epileptogenic effects of some porphyrins. Psychiatric and cognitive disturbances have also been documented.[10] A deteriorating state of awareness can rarely occur. Both transient and permanent brain structural damage has been reported.[8,11–16]

We present a series of patients with biochemically confirmed porphyria. All of them had neurological complications during their clinical course. In some cases, the neurological symptoms were not directly related to porphyria, but they are included as patients were treated with medications routinely used in neurological practice and we wished to study the impacts of these drugs.

2. Clinical picture: details of the series

Demographic data of the patients are summarised in Table 1. Fourteen patients (four males, 10 females) are presented, 13 of whom were evaluated personally by the investigators at the Neurology Clinic, St. Vincent's Hospital. Some of the diagnostic investigations had already been performed, and other laboratory tests were carried out when necessary. One patient contacted the investigators by telephone, and his medical history and investigations were analysed retrospectively with the help of the patient's general practitioner and neurologist. Patients with suspect neurological problems were referred to our clinic by their general practitioners with the help of a lay association, as we had published a previous report on the effect of antiepileptic drugs (AEDs) on porphyria and we were interested to analyse the neurological complications of porphyria in more detail. The average age of patients at presentation was 38.9 (±14.04) years, and mean age at diagnosis of porphyria was 31.8 (±15.3) years.

Table 1
Demographic data of patients

Patient	Sex	Age (years)	Age at diagnosis of porphyria	Porphyric syndrome	Main neurological problem
1	F	23	12	HC	Seizures
2	F	36	26	HC	Seizures
3	M	35	31	HC	Seizures
4	M	47	12	PV	Seizures, intellectual disability
5	F	64	58	HC	Polyneuropathy
6	F	46	26	AIP	Polyneuropathy
7	M	55	49	AIP	Polyneuropathy
8	F	49	45	PCT	Neuropathic pain
9	F	21	16	HC	Transient sensory-motor symptoms
10	F	53	50	AIP	Transient sensory-motor symptoms
11	F	37	29	AIP	Transient sensory-motor symptoms
12	M	17	15	EPP	Impaired alertness
13	F	59	49	HC	Ataxia
14	F	31	22	HC	Bell's palsy

HC, hereditary coproporphyria; AIP, acute intermittent porphyria; PV, porphyria variegata; PCT, porphyria cutanea tarda; EPP, erythropoietic porphyria; M, male; F, female.

Seven patients were affected by hereditary coproporphyria (HC), four by acute intermittent porphyria (AIP), one by porphyria variegata (PV), one by porphyria cutanea tarda (PCT), and one by erythropoietic porphyria (EPP). The principal neurological symptoms were polyneuropathy, seizures, transient sensory-motor abnormalities clearly related to the attacks, mood disturbances and cognitive, behavioural and neuropsychological abnormalities. Not all patients attended the same hospital, hence we cannot infer prevalence figures from these data.

2.1. First mode of presentation: seizures

Four patients had epileptic seizures, either at presentation or earlier in life.

Patient 1, a female, was diagnosed with HC at the age of 12, and her mother and older sister were also affected. Since diagnosis, she had suffered frequent porphyric attacks characterised by abdominal pain, nausea and vomiting associated with lower limb numbness. During hospital admissions she was often treated with chlorpromazine, morphine and pethidine. Six witnessed tonic-clonic seizures were documented, coinciding with porphyric attacks; three seizures were associated with documented hyponatraemia (122–126 mmol/L). EEG demonstrated bilateral posterior slowing (5–6 Hz sharply contoured theta) without obvious epileptiform activity. Brain magnetic resonance imaging (MRI), performed months after the first seizure, showed scattered T2 hyperintense lesions present in the subcortical frontal and parietal white matter, and in the vertex region bilaterally. Surprisingly, brain MRI performed a year later was normal. Gabapentin (GBP) was started at 900 mg/day, which is generally regarded as a low dose. It failed to achieve satisfactory seizure control.

Patient 2, a female now aged 36 years, had frequent simple partial seizures that began at the age of 16 years, after a left post-traumatic parietal subdural haematoma. Events comprised initial bilateral auditory phenomena, nausea, dysphasia and clouding of consciousness, followed by post-ictal headache. Routine EEG and one-day video-EEG monitoring did not reveal epileptiform abnormalities. Brain MRI demonstrated encephalomalacia in the right temporal and parietal lobes with marginal gliosis. The patient was initially treated with sodium valproate that induced attacks characterised by abdominal pain, headache, and confusion. HC was diagnosed after biochemical evaluation. When the patient presented with persistent complex partial seizures, GBP was introduced at a dosage of 1200 mg/day, later increased to 1600 mg/day. This treatment reduced the frequency and severity of events significantly.