**Review**

**Acute porphyrias and porphyric neuropathy**

Doungporn Ruthirago MD, Parunyou Julayanont MD, Supannee Rassameehiran MD

**Abstract**

The porphyrias are a group of uncommon inherited metabolic disorders of heme biosynthesis. Acute porphyrias are specific types of porphyrias characterized by the presence of acute attacks that usually present with abdominal pain, psychiatric symptoms, and neuropathy. The nonspecific porphyria presentations, the complexity of heme biosynthesis, and difficulty in interpreting the laboratory tests make the diagnosis of porphyria challenging. Treatment of acute porphyria and avoidance of precipitating factors should be initiated early to prevent potentially severe long-term sequelae from nerve damage. Porphyric neuropathy is one such complication and is characterized by an axonal neuropathy with predominant motor involvement. Sensory neuropathy is also found but is less common. Although the exact pathophysiology of porphyric neuropathy remains uncertain, neural energy failure from heme deficiency and neurotoxicity from porphyrin precursors are probably the two main mechanisms. The understanding of porphyric neuropathy and manifestations of each type of porphyria along with timely implementation of appropriate tests can significantly assist in the diagnosis of these rare diseases.

**Key words:** porphyria; porphyric neuropathy; neuropathy; nervous system; heme

**Introduction**

The porphyrias are groups of uncommon diseases occurring secondary to an autosomal dominant inherited deficiency of enzymes in the heme biosynthetic pathway. Each porphyria is caused by a different enzymatic alteration that leads to accumulation of heme precursors, causing various clinical symptoms. Porphyrias have a high degree of symptom variance, including gastrointestinal, neurological, cutaneous, and psychiatric manifestations. Each presentation is nonspecific, mimicking other diseases that are much more common and making the diagnosis of porphyrias challenging. A high index of suspicion and appropriate laboratory investigation at the proper time are essential to establish the diagnosis.

Porphyrias can be broadly categorized into acute porphyrias and non-acute porphyrias depending on the presence of acute porphyrinic attacks. Patients who present with acute attacks need more urgent diagnosis and treatment to prevent potentially severe long-term sequelae. The well-known triad of...
abdominal pain, neuropathy, and psychiatric disturbances helps the clinician recognize acute porphyrias. However, in many cases patients present with only one or two symptoms. Sensory or motor neuropathy may be the most objective clinical manifestation that assists in the diagnosis of these uncommon diseases. Comprehensive reviews of the porphyrias are currently available in other literatures. The objective of this article is to simplify the understanding of the acute porphyrias and porphyric neuropathy.

The word “porphyria” is derived from the Greek word “porphura” which means purple. This is from the observation that the urine of porphyria patients has a red-purple color and becomes darker when exposed to light. Due to their enzymatic deficiency these patients have excess porphyrins and porphyrin precursors which accumulate in the body and are later excreted into urine and feces.

**PATHOPHYSIOLOGY**

**HEMЕ BIOSYNTHESES**

Heme is an oxygen carrier which is important to all aerobic reactions. It also functions as a source of electrons in the mitochondrial electron transport chain. Heme is synthesized in the bone marrow and liver and is required for the synthesis of hemoproteins—hemoglobin, myoglobin, and cytochromes, etc. Heme synthesis starts in the mitochondria where succinyl coenzyme A combines with glycine to form aminolevulinic acid (ALA). This process is catalyzed by aminolevulinic acid synthase (ALAS) which is the rate-limiting step of heme synthesis. Aminolevulinic acid synthase is inhibited by heme in a negative feedback pathway. When the requirement for heme increases or the reserves are depleted, ALAS is disinhibited and the heme metabolic pathway is activated. The next steps occur in the cytoplasm where two ALAs are converted to porphobilinogen (PBG) by aminolevulinic acid dehydratase (ALAD). Four PBGs are combined to form uroporphyrinogen by uroporphyrinogen cosynthase (UROS) enzyme. Uroporphyrinogen is later changed to coproporphyrinogen by the uroporphyrinogen decarboxylase (UROD) enzyme. Coproporphyrinogen enters the mitochondria where it is converted by the coproporphyrinogen oxidase (CPOX) enzyme to protoporphyrinogen. Protoporphyrinogen is changed into protoporphyrin IX by protoporphyrinogen oxidase (PPOX). The last step of synthesis is adding iron to protoporphyrin IX by the ferrochelatase (FECH) enzyme to form heme (Table).

Enzymatic defects in each step of the heme biosynthetic pathway cause susceptibility to different types of porphyria. The specific deficiency predicts which heme precursors or intermediates will accumulate and later be excreted in the feces or urine. These excess metabolites are sometimes oxidized into pigmented porphyrins and produce red/purple urine. Environmental factors also have an important role in development of acute porphyras. Acute attacks occur from events that induce ALAS directly or increase the requirements of heme synthesis which indirectly dis-inhibit ALAS. For example, porphyrinogenic drugs, such as barbiturates and sulfa antibiotics, induce cytochrome P450, causing increased hepatic heme turnover. Infection and inflammation induce the expression of hepatic acute phase protein that catabolizes heme. Transcription of ALAS is stimulated by peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), which involves energy metabolism and explains why acute porphyria is precipitated by starvation.

**PATHOPHYSIOLOGY OF PORPHYRIC NEUROPATHY**

Every symptom of acute porphyrias can be explained by dysfunction of the nervous system. Abdominal pain during acute attacks reflects autonomic neuropathy that causes ileus, abdominal distension, followed by pain, constipation, nausea, and vomiting. Psychiatric disturbances can be explained by central nervous system involvement. Acute porphyric neurovisceral attacks develop in genetic-susceptible individuals when environmental triggers activate ALAS1, making deficient enzymes in later steps of heme biosynthesis become the rate-limiting step, leading to accumulation of porphyrin precursors, such as ALA and PBG.

Porphyric neuropathy may be explained by 2 mechanisms. The first mechanism is direct neu-
### Enzymatic defects

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Genes</th>
<th>Disease</th>
<th>Mode of inheritance</th>
<th>Neuro-</th>
<th>Cutaneous involvement</th>
<th>Laboratory findings (increased level)</th>
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rotoxicity of accumulated porphyrin precursors, especially ALA. Aminolevulinic acid increases in acute attacks of porphyria and other porphyria-like neuropathies, such as lead poisoning and hereditary tyrosinemia. Aminolevulinic acid induces the formation of free radicals, causing oxidative damage to cell structures. The second mechanism is energy deficits due to inadequate heme synthesis, which is an essential component of electron transport system. Dysfunction of Na+/K+ ATPase, which is energy-dependent, causes abnormal axon transport and neural dysfunction. Energy deficits also cause impaired detoxification systems in which cytochrome P450 fails to detoxify drugs and mitochondria cannot prevent oxidative damage (Figure).

Neuropathy occurs in 20-68% of porphyria patients. The typical pattern of porphyrin neuropathy is predominantly motor axonal neuropathy. Abdominal pain usually starts days to weeks before neuropathy. The motor neuropathy is normally symmetrical and begins in proximal part of the upper extremities. However, the patterns of motor involvement are variable. Sensory neuropathy is less common, presents as neuropathic pain and distal limb paresthesia, and sometimes occurs in proximal distribution. Cranial nerve involvement can also occur but is infrequent.

**Classifications**

The porphyrias may be classified based on the primary clinical manifestations as either acute or cutaneous or by the major site of the enzymatic defect as either hepatic or erythropoietic. This review will be based on porphyria classification by clinical manifestation and will mention nine types of porphyria according to the enzyme deficiency in each step of heme synthetic pathway with the exception of the X-linked dominant protoporphyria which occurs from a gain of function mutation. Only four types of acute porphyrias are discussed in this review, and the five types of cutaneous porphyrias are listed at the end of the section. The Table shows the classification of porphyrias, related enzymatic deficiencies, gene mutations, mode of inheritance, clinical presentations, and laboratory finding.

**Acute Porphyrias**

An acute life-threatening crisis or acute attacks are characteristic of acute porphyrias. Patients may present with prodromal symptoms, such as behavioral change, insomnia, anxiety, and later develop symptoms of acute attack. Acute attacks usually last no longer than 1-2 weeks before entering a recovery phase; they can be fatal if the patient develops severe neurological dysfunction. The acute attacks usually occur after puberty and rarely occur after menopause. Less than 10% of patients develop recurrent acute attacks. The mode of inheritance of acute porphyrias
is autosomal dominant with incomplete penetrance except for aminolevulinic acid dehydratase deficiency porphyria which is an autosomal recessive disorder.

1. **Acute Intermittent Porphyria (AIP)**

Acute intermittent porphyria is the most common acute porphyria with an incidence of 1 in 20,000.\(^1\) It occurs due to a mutation in the porphobilinogen deaminase (PBGD) gene, which causes decreased PBGD enzyme activity (previously called hydroxymethylbilane synthase). Despite being inherited in an autosomal dominant pattern, AIP has variable penetrance which explains why some patients do not have a family history and why more than 90% of patients with an abnormal gene never develop an acute attack. Acute attacks occur in patients with genetic susceptibility who also have precipitating factors, such as hormones, drugs, or starvation.\(^3\)

Acute attacks of AIP usually develop over two or more days with symptoms of abdominal pain, muscle weakness, neuropathy, sympathetic overactivity, hyponatremia, but no skin lesions.\(^1\) Urine tests during acute attacks demonstrate elevated urine porphobilinogen (PBG) which is sensitive and specific for acute porphyrias. Low PBGD enzyme activity in red blood cells confirms the diagnosis of AIP; however, some patients may not have an enzyme deficiency. The gold standard for diagnosis of AIP is genetic testing for specific mutations.\(^1,3\)

2. **Hereditary Coproporphyria (HCP)**

Patients with HCP present with classic neurovisceral symptoms of acute attack. In some cases cutaneous photosensitivity is also present associated with blistering skin lesions similar to those in porphyria cutanea tarda (PCT). Hereditary coproporphyria occurs from a mutation in the coproporphyrinogen oxidase (CPOX) gene, causing decreased CPOX enzyme activity. Laboratory tests during acute attacks show elevated urine coproporphobilinogen (PBG) which is sensitive and specific for acute porphyrias. Low PBGD enzyme activity in red blood cells confirms the diagnosis of AIP; however, some patients may not have an enzyme deficiency. The gold standard for diagnosis of AIP is genetic testing for specific mutations.\(^1,3\)

3. **Variegate Porphyria (VP)**

Variegate porphyria, similar to HCP, presents with neurovisceral symptoms similar to other acute porphyrias though frequently less severe. Patients may present with cutaneous photosensitivity developing blistering skin lesions more frequently than HCP patients. The incidence of VP is highest in South Africa. It occurs from a mutation of the protoporphyrinogen oxidase (PPOX) gene, causing decreased PPOX enzyme activity. Urine delta-ALA and PBG are elevated during acute attacks but usually are normal between attacks. Plasma porphyrins are increased during attacks. In asymptomatic carriers, urine tests show elevated coproporphyrin, and fecal tests show excess coproporphyrin and protoporphyrin. Genetic testing should be performed to confirm the diagnosis.\(^1\)

4. **Aminolevulinic Acid Dehydratase Deficiency Porphyria (ADP)**

Aminolevulinic acid dehydratase deficiency porphyria is the only acute porphyria that is transmitted in an autosomal recessive pattern. It is extremely rare with less than 10 cases reported worldwide. It occurs from a mutation of the aminolevulinic acid dehydratase (ALAD) gene, causing decreased ALAD enzyme activity. Patients present with symptoms of acute attack similar to AIP. Skin lesions are not present. Laboratory tests during acute attacks show elevated urine ALA but normal PBG.\(^1\)

5. **Cutaneous Porphyrias**

5. Sporadic Porphyria cutanea tarda and familial porphyria cutanea tarda (sPCT and fPCT)
6. Erythropoietic protoporphyria (EPP)
7. X-linked dominant protoporphyria (XLP)
8. Congenital erythropoietic porphyria (CEP)
9. Hepatoerythropoietic porphyria (HEP)

The details of cutaneous porphyrias are beyond the
scope of this review. However, the summary of their enzymatic defects, mutations, modes of inheritance, clinical presentations, and laboratory findings are also shown in the Table.

**Clinical Manifestations**

The presentation of the acute porphyrias is variable and nonspecific; patients usually develop symptoms in several systems.

**Visceral Manifestations**

Abdominal pain is the most common and most troublesome presenting symptom of acute porphyria with an occurrence rate of 85-95%. Patients usually complain of constant, poorly localized pain associated with nausea, vomiting, abdominal distension, and constipation that mimics an acute abdomen. Fever and leukocytosis rarely occur since the pain is neuropathic and not inflammatory. Bladder dysfunction can also develop with urinary retention, incontinence, and dysuria.

**Neurological Manifestations**

Central nervous system symptoms, such as seizure and encephalopathy, are reported in 5-30% and 2-10% of patients, respectively. Seizure in acute porphyrias may be triggered by hyponatremia and hypomagnesemia. In acute attacks associated with encephalopathy, abnormal magnetic resonance imaging similar to that found in posterior reversible encephalopathy syndrome (PRES) has been reported. Peripheral neuropathy can present as weakness, sensory disturbances, pain, and respiratory muscle weakness in 20-68%, 7-38%, 20-70%, and 9-20%, respectively. Motor symptoms are more common than sensory symptoms. Autonomic dysfunction also occurs commonly, presenting as tachycardia, hypertension, restlessness, tremor, and sweating.

**Psychiatric Manifestations**

Psychiatric symptoms are reported in 20-30% of patients during acute attacks. These include anxiety, depression, insomnia, restlessness, disorientation, hallucinations, and paranoia. Chronic pain and depression may also be present in some patients after frequent exacerbations and are associated with increased risk of suicide.

**Cutaneous Manifestations**

Photosensitivity presenting as redness, pain, swelling in sun-exposed areas, and bullous lesions occurs in several types of porphyrias. Cutaneous lesions were reported in 60% of patients with variegate porphyria and 5% of hereditary coproporphyria but are not found in acute intermittent porphyria.

**Other Manifestations**

Hyponatremia occurs in 30% of patients, sometimes due to the syndrome of inappropriate antidiuretic hormone secretion but also due to excessive gastrointestinal loss from vomiting, poor oral intake, and excess renal losses. Dark or red urine may also be an early symptom, but it does not always occur during acute attacks. If present, it suggests the diagnosis. Patients with porphyrias also have an increased incidence of hypertension and chronic kidney disease and have an increased risk for chronic liver disease and hepatocellular carcinoma.

**Diagnosis**

Porphyrias usually present with nonspecific symptoms. Therefore, laboratory tests are essential to confirm or exclude the diagnosis. Common investigations in acute porphyrias include biochemical tests to measure porphyrins and porphyrin precursors, to detect enzyme activities, and to confirm the diagnosis with DNA tests. For patients who present with neuropathy, electrophysiological tests assist in differentiating the type of neuropathy. Pathological studies are not usually required for diagnosis but help improve the understanding of porphyric neuropathy.

**Biochemical Tests**

Deficiency of enzymes in each type of porphyrias causes accumulation of different precursors and intermediates. During acute attacks, these excess
substances accumulate in the liver or bone marrow and later enter the blood. The water-soluble intermediates are excreted in the urine, while the water-insoluble intermediates are excreted in the feces. Porphy- 
rins are named according to the number of carboxyl 
groups as octacarboxyl porphyrin (uroporphyrin), hept-
tacarboxyl porphyrin, hexacarboxyl porphyrin, penta-
carboxyl porphyrin, tetracarboxyl porphyrin (copro-
porphyrin), tricarboxyl porphyrin (harderoporphyrin), 
dicarboxyl porphyrin (protoporphyrin). The more car-
boxyl groups present, the more water-soluble is the 
compound. Tricarboxyl and dicarboxyl prophyrins are 
excreted in bile and feces, while coproporphyrin are 
excreted in urine and feces. Porphyrin precursors, 
such as ALA and PBG, are elevated in all types of 
acute porphyrias, except for ADP which has isolated 
ALA elevation.

During acute attacks, the first-line tests with 
high sensitivity and specificity are measuring urinary 
ALA, PBG, and total porphyrins. If all the levels are 
normal, acute porphyrias can be excluded. If the lev-
els are increased more than 5 times normal, acute 
porphyria is highly possible, and second-line tests 
should be done to differentiate the type of porphyria. 
Nonspecific elevation of less than three times can be 
found in dehydration. However, if the urine level is 
done after the onset of acute attack, ALA and PBG 
levels can be normal. Urine porphyrins may remain 
elevated longer than the precursors, but they are less 
specific for porphyrias. Measurement of individual 
porphyrins in plasma, urine, and feces can be done to 
help differentiate the type of porphyrias by using high 
performance liquid chromatography (HPLC). How-
ever, the patterns of elevation are difficult to interpret 
and other conditions can cause elevation of porphy-
rins. For example, liver diseases, some bone marrow 
diseases and lead poisoning can cause increase in 
total urine porphyrin and coproporphyrin. This pattern 
is also found in hereditary coproporphyria and in var-
iegate porphyria.

For cutaneous porphyrias and acute porphy-
rias with cutaneous manifestations, such as hereditary 
coproporphyria and variegate porphyria, measure-
ment of plasma porphyrins when the patient presents 
with skin symptoms can be used as a first-line test 
to screen for porphyria. If total plasma porphyrin is 
increased, further tests should be done to confirm the 
diagnosis.

Measurement of enzyme activity in erythro-
cytes (PBGD, ALAD) and lymphocytes (CPOX and 
PPOX) can help to support diagnosis of AIP, ADP, 
HCP, and VP, respectively. However, there is some 
overlap between the normal range and the spectrum 
of porphyrias, and some mutations do not cause de-
ciciency in blood cells. It is recommended that an en-
zyme activity assay be used to detect carriers in the 
family when a deficiency in the index case is already 
confirmed.

**GENETIC TESTS**

The gold standard test to confirm diagnosis of 
porphyria is DNA testing to identify specific mutations. 
It can also be used to detect carriers of gene mutation 
in families after the mutation is identified in the index 
case. DNA testing can detect more than 97% of dis-
ease-causing mutations, especially with significantly 
elevated PBG levels. Therefore, porphyrin precursors, 
such as ALA and PBG, and biochemical testing in 
plasma, urine, and feces should be done before 
requesting a DNA test. DNA tests from blood samples 
can be done either during acute attacks or in asymp-
tomatic phases. In patients who present with acute 
attacks without skin lesions, the “Triple test” can be 
requested to detect mutations for AIP, VP, and HCP.

**ELECTROPHYSIOLOGICAL FINDINGS**

As porphyric neuropathy is fundamentally an 
axonal neuropathy with predominant motor nerve 
dysfunction, electrodiagnostics findings typically sup-
port this pattern of neuropathy. Nerve conduction 
studies (NCS) during acute attacks show reductions 
in compound motor unit action potential (CMAP) with 
relatively preserved conduction velocities. Conduction 
abnormalities of sensory nerves are sometimes dem-
onstrated but are less common than motor nerves. 
In later stages, when muscle weakness is more 
prominent, NCS may show progressive reductions in 
CMAP amplitudes. Electromyography (EMG) demon-
strates wide spread fibrillation potentials compatible with denervation, especially in proximal muscles. In later stages, EMG may show polyphasic motor unit action potentials with higher duration and amplitude, predicting denervation and re-innervation patterns. Between acute attacks, even without clinical neuropathy, NCS may show reduced inward rectification (I_H), which indicates subclinical dysfunction of axonal metabolism. During acute attacks, axon excitability recordings show depolarization of axonal membrane secondary to impairment of Na+/K+ ATPase function. Appropriate treatment in early phase of porphyric attack can resolve these neuropathic patterns. However, if the treatment is delayed or if the attack is severe, neuropathy may persist and only partially improve over time.

The clinical manifestations of porphyric neuropathy can overlap with Guillain-Barre syndrome (GBS). The electrophysiological patterns of axonal neuropathy, such as reduced amplitudes, relative preservation of H reflexes, F waves and distal latency, minimal conduction slowing, and absence of conduction block, may help differentiate it from demyelinating patterns typically found in GBS. However, differentiating porphyric neuropathy from the axonal type of GBS is difficult and may need serial electrophysiological studies and other laboratory tests.

**Pathological findings**

Pathological studies demonstrate severe denervation of motor nerves and central chromatolysis of anterior horn cells, suggestive of dying-back Wallerian degeneration, with relatively spared sensory nerves. Muscle biopsy shows significant loss of nerve fibers compatible with neurogenic change and limited changes of muscle denervation atrophy.

The proximal predominant pattern of porphyric neuropathy may be explained by retrograde axonal transport of neurotoxic substances, such as ALA, from the distal part of the axon to motor neuron. Heme precursors may enter at neuromuscular junctions which do not have a blood-nerve barrier and are transported initially to neurons innervating proximal muscles, causing proximal more than distal weakness.

**Treatment**

Most patients who present with acute attacks of porphyrias require hospitalization for pain control, hydration, and treatment of nausea and vomiting. Treatments can be broadly divided into symptomatic treatment, specific treatment of porphyrias, and counseling.

**Symptomatic treatment**

Abdominal and limb pain can be controlled with acetaminophen, nonsteroidal anti-inflammatory drugs, and opiates as needed. Nausea and vomiting can be treated with promethazine, ondansetron, or other antiemetic drugs. Maintaining water and electrolyte balance is very important. Adequate hydration is needed, as well as preventing hyponatremia which can provoke seizures. Constipation can be treated with bulk laxatives or lactulose. Some patients who have hypertension and tachycardia from sympathetic overactivity may need β-blockers, such as propranolol and atenolol. Physical and speech therapy are helpful for patients who develop muscle weakness or bulbar involvement. Some patients with respiratory muscle weakness may need mechanical ventilation. Close monitoring in the intensive care unit is needed in patients with severe acute attacks. Insomnia and anxiety can be managed with benzodiazepines. Antipsychotic medications are sometimes required for psychotic symptoms.

**Specific treatment of acute porphyrias**

Glucose inhibits ALAS and decreases porphyrin synthesis in the liver. Adequate carbohydrate and calorie intake is important to suppress disease activity and accelerate recovery. Intravenous glucose should be administered if the patients cannot tolerate oral diets. Intravenous heme (or hemin) 4 mg/kg/day, given daily for 4-14 days, is a specific and effective treatment if started early before severe nerve damage occurs. It replaces heme deficiency in the liver and suppresses production of porphyrin precursors. Some porphyria experts recommend starting hemin if symptoms do not improve within 1-2 days of intravenous glucose. It should be started in patients...
who have elevated urinary PBG levels. Delayed treatment can lead to nerve damage, chronic pain, and muscle weakness. Hemin has some side effects, such as phlebitis and coagulopathy, which could be prevented by dilution with human albumin and using a central line or large peripheral vein. Less than 10% of patients with recurrent acute attacks need preventive treatment with intravenous hemin and rarely liver transplantation.1, 3

Counseling

Counseling is one of the most important management steps in acute porphyrias. Patients should be advised to avoid precipitating factors. Alcohol and porphyrinogenic drugs, such as barbiturates, sulfonamide antibiotics, hormonal substances, some anti-epileptic medications, should be avoided. Infections should be treated.1 The patients and their physicians should check with reliable sources regarding the safety of drugs before initiating any new treatment. Adequate carbohydrate and calorie intake is important. Porphyria patients should be educated to avoid starvation. A dietitian should be consulted if weight loss is truly necessary.1, 3 Genetic counseling for the patient and their relatives is another important issue. Children of patients with acute porphyrias have a 50% chance of acquiring an abnormal gene. Genetic testing for relatives to detect heterozygous carriers and educating them to avoid precipitating factors can prevent acute attacks.

After specific treatment, the symptoms of acute attacks are usually abolished. Levels of ALA and PBG excreted in the urine return to normal. Prognosis of porphyrias is generally good if the treatments are initiated early and the precipitating factors are removed before severe nerve damage has developed. On the other hand, with delayed treatment, patients may develop nerve damage that results in chronic pain and muscle weakness for several months or an incomplete recovery.10

Conclusions

Porphyrias are rare inherited metabolic disorders that present with neurovisceral, cutaneous, and psychiatric symptoms. Acute porphyrias occur from environmental triggers in the presence of genetic susceptibility, leading to accumulation of porphyrins and their precursors. Porphyric neuropathy is believed to develop from conditions that cause relative heme deficiency and neurotoxicity from porphyrin precursors. The typical electrophysiological pattern of porphyric neuropathy is axonal neuropathy with predominant motor involvement. The timely diagnosis and early initiation of specific treatment are important to prevent severe porphyric neuropathy and its sequelae. Symptomatic treatment during the attacks and counseling about carrier detection and avoidance of precipitating factors should be provided to the patients.

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References

8. Meyer UA, Schuurmans MM, Lindberg RL. Acute por-
Acute porphyrias and porphric neuropathy