Acute intermittent porphyria: is oseltamivir safe in these patients?

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ABSTRACT

A 40-year-old man attended the emergency room with abdominal pain and inappropriate behaviour associated with stress, and the consumption of alcohol and cannabis. Examination revealed hypertension (155/100 mmHg), tachycardia (95 beats per minute), abdominal pain and leucocytosis with neutrophilia, hyponatraemia and hypokalaemia. Urine was positive for nitrites, elevated bilirubin and cannabinoids. The patient was diagnosed with acute intermittent porphyria (AIP) and immediately treated. After initial treatment, the patient improved. However, he subsequently relapsed after initiating treatment with oseltamivir for a flu-like illness. Treatment was discontinued and the patient progressed favourably. AIP recurrence could have been mediated by oseltamivir; an association not previously described in the literature.

KEYWORDS: oseltamivir, acute intermittent porphyria, antivirals

DOI: 10.7861/clinmed.2022-0100

Introduction

Porphyrias are a group of genetic disorders caused by enzymatic defects in haem biosynthesis that increase the production and elimination of intermediate products of haem synthesis in blood, urine and faeces, and their pathological deposition in some tissues. Porphyrias are divided into two large groups: acute hepatic forms and chronic cutaneous forms. Acute intermittent porphyria (AIP), the most common form of acute porphyria, is an autosomal dominant genetic disorder caused by porphobilinogen deaminase (PBGD) deficiency. Like other forms of acute porphyria, it manifests as an attack with acute neurovisceral involvement that is difficult to diagnose due to nonspecific symptoms. Only around 10% of patients present with severe forms of the disease and recurrent attacks.[1]

Attacks may be precipitated by alcohol consumption, chronic or recurrent infections, reduced calorie intake or fasting, and the use of some drugs. Widely used guidelines have been published to help clinicians and patients determine which drugs are safe and which are potentially harmful.[2]

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Case presentation

A 40-year-old man presented in the emergency department with abdominal pain, constipation, confused ideation and inappropriate behaviour, and a history of several days of autolytic ideation. The patient was a cannabis user and occasional drinker, with a history of depressive syndrome, absence seizures and a laparotomy operation in 2011 for intestinal intussusception.

Diagnosis and initial management

The episode began after the patient experienced a stressful work situation, compounded by fasting and consumption of alcohol and cannabis.

Physical examination revealed confused speech, marked distress, hypertension (155/100 mmHg), tachycardia (95 beats per minute) and abdominal pain with no signs of peritoneal irritation. Leucocytosis with neutrophilia, hyponatraemia and hypokalaemia were detected in his blood, while nitrites, high bilirubin levels and cannabinoids were detected in his urine.

Imaging tests (simple radiology and abdominal computed tomography) revealed several biliary cysts and a left adrenal nodular lesion measuring 23 mm of uncertain characteristics.

During this event, a reddish-coloured urine residue was observed, and an urgent Hoesch test was requested, which was positive, so specific treatment was started: carbohydrate-rich diet and serum therapy, avoidance of drugs that could aggravate or trigger seizures, and the administration of intravenous haemin. Porphyrins, delta-aminolevulinate and porphobilinogen were evaluated in blood, urine (Table 1) and faeces, while a genetic study determined that the patient had a mutation in the *PBGD* gene (c.788_789 of the TG), which confirmed a diagnosis of AIP.

Key points

- Acute intermittent porphyria is a genetic disorder characterised by the presence of neurovisceral symptoms and behavioural changes.
- Alcohol consumption and cannabis use can trigger acute attacks.
- The rapid onset of treatment is essential for improving the patients' condition.
- Oseltamivir treatment may be related to the onset of an attack in patients with acute intermittent porphyria.

Table 1. Course of catecholamines and porphyrins during admission

	Normal	Attack	After treatment
Catecholamines in urine			
Metanephrine, µg/24h	64–302	516	259
Normetanephrine, µg/24h	162–527	2,212	1,135
3-methoxythyramine, µg/24h	103–404	532	296
Porphyrins in urine			
Delta-aminolevulinate, µg/g	<5	101	41
Porphobilinogen, mg/24h	<2	205	124
Uroporphyrin, µg/24h	0–50	2,540	608
Coproporphyrin, µg/24h	0–160	1,306	671

Course and outcome

Despite starting specific treatment, the patient began to develop predominantly proximal weakness in his upper and lower limbs. Electromyography/electroneurography showed a neurogenic loss of motor units in both deltoids with signs of active axonal injury and increased distal motor latencies with dispersion of axillary nerve action potential. Magnetic resonance imaging of the head and cerebrospinal fluid analysis were normal, as were lead levels in blood.

The patient slowly improved 5 days after starting treatment: abdominal pain improved, behavioural disorders, constipation, hypertension and tachycardia resolved, and blood sodium levels normalised.

The adrenal lesion was evaluated by methoxyisobutylisonitrile (MIBI) scintigraphy and no pathological deposits of the tracer suggesting chromaffin tumours were identified. Catecholamines in blood and urine, that were initially high, normalised following a pattern similar to the course of porphyrins in urine (Table 1).

The initial re-evaluation after the patient was discharged showed gradual improvement of his neurological symptoms.

However, the patient presented with a second attack characterised once again by abdominal pain and behavioural disorders precipitated by a flu-like illness, for which he received oseltamivir, a drug initially catalogued as safe in the therapeutic guidelines consulted.

After the patient was hospitalised, oseltamivir was discontinued and specific treatment for AIP was reintroduced. The patient rapidly responded favourably with no other complications.

Discussion

AIP is a genetic disorder that occurs with behavioural changes and abdominal pain, among other symptoms.[1] Our patient, who had AIP with severe clinical manifestations, developed severe polyneuropathy initially controlled with medication, followed by a subsequent relapse that could be associated with oseltamivir, a relationship not previously described in the literature. During the patient's first attack, several unusual events occurred that are worth discussing.

Firstly, an adrenal lesion associated with high levels of catecholamines in blood and urine was detected. This finding has been previously described in the literature, although it is still quite exceptional.[3]

Secondly, the neurological involvement, presenting as severe, predominantly axonal motor polyneuropathy, responded unusually well to specific treatment. These lesions generally leave severe and lasting sequelae, but our patient recovered a practically normal status.[1] It should be noted that the neurological symptoms began to resolve almost on the same day that treatment with intravenous haemin was started, and it may have been the rapid onset of treatment that led to the favourable response of this patient.

Finally, the synchronicity of the second attack with oseltamivir treatment is of interest. Such an event has not been reported in the literature until now, and oseltamivir is listed as safe in the prospectuses of various health organisations. The decision to start this treatment was based mainly on a serological diagnosis of influenza A virus infection, the patient's recent hospital admission and associated motor polyneuropathy in the recovery phase.

Porphyric attacks have been documented in patients who received antiviral treatment with efavirenz and ritonavir/atazanavir.[4,5] The mechanism by which these drugs cause a porphyric attack seems to be mediated by the activation of cytochrome 3A4 (CYP3A4), although this does not seem to be the fundamental route of oseltamivir metabolism. To our knowledge, no reports have documented a link between the administration of oseltamivir and the development of a porphyric attack.

Our patient's second attack could have been mediated by the infectious state itself. However, the synchronicity of oseltamivir administration and the subsequent development of a porphyric episode raises questions about the association of this antiviral with the episode. ■

Acknowledgements

The authors would like to thank Víctor Latorre at Medical Science Consulting (Valencia, Spain) for medical writing support.

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