Diagnostic Dilemmas in Acute Intermittent Porphyria

A Case Report

Vembu Periasamy^a Asmahan Al Shubaili^a Y. Girsh^b

Departments of ^aNeurology and ^bLaboratory Medicine, Ibn Sina Hospital, Kuwait, Kuwait

Key Words

Acute intermittent porphyria · Porphobilinogen · δ -Aminolevulinic acid · Intravenous immunoglobulin

Abstract

Objective: To present the importance of early diagnosis of acute intermittent porphyria (AIP) in patients with atypical presentation and discuss the diagnostic problems encountered in this case. **Clinical Presentation:** A 15-year-old girl presented with upper respiratory tract infection, fever, seizures and abdominal pain. An initial diagnosis of encephalitis was made. She received antiviral drugs and anticonvulsants. Two weeks later, she developed progressive flaccid quadriplegia and facial weakness. She also developed respiratory paralysis and was intubated. Cytoalbuminous dissociation was seen in the cerebrospinal fluid. A diagnosis of severe Guillain-Barré syndrome was made. **Intervention:** The patient received a course of intravenous immunoglobulins which did not result in any clinical improvement. Plasmapheresis, started after 12 weeks, led to partial improvement. The patient continued to have attacks of seizures, abdominal pain and vomiting with severe quadriparesis. A repeat screening test for urine porphyrins was positive, and AIP was confirmed by specific porphobilinogen deaminase in the blood. The patient was treated

with large doses of intravenous glucose, followed by injections of hematin. The patient improved remarkably. She was extubated, discharged from Intensive Care Unit and started on a rehabilitation program. **Conclusion:** This patient was initially diagnosed erroneously with a negative screening test for AIP and consequently treated inappropriately. The proper diagnosis was made after repeating the screening test followed by specific tests of porphobilinogen deaminase.

Copyright © 2002 S. Karger AG, Basel

Introduction

Acute intermittent porphyria (AIP) is a rare metabolic disorder which can be life-threatening, especially when porphyric crisis leads to generalized paralysis. It is an autosomal dominant disorder resulting from deficiency of the enzyme hydroxymethylbilane synthase (previously called porphobilinogen deaminase) that can remain undetected until exacerbations appear after a precipitant factor. Precipitation of attacks with the use of drugs is a principal feature of AIP. Porphyric crisis may manifest with abdominal pain, psychiatric or neurologic manifestations. Abdominal pain, vomiting, paralytic ileus, tachycardia, and hypertension have been attributed to autonomous neuropathy.

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

© 2002 S. Karger AG, Basel
1011–7571/02/0112–0108\$18.50/0

Accessible online at:
www.karger.com/journals/mpp

Dr. V. Periasamy
Department of Neurology, Ibn Sina Hospital
PO Box 25427
13115 Safat (Kuwait)
Tel. +965 4840837, Fax +965 4849226, E-Mail thomas_tom@go.com

In most European countries, the estimated prevalence of clinically overt acute porphyria is 1–2 per 100,000 population [1]. AIP is the most common neurologic porphyria with an estimated prevalence of 1 in 10,000 to 1 in 50,000 people of north European ancestry. Ninety percent of individuals with AIP are clinically latent. Biochemical studies of relatives of patients with symptoms indicate a frequency of 1–2 per 10,000 individuals for AIP [1]. There are no reports on the occurrence or incidence of AIP among Arabs, including Kuwaitis. We report the case of a 15-year-old girl, in whom the diagnosis of AIP was delayed.

Case Report

A 15-year-old Kuwaiti girl was admitted to Jahra Hospital, Kuwait with the complaints of sore throat, upper respiratory tract infection, associated with vomiting, severe abdominal pain and a fever of 5 days' duration. Three days later she developed recurrent generalized tonic clonic convulsions and became drowsy.

Initial central nervous system examination showed generalized muscle weakness, with motor power of 3 out of 5 in all four limbs, brisk deep tendon reflexes, flexor plantar responses and no meningeal signs. Computed tomography of the brain revealed diffuse edema. Her EEG was grossly abnormal due to diffuse slowing of activities. Initial cerebrospinal fluid (CSF) study was also traumatic; it contained 105 white blood cells with 90% lymphocytes and a raised CSF protein level of 700 mg/l. Urine porphyria screening was negative.

A provisional diagnosis of acute encephalitis was made, and the patient was treated with antiviral drugs and anticonvulsants. After 2 weeks, her general condition deteriorated with generalized muscle weakness, hypotonia of limbs, with motor power of 1–2 out of 5, depressed deep tendon jerks and retention of urine.

Three weeks later, she was transferred to the Department of Neurology, Ibn Sina Hospital, Kuwait for further management. Her central nervous system assessment upon admission in the department showed bilateral lower motor neuron facial palsy, severe weakness of limbs, with muscle power of zero, total areflexia with mute plantar responses. A second lumbar puncture and CSF study were normal. Nerve conduction velocity (NCV) study revealed signs of mixed demyelinating and axonal neuropathy. Repeat porphyria screening tests were again negative. An initial diagnosis of acute Guillain-Barré syndrome was made.

A few days later, she developed signs of severe respiratory failure and was transferred to the intensive medical care unit for ventilatory support. She received two courses of intravenous immunoglobulins 2 weeks apart. Her neurological status improved slightly. After 8 weeks of illness, a tracheostomy was necessary for prolonged ventilation. A third lumbar puncture was performed, which showed CSF protein of 4.295 g/l, glucose 3.46 mmol/l; no blood cells were found. During her stay in the intensive care unit, she had persistent low levels of serum sodium and potassium, and showed signs of autonomic dysfunction and severe liver impairment. Since there was no improvement 12 weeks after the onset of her illness, a full course of plasmapheresis was carried out, after which her neurological status improved mildly. A repeat NCV study showed total inexcitability of the nerves, indi-

Fig. 1. This figure illustrates the wasted legs with bilateral foot drop after 2 years of illness.

cating severe axonal neuropathy and repeat urine screening test for porphyrins was positive. After 4 months of illness, the diagnosis of AIP was made and the contraindicated drugs for porphyria were stopped.

The diagnosis of AIP was further confirmed by the following biochemical tests: δ -aminolevulinic acid in the urine was 7.9 mg/24 h (reference range <5 mg/24 h) and porphobilinogen in the urine was 10.4 mg/24 h (reference range <2 mg/24 h) and porphobilinogen deaminase in the blood was 66 units/l (reference range 85–165 units/l).

Since the patient was not responding to intravenous glucose, a drug specifically for porphyria, injection of PanHematin (hemin), 4 mg/kg body weight, was given intravenously every 12 h for 7 days. The patient tolerated the drug well and had very few minor relapses, which were treated symptomatically. However, the patient developed severe generalized muscle wasting, resulting in claw hands and foot drops. She subsequently underwent physiotherapy and a prolonged rehabilitation program. Slowly she gained body weight and her motor power improved well enough to walk with support. A residual bilateral foot drop with mild paraparesis was observed (fig. 1).

Discussion

Porphyric neuropathy is a rare and often a neglected differential diagnosis of Guillain-Barré syndrome [3]. Of those individuals who inherit the gene, only 10% become symptomatic. Typically young adults present with intermittent attacks, which occur in more women than men in the ratio 4:1. It is characterized by severe progressive motor neuropathy, leading to respiratory muscle paralysis. Moreover, it mimicks Guillain-Barré syndrome, which occurs in approximately 4–5% of patients with AIP.

The pathophysiology of the neurologic manifestation is not clearly understood. Current theories implicate δ -aminolevulinate as a neurotoxin, which causes neurotransmitter disturbances, secondary to the deficiency of heme and tryptophan dioxygenase in the liver or depletion of heme in the nerve cells [1]. The neurologic porphyrias are a diagnostic challenge because the signs and symptoms mimic other more common disorders like Guillain-Barré syndrome, acute encephalitis and acute abdominal conditions [2].

Grave neuropathy affecting mainly motor nerves directly after an attack could be of different pathogenesis [3, 4]. The neurological complications of AIP are cranial neuropathy, peripheral neuropathy, autonomic neuropathy and generalized convulsions [5, 6]. Peripheral neuropathy is caused by segmental demyelination or axonal degeneration with secondary loss of myelin. A severe attack may progress to a motor neuropathy with absent deep tendon jerks, which may resemble acute Guillain-Barré syndrome. The abnormal activity of the heme biosynthetic enzymes in the peripheral nerves may have an important role in the genesis of axonal and myelin degeneration [1, 5].

The phrenic nerve involvement could explain the respiratory failure in AIP. Indeed, abdominal pain with vomiting is almost universal in acute porphyria [1, 7, 8]. Severe hyponatremia due to syndrome of inappropriate antidiuretic hormone is provoked by AIP. Damage to the hypothalamic hypophyseal tract during exacerbation may lead to an increase in circulating antidiuretic hormone, resulting in the abnormal electrolyte concentration [9].

In this patient, initial diagnosis of acute encephalitis was made because of an atypical combination of symptoms. Later on, the patient developed bilateral facial palsy, progressive quadriparesis, total areflexia and respiratory failure. The CSF study showed albuminocytological dissociation with abnormal NCV study. These features were consistent with the erroneous diagnosis of acute

Guillain-Barré syndrome. Despite intensive treatment with intravenous immunoglobulins and plasmapheresis, the patient did not improve satisfactorily. So a high index of clinical suspicion was raised and we repeated screening the urine again for porphyrins, which became positive. Thus, the presented case represents severe Guillain-Barré-like syndrome due to AIP, rather than the association of Guillain-Barré syndrome.

The diagnosis was confirmed by specific biochemical tests of the patient, who improved considerably with specific treatment for porphyria. The specific drug panhema-tin (heme) acts to limit the hepatic and bone marrow synthesis of porphyrins. This action is likely due to the inhibition of activity in the enzyme δ -aminolevulinic acid synthase, which limits the rate of the porphyrin/heme biosynthetic pathway [1, 10].

Increased urinary excretion of porphobilinogen and δ -aminolevulinic acid confirmed the diagnosis [10]. Screening tests for porphobilinogen have been criticized because they lack sensitivity and produce occasional false positive results [1]. A positive screening test is still useful in an emergency, but should always be confirmed by a specific quantitative assay. Excretion of porphobilinogen may fall below the detection limit of screening tests soon after the onset of the symptoms [1]. This probably explains why earlier screening tests were negative in this patient. Therefore, when a high index of clinical suspicion is raised, it is important to avoid delay in diagnosis, which may lead to the inadvertent use of contraindicated drugs leading to a poor prognosis as noted in this patient [1].

Conclusion

When the clinical features are highly suggestive of AIP, even with a negative screening test, porphyrogenic drugs should be avoided and conventional treatment with large doses of intravenous glucose for 2–3 days should be started. Improvement is expected within 48 h. If there is no improvement with glucose and other symptomatic treatment, and when the neurological manifestations are progressing, specific drug therapy for AIP (heme-panhema-tin) should be started to avoid complications and further exacerbations.

Acknowledgment

The authors gratefully acknowledge the secretarial assistance of Ms. Asha.

References

- 1 Elder GH, Hift RJ, Meissner PN: The acute porphyrias. *Lancet* 1997;349:1613–1617.
- 2 Chaix Y, Gencourt C, Grouteau E, Carriere JP: Acute intermittent porphyria associated with epilepsy in a child: Diagnostic and therapeutic difficulties. *Arch Pediatr* 1997;4:971–974.
- 3 McEneaney D, Hawkins S, Trimble E, Smye M: Porphyric neuropathy: A rare and often neglected differential diagnosis of Guillain-Barré syndrome. *J Neurol Sci* 1993;114:231–233.
- 4 Wikberg A, Andersson C, Lithner F: Signs of neuropathy in the lower legs and feet of patients with acute intermittent porphyria. *J Intern Med* 2000;248:27–32.
- 5 Suarez JJ, Cohen ML, Larkin J, Kernich CA, Hricik DE, Daroff RB: Acute intermittent porphyria, clinicopathologic correlation: A report of a case and review of the literature. *Neurology* 1997;48:1678–1683.
- 6 Bylesjo I, Forsgren L, Lithner F, Boman K: Epidemiology and clinical characteristics of seizures in patients with acute intermittent porphyria. *Epilepsia* 1996;37:230–235.
- 7 Owusu SK, Asamoah EO, Ofori-Darko VA: Acute intermittent porphyria: An often forgotten diagnosis in acute abdomen. *West Afr J Med* 1992;11:162–164.
- 8 Usalan C, Erdem Y, Altun B, Gursay M, Celika I, Yasavue U, Turgan C, Caglar S: Severe hyponatremia due to SIADH, provoked by acute intermittent porphyria. *Clin Nephrol* 1996;45:418.
- 9 Grandchamp B: Acute intermittent porphyria (reviews). *Semin Liver Dis* 1998;18:17–24.
- 10 Schreiber WE: Acute intermittent porphyria: Laboratory diagnosis by molecular methods. *Clin Lab Med* 1995;15:943–956.