Fatal Neurological Manifestations of Acute Intermittent Porphyria

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Three patients of acute intermittent porphyrias (AIP) with severe neurological involvement from Bahrain are reported. All had some symptoms referable to gastrointestinal tract. One patient had presented at the age of fifty years for the first time. One was treated with Hematin. All of them had fatal outcome. This is the first report of porphyria from Bahrain.

Bahrain Med Bull 2004;26(2):

Porphyrias belong to a group of diseases, due to genetic defect of enzymes, engaged in the formation of heme[1]. Hemoproteins are essential for aerobic metabolism and therefore all of the body cells appear to contain the mechanisms for making heme. A partial deficiency of one of the seven enzymes in the pathway causes the characteristic clinical and biological features[2] Congenital erythropoietic porphyria (CEP) is inherited as autosomal recessive and characterized by marked skin photosensitivity and usually manifests at birth and usually associated with hemolysis. Porphyria cutanea tarda (PCT) is the most common form of Porphyria and usually begins in middle and late adult life. These patients have mild to severe photosensitivity and often have obvious liver disease. Alcohol and estrogens are common aggravating factors. AIP is the most common autosomal dominant form of acute hepatic porphyria and these patients lack cutaneous photosensitivity.

Most patients of hereditary porphyria are asymptomatic. Only one third of them manifest clinically.

Various factors precipitate an acute attack of porphyria. There is a long list of drugs, which can precipitate an acute attack of porphyria[3,4]. The enzymatic defect in porphyria is never total, because it is not compatible with life.

Out of the seven types of porphyrias, four are classified as AIP. These four types are associated with neuro visceral symptoms. Abdominal symptoms are almost always seen in patients with clinical manifestations of AIP[11]. Among the various neurological symptoms, the predominant are those of peripheral neuropathy, which occurs over few days, particularly motor type characterized with wrist and foot drops and areflexia. Sensory symptoms are usually mild. Cranial nerve involvement may occur especially III, VII, and X nerves. Rarely optic nerves are involved. It may mimics Guillian Barre syndrome and lead poisoning.

Involvement of central nervous system results in bulbar paralysis, cerebellar, basal ganglion manifestations, hypothalamic dysfunctions, seizures, psychosis and coma[6]. Seizures are relatively rare. Epilepsy may be the presenting symptom in porphyria[2].

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Pathological changes are dominated by axonal degeneration and central chromatolysis of peripheral nerves. The course of the disease is unpredictable. Management is mainly symptomatic, and treatment with Hematin/Heme arginate in the early phase of the illness is recommended.

This is a report of the first three patients of AIP with severe neurological involvement from Bahrain.

THE CASES

Patient one

Sixteen years old male was admitted for weakness of both upper and lower limbs of one-week duration. It was associated with numbness of all the limbs. There was no cranial nerves symptom, no febrile illness in the near past. On further enquiry, he was admitted twice under surgical care for 'acute abdomen' six months prior to the recent admission, and discharged without a definitive diagnosis. He was diagnosed to have paranoid schizophrenia three months ago and was receiving antipsychotic medication from the psychiatrist. There was no family history of any significant illness and screening for porphyrias was negative.

On admission, his vital signs were normal. Nervous system examination revealed a fully conscious male. His speech was of very low volume. He had bilateral lower motor facial weakness and bilateral vocal cord paralysis. There was hypotonia with grade 2/5 power in all limbs. Sensory examination was normal. All deep tendon reflexes were absent and plantars were flexor. Other systemic examination was normal. His routine blood and biochemistry including full blood counts, erythrocytes sedimentation rate, urea, electrolytes, calcium, phosphorous, magnesium and liver functions tests were normal. Urine was positive for porphobilinogen on repeated examinations. Nerve conduction studies showed grossly reduced velocities with very low amplitudes of median, ulnar, common peroneal, and tibial nerves in all limbs. The sensory latencies were normal.

His condition worsened rapidly over the next three days with respiratory muscle involvement where he needed mechanical ventilation, therefore, tracheostomy was done. He was treated with Hematin for three days. He made significant recovery in the following two months and was ambulant with assistance. Unfortunately, over the following three months he developed tracheal stenosis at the site of tracheostomy and expired due to acute respiratory failure, secondary to aspiration pneumonia.

Patient two

Seventeen years old male was admitted for recurrent vomiting and slurred speech of three days duration. There was no headache. One of his elder brothers had died of similar symptoms six years ago who became comatosed rapidly, and probably had encephalitis and died within few days.

On admission, his vital signs were normal, systemic examination was normal except for mild tachycardia. Nervous system examination revealed conscious male with slurred speech, bilateral deafness, and signs of sensori-motor peripheral neuropathy in both upper and lower limbs along with disturbed autonomic functions, manifesting in the form of sweating and tachycardia. His routine blood and biochemistry investigations were normal. CSF study was normal. His respiration was not satisfactory and needed mechanical ventilation. His urine was positive for

porphobilinogen. Assay of erythrocyte PBG diaminase was positive for coproporphyrin.

Hematin was not available for treatment. His autonomic dysfunction started to worsen. He developed few episodes of cardiac stand still and died.

Patient three

Fifty year old man was admitted for recurrent vomiting and giddiness of three days duration. He had abdominal pain, which was diffuse. He had mild fever for two days prior to the previous symptoms. There was no headache or weakness of limbs.

On the day of admission, his vital signs were normal. Nervous system examination showed fully conscious man, with severe dysarthria. He had bilateral sixth nerve palsies. His gag reflex was bilaterally poor. Motor and sensory examinations in limbs were normal. Deep tendon reflexes were absent in all limbs and plantars were flexor.

His urine for porphobilinogen was negative. He was treated with high doses of glucose and his symptoms had completely improved over a short time. He was admitted for the second time after three years with backache for which he took Diclofenec and then developed giddiness and vomiting, associated with abdominal pain of two days duration. He had limited abduction of the eyes and restriction of the upward movements. The power was normal in all limbs and there was generalized areflexia. Urine examination for porphobilinogen was positive as well as stool for coproporphyrins. Family screening for porphyria was negative. He was treated with high doses of Dextrose and other symptomatic measures. Hematin was not available for immediate use. He rapidly worsened over the next three days and died of acute respiratory failure.

DISCUSSION

Porphyrias are rare metabolic disorders. The three important features are abdominal pain, psychiatric, and neurological symptoms of acute onset, which should raise the suspicion of AIP, especially if there is positive family history of similar symptoms. The estimated prevalence of AIP is 1-2 in 100,000 population[11].

Nearly 80% of people who have deficiency of the enzymes involved in heme synthesis remain asymptomatic. All patients had very significant neurological involvement, even though patients may have one or all of the symptoms of porphyria. The most common feature, seen was abdominal and manifest as pain, vomiting, constipation and paralytic ileus. Patient two had initial manifestation of only vomiting. The visceral symptoms are secondary to autonomic neuropathy[11]. The common age group affected is between puberty and thirty years[6].

In this study, the third patient manifested for the first time at the age of fifty years, at which time urine examination was negative for porphyrins, but was positive on more than one occasion during the second admission. Traditionally, at least four factors can result in activating the disease manifestations in those who have latent disease. There are a large group of drugs, infections, certain steroids and starvation[6]. In the first patient the antipsychotic drug may have precipitated his porphyric symptoms. Even though any part of nervous system can be affected, peripheral nervous system involvement masks the other symptoms[6]. The first and third patient in this report had severe peripheral neuropathy, whereas second patient had predominantly bulbar symptoms. The possible cause of death in the second and third patients is acute neuropathy of peripheral and autonomic system leading to cardiac arrhythmia,

intercostals and diaphragm paralysis, whereas first patient possibly died due to acute aspiration pneumonia.

Acute intermittent porphyria should be considered in all peripheral neuropathy of unknown etiology. The convulsion could be due to dangerously low level of serum sodium due to syndrome of Inappropriate Antidiuretic Hormone Secretion[10,11].

The diagnosis of acute porphyria is by detecting increased urinary excretion of porphobilinogen. The type of porphyria is established by measuring the fecal and plasma porphyrins[11,5].

Two of patients had no detectable porphobilinogen in urine or in stool. On repeated examination it was positive. Various electrophysiological changes have been described, which are not specific to porphyria.

The management of AIP includes increased carbohydrate intake by IV glucose infusion 2000 Kcal/24 hours[4]. The definitive management is by administration of Hematin (Heme arginate) intravenously at the beginning of the disease. It is well known to reverse the biochemical changes in porphyrias[2,7]. In established neuropathy the role of Heme is not clear. Thadani and her colleagues believe that Hematin produces definite remission if administrated in the early course of the disease[2].

In patients who show underlying epileptogenic structural lesions on CT or MRI scan, antiepileptic drug therapy may be indicated[8]. Except for Gabapentin and vigabatrin almost all other antiepileptic drugs could exacerbate porphyric crisis[9,12].

In this report, Hematin was used for one patient only who survived the acute episode. All three patients in this study had a fatal outcome even though one had made a satisfactory improvement for few months but eventually he succumbed to respiratory failure and aspiration pneumonia. Heme arginate was administrated in a dose of 3 mg /kg/day for 4 days, each session over 15 minutes by intravenous route as recommended by Thadani et al[2].

It is important to note that the second patient had run a rapid fatal course like his elder brother. The family members of patient one and three were screened for porphyria and were negative.

CONCLUSION

For the first time from Bahrain, three male patients who had severe neurological manifestations secondary to acute intermittent porphyria are reported. All patients had fatal outcome.

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