

Jacobs Journal of Neurology and Neuroscience

Research Article

The Acute Porphyrrias: Still A Misdiagnosed Cause of Neurological Syndromes

Paolo Ventura^{*1}, Matteo Marcacci¹, Stefano Marchini¹

Center for Porphyrrias, Internal Medicine 2 Unit, Department of Medical and Surgical Science for Children and Adults, University of Modena and Reggio Emilia

**Corresponding author: Dr. Paolo Ventura, MD, Università di Modena e Reggio Emilia, Department of Medical and Surgical Science for Children and Adults, Policlinico di Modena, Largo del Pozzo 71, 41124 Modena (Italy), Tel. 059-4222807; Fax 059-4224363; E-mail: paoloven@unimore.it*

Received: 08-30-2014

Accepted: 12-16-2014

Published: 12-19-2014

Copyright: © Paolo

Abstract

Porphyrrias are a heterogeneous group of rare metabolic disorders, caused by a partial deficiency in one of the enzymes in the heme biosynthetic pathway.

Four forms of porphyrias, also referred as the acute porphyrias [acute intermittent porphyria, hereditary coproporphyria, variegate porphyria and the very rare porphyria due to ALA-dehydratase deficit] may present clinically with recurrent and severe acute neurovisceral crises [acute porphyric attack (APA), including severe abdominal pain and moderate to severe symptoms due to involvement of both peripheral and central nervous system imputable to an accumulation in tissues and plasma of non-porphyrin heme precursors [α -aminolevulinic acid (ALA) and porphobilinogen (PBG)]. During the most severe and prolonged attacks, all parts of nervous system may be involved and severe forms of acute peripheral neuropathy or acute encephalopathy can develop. The clinical presentation of APAs may be greatly variable and may lead to other most common diagnostic hypothesis, such as acute abdomen (acute appendicitis, renal or biliary colic, acute pancreatitis, perforated gastric ulcer or intestinal obstruction), Guillain-Barre' syndrome or acute psychotic attack. The different possible expressions of the neurological involvement along the course of APAs and suggestions for the correct diagnosis and the clinical management of these disorders will be the object of the present review.

Keywords: Acute Porphyric Attack; Acute Porphyrrias; Acute Intermittent Porphyria; Variegate Porphyria; Hereditary Coproporphyria; Heme Arginate; Neuropathy; Psychosis; Paralysis

Introduction

The porphyrias are a heterogeneous group of rare metabolic disorders, caused by a partial deficiency in one of the enzymes in the heme biosynthesis (Figure 1). In some circumstances (such as in some cases of porphyria cutanea tarda or in case of lead poisoning), the metabolic disturbance may be acquired, as

a consequence of the exposition to exogenous toxic substances, able to induce a variably reversible enzymatic inhibition [1-4]. Heme is a complex molecule, constituting the prosthetic group of many different key-proteins (haem proteins) and it is synthesized in every human cell containing mitochondria, but especially in erythroid cells and in the liver [2,5,6].

The porphyrias (Figure 1) are currently classified as erythropoietic [congenital erythropoietic porphyria (CEP) and erythropoietic protoporphyria (EPP)] or hepatic (all the other forms), depending on the main tissue responsible for the enzymatic defect and where the excessive production of protein precursors and/or porphyrins occurs [2,3,7,8].

All the erythropoietic porphyrias and three hepatic porphyrias [porphyria cutanea tarda (PCT), hereditary coproporphyria (HCP) and variegate porphyria (VP)] present clinically with variable grade of cutaneous symptoms, consequent to photosensitivity due to accumulation in plasma and skin of porphyrins (which are highly photoactive molecules). Four hepatic porphyrias [acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP) and the very rare porphyria due to ALA-dehydratase deficit (ALAd-P)] may present clinically with recurrent and severe acute neurovisceral crises [the acute porphyric attack (APA)], including severe abdominal pain and moderate to severe symptoms due to involvement of both peripheral and central nervous system, imputable to an accumulation of non-porphyrin precursors of heme [2,9-12]. According to a strictly clinical point of view, the porphyrias presenting with APAs are also referred to as the acute porphyrias [2-4,13,14]. During severe and prolonged APAs, serious forms of acute peripheral neuropathy (aPNP) or acute encephalopathy can develop. The clinical presentation of APAs may be greatly variable and may mislead to other most common diagnostic hypothesis, such as acute abdomen (acute appendicitis, renal or biliary colic, acute pancreatitis, perforated gastric ulcer or intestinal obstruction), Guillain-Barre' syndrome or acute psychotic attack [9,15]. The correct diagnosis and the prompt treatment of APA are mandatory in order to prevent the progression both of neuropathy and encephalopathy, because the mortality of APAs is still significant (higher than 20% of cases) [16]. The different possible expressions of the neurological involvement along the course of APAs and suggestions for the diagnosis and the clinical management of these disorders will be the object of the present review.

Material and Methods

Studies and review articles related to neurological manifestations associated with an acute porphyric attack (APA) were referred in this article were sought via electronic databases (PubMed®, Medline®, Embase®) and were identified from key references within articles. Search terms and MeSH headings we used included the word *porphyric crisis, acute porphyric attack, drugs, precipitating factors, neuropathy, psychosis, hallucinations, mental disturbances, paresis, paralysis, pain, agitation* combined with each of the following: *porphyrias, ala-synthase, haem, heme, haematin, haem arginate, acute intermittent porphyria, variegate porphyria, hereditary coproporphyria, ala-d deficiency porphyria, lead poisoning*. Due to the matter of content, we did not conducted any formal evaluation

of level of evidence in developing this narrative review.

The Acute Porphyric Attack: Neurological Manifestations

The clinical landmark of acute porphyrias is the acute porphyric attack (APA), characterized by acute crisis expressing with a severe neuro-visceral involvement, whose clinical pictures may be greatly variable and able to mimic many other diseases (Table I); this is the reason why these disturbances are often misdiagnosed and many different specialists, such as surgeons, psychiatrists, gastroenterologists, neurologists and emergency physicians may be involved in the diagnostic process, especially in the cases presenting with very severe and life-threatening symptoms [15]. According to a retrospective study, where porphyrin metabolites were screened in patients who attended neurological wards due to acute polyneuropathy or encephalopathy associated with pain and/or dysautonomia, a detection of 11% of previously undiagnosed forms of acute porphyria was carried out [17].

Table I. Neurological Signs and symptoms of Acute Porphyric Attack (percentage indicate the frequency)* and conditions that may frequently mimicked by APA.

Signs/symptoms	%	Differential Diagnosis (more common)
(Severe) abdominal pain	95-97	Surgical Conditions Associated with acute abdomen (Peritonitis, appendicitis, acute pancreatitis, intestinal occlusion, intestinal ischemia etc.)
Constipation	46-52	Gastroenterological conditions Paralytic Ileus
Tachycardia	65-80	Cardiovascular conditions
Hypertension (diastolic > 85 mmHg)	38-64	Hypertensive crisis
Chest pain	8-15	Tachyarrhythmia Acute Coronary Syndrome
		Dismetabolic/Disendocrine conditions Pheochromocytoma
Hypotension	15-22	Dismetabolic/Disendocrine conditions
Hyponatremia (<120 mEq/L)	25-35	Acute hypoadrenalism (Addisonian crisis) SIADH
Peripheral motor neuropathy	40-60	Neurologic conditions
Cefalea	20-30	Guillain-Barre' syndrome
Sensory neuropathy	20-28	Idiopathic/autoimmune/metabolic polineuropathies
Hypo/areflexia	20-30	Emicrania
Back pain	20-30	Epilepsy
Seizures	10-20	Acute myopathies
Coma	2-10	Dismetabolic/Disendocrine conditions Acute hypoparathyroidism and hypocalcemic crisis Acute hyperparathyroidism and hypercalcemic conditions
Mental changes/psychosis	10-40	Psychiatric conditions Acute psychotic attack Delirium Acute Panic attack
Urine Darkening	70-75	Causes of Macroematuria

*NB More symptoms may be present contemporary during an APA.

An APA is often preceded by a variable period of minor behavioral changes, such as anxiety, irritability, restlessness and insomnia: these symptoms may evolve rapidly to a severe

autonomic and acute motor and/or sensory neuropathy accompanied by a variable grade of involvement of the central nervous system (see below) [13]. APAs develop over hours or days and can last up to several weeks, depending on their correct treatment; they have variable recurrence in different patients, especially if exposed to triggering factors (see below) [13,14,18].

Autonomic Acute Neuropathy

The by far most common symptom of an APA is the onset of severe abdominal pain. The pain is described as excruciating by the patients and often it mimics an “acute abdomen”; in most cases, the symptoms appear disproportionate with respect to the physical examination (abdominal tenderness and/or peritoneal signs are usually absent) and are accompanied by a variable grade of neurological involvement (ranging from agitation to psychotic-like status, see below). Back pain, often extending to the proximal limbs is also frequently present. The abdominal complaints are generally accompanied by gastroenteric (mostly nausea and vomiting, but also constipation and bowel distention, as possible consequence of paralytic ileus) and cardiovascular symptoms (hypertension and tachycardia). During APAs, orthostatic hypotension [19], bladder paresis, isolated diastolic hypertension [20] and diarrhea [21] have also been described.

All these symptoms have been ascribed to an autonomic acute neuropathy: particularly, abdominal signs and symptoms are considered to be the consequence of a splanchnic neuropathic dysfunction; another possible speculated mechanism is a local vasoconstriction with intestinal ischemia [22,23]. Autopic studies have reported a direct involvement of autonomic fibers, through vagus nerve demyelination, axonal loss and chromatolysis of sympathetic ganglion cells, all features contributing to explain the features of dysautonomia characterizing APAs [24,25]. In acute porphyrias, the autonomic neuropathy seems to resemble an acute panautonomic neuropathy (pandysautonomia) with predominance of parasympathetic insufficiency, rather than sympathetic activation [26]. Recently, receptors able to mediate a direct gut-spasmodic effect of ALA (see below) have been recognized [27,28].

Acute Peripheral Neuropathy

An acute peripheral neuropathy (aPNP) is also quite common in case of severe and prolonged APAs (and in some circumstances has been described as the sole clinical complaint). It is mainly a motor neuropathy, characterized by diffuse muscle weakness with symmetrical distribution and equal involvement of the proximal and distal muscle groups of the upper extremities; in the lower limbs the muscle weakness is often greater in the proximal muscles [29]. Motor weakness may also be asymmetric or focal. Muscular weakness usually begins

in the extremities of the limbs but can involve any motor neuron or cranial nerve: it can proceed to tetraplegia (resembling a Guillan-Barre' syndrome) [30, 31]. Cranial nerves (mainly III, VI, IX and X) may also be involved in acute attacks with PNP [19,32]. In literature, although rare, is also described the involvement of the optic nerves or occipital lobes, which may lead to blindness [33, 34]. Bulbar involvement can proceed to respiratory failure [15,35].

Tendon reflexes are reduced and in most severe cases a total areflexia can be observed. Muscle tone is reduced, whereas fasciculations are mostly absent. An exceptional feature of aPNP in APAs is the preservation of the ankle jerks in about half of patients while otherwise there is global areflexia [32]. The most severe (and potentially fatal) complication of this motor neuropathy is the respiratory failure caused by diaphragm paresis: this event is currently uncommon, for most patients are treated at the early phase of an acute attack [31,36-39].

The motor neuropathy may be also associated to sensory symptoms, usually ascribed to nerve irritation: painful paresthesia, hyperesthesia and, although less common, a variable grade of sensory loss [29,32,35,40]. In the literature, less common presentations of sensory symptoms have also been described: a “glove and stocking” distribution (resembling PNP of length-dependant polyneuropathies, as those complicating diabetes mellitus) or a patchy proximal polyneuropathy [32,41]. The regression of motor deficit is often, but not always, complete after therapy (see below); in some cases foot drop and wasting of intrinsic muscles of hands and feet may persist indefinitely [42]. The neurological improvement seems to depend on the duration of the motor deficit itself with respect to the time of therapy: if the deficit is of short duration, the recovery will be quick, but if the deficit is severe and prolonged, the improvement will be slow and the recovery will be more rapid in the proximal than in the distal muscles [36]. This leads to the assumption that the motor nerves undergo axonal degeneration that requires a subsequent regeneration.

Acute Encephalopathy

The involvement of central nervous system during severe APAs is frequent. Headache, altered consciousness and behavior or seizures are well-described possible manifestations of APA [16,40,43-46].

During an APA, the cerebrospinal fluid examination is always normal. Mental confusion, delirium, seizures, and coma may be an effect of the metabolic acute derangement itself, but also of hyponatremia, another frequently described complication of APAs. Hyponatremia has been ascribed to an inappropriate release of antidiuretic hormone (SIADH), caused by a neuronal dysfunction involving the hypothalamus [47]. In literature it has been described a case of a patient with AIP with a reduced

bright signal of posterior pituitary lobe in MRI (T1-weighted) after severe hyponatremia, this suggesting an inappropriate release caused by the breakage of blood-brain barrier as the basis of SIADH rather than inappropriate synthesis of ADH [48-50].

Hyponatremia (but also hypomagnesaemia) may occur also as a result of dehydration (vomiting, diarrhea), nephrotoxicity, and also as an effect of inadequate intravenous administration of 10% or 20% glucose (or dextrose) solutions, a standard first-line therapy for APAs (see below) [51]. These water/electrolyte disturbances may contribute to neurological and psychiatric symptoms of APAs.

At neuroimaging, the acute encephalopathy complicating APAs in AIP patients may present with a posterior reversible encephalopathy syndrome (PRES) [52]. PRES is characterized by a cortical-subcortical vasogenic edema, this supporting the hypothesis about the presence of breakage of blood-brain barrier in patients with AIP. This report is also consistent with the hypothesis that endothelial toxicity would be at the basis of vasogenic edema and hypertension and may act as a cofactor, as it is in other metabolic disturbances, such as eclampsia and uremia [52,53].

Seizures have been also described during APAs: they also may be caused by hyponatremia or, perhaps, hypomagnesaemia. The management of seizures in these patients is very difficult because most drugs normally used to treat seizures are contraindicated in acute porphyrias [45,54-57].

The psychiatric disorders are very unpredictable but rather frequent, especially in patients with chronic or recurrent APAs with severe pain and paresthesias [9,29,40,43,44,58,59]. These events often bring these patients to the observation of a specialist psychiatrist and it is not uncommon in these patients an history of psychiatric observation periods or hospitalization in psychiatric units [43,60]. Mental disorders encountered in the course of APA are highly variable and may occur with simple emotional instability, irritability, psychomotor agitation with or without hallucinations, anxiety, insomnia and depression. It is also frequent the presence of various degrees of abnormal behavior that may mimic a psychosis [9,29,40,43,44,58,59].

PATHOGENESIS OF NEUROLOGICAL SYMPTOMS DURING Apas

In order to explain the neurological manifestations of acute porphyrias, many different hypotheses have been advanced. Currently, most supported theories about the pathogenesis of porphyric neuropathy implicate: 1) α -aminolevulinic acid (ALA) as a direct neurotoxin; 2) a neurotransmitter disturbance secondary to hepatic heme deficiency and 3) severe heme depletion in nerve cells. Other hypotheses, all charac-

terized by a lower grade of evidence from experimental and clinical studies, are: a) the depletion of essential substrates or cofactors (such as pyridoxal phosphate, zinc and glycine) resulting from the disturbance of heme synthesis and b) the presence of abnormal neurotoxic products derived from ALA or Porphobilinogen (PBG) (free radicals, hydroxyhemopyrrole-2-one, porphobilin) [12,61,62].

The presence of neurological manifestations quite similar to those characterizing APAs in patients affected by the very rare form of porphyria due to ALA dehydratase deficiency (ALAd-P), in patients affected by hereditary tyrosinemia (type I) and in case of lead poisoning, all conditions characterized by accumulation of ALA, but not of PBG, strongly support the hypothesis of neurotoxicity of ALA [63-68]. ALA shows a structural similarity with α -amino butyric acid (GABA), an inhibitory neurotransmitter widely distributed in the central nervous system. The involvement of the central nervous system during acute attacks may be due to ALA and GABA interactions: a loss of normal GABAergic function is thought to lead to epilepsy [69]. It has been postulated that, depending on the circumstances, ALA may mimic or antagonize the effects of GABA. Another described effect is an agonist effect of ALA on presynaptic receptors of the GABAergic terminals, whose stimulation would block the release of GABA (negative feedback control of GABA release) [70].

Heme is synthesized locally into the brain, but the role of intra-neural synthesis of porphyrins and their precursors in neurological manifestations of an APA is still ill-defined [71,72]. The reduction in hepatic heme synthesis is responsible for a decrease in the activity of the heme protein tryptophan dioxygenase, the rate-limiting enzyme in the oxydative metabolism of tryptophan to kynurenine, this leading to an increase of the levels of tryptophan. In the literature, an increased urinary excretion of tryptophan (serotonergic) metabolites (5-hydroxy indole acetic acid) in symptomatic patients affected by acute porphyrias has been reported. Many clinical features of the APAs resemble the effects of an increased serotonergic activity, especially those related to autonomic neuropathy and mood disorders (such as depression and anxiety) [73]. Demyelination in severe polyneuropathy seems to be reproduced, in vitro conditions, by free radicals originating from ALA accumulation and Schwann cells seem to be more vulnerable than neurons to oxidative damage induced by ALA [74].

The reversibility of the symptoms with therapy able to reduce ALA levels (see below) supports the hypothesis of possible neurotoxicity of this heme precursor compared to that about the role of heme deficiency itself. The clinical remission of most neurological symptoms in a patient after liver transplantation also suggests the role of porphyrin metabolites, as well as the liver as the main source of porphyrin production [75,76].

The Acute Porphyric Attack: Diagnosis and Differential Diagnosis

The correct diagnosis of an APA greatly depends on the awareness and the experience of the clinician: the misdiagnosis is still quite common, because the APAs are easily confused with other causes of acute abdomen (sometimes leading to unnecessary surgery) or other primary neuropsychiatric disturbances [14,77].

The probability of facing an APA may be higher if the patient is known to be a member of an acute porphyria kindred and/or to be a carrier of genetic mutation consistent with a form of acute porphyria [78]. If a patient known to be affected by acute porphyria shows symptoms consistent with APA, the obvious question is whether the current clinical picture is due to its disease or not: not all symptoms in patients affected by acute porphyrias may be due to APA and these patients may be suffering from other (and more common) diseases. In case of signs indicating involvement of central nervous system, prior to classify such symptoms as APA-related, other causes of acute encephalopathy such as encephalitis or sinus thrombosis, should be always ruled out [29]. Table I summarizes some of the most common clinical pictures whose differential diagnosis should include an APA. Emission of dark (red or reddish-brown) urine, coinciding with the onset of symptoms, is still considered a cardinal sign and it is quite common during an APA [15,77,79,80].

Universal signs or symptoms of APA do not exist, and in up to 10% of patients the crises may express without the most common clinical features (namely, the severe abdominal pain) [44,81]. For this reason, in order to make an accurate diagnosis, and to start an appropriate treatment, an immediate (if it is possible at the onset of symptoms) assessment and interpretation of some appropriate laboratory biochemical tests (namely, determination and quantification of non-porphyrin precursor in biological samples) are mandatory [4,15,77,79,80,82-84]. According to the current knowledge and consensus, an APA is invariably associated with an accumulation, and hence increased urinary excretion, of non-porphyrin precursors [ALA and PBG] [13,77,83,85,86]. For this reason, in case of suspected APA, a fresh light-protected urine sample should be assessed for ALA and PBG concentrations [to date, HPLC assays are the most accurate, but rapid, ion-exchange column tests are also available] (first-line test) [87-92]. In case of significant renal dysfunction, ALA and PBG levels should be assessed in serum [92]. PBG and ALA levels higher than 4-5 times the normal range are highly suggestive of APA (except in case of acute porphyrias gene carriers in whom ALA and PBG excretion occurs at high levels even during the latent phase of the disease) [15,79,93].

If only the ALA level is substantially increased, ALAd-P por-

phyria and other causes of ALA-dehydratase deficiency, such as lead poisoning (plumboporphyria) or hereditary tyrosinemia type 1, should be taken into account before starting treatment [4,14,63,65,77,86]. If urinary PBG and ALA levels are normal, an alternative diagnosis to APA must be considered.

Different Ehrlich's reagent-based tests (such as the Watson-Schwartz test or the Hoesch test, where the colourless pyrrole PBG forms a red-violet pigment after reaction with p-dimethylaminobenzaldehyde) may be used as a rapid assay ("bed-side") to test the presence of urinary PBG (qualitative test) [94,95]. These tests should be considered a "first-line" guide, able to confirm (or to rule-out) a suspicion of APA if made at, or near, the time of the clinical onset of symptoms in case of the most common forms of acute porphyrias (AIP, VP and HCP).

It should be noted that these "bed-side" assays may miss the diagnosis in some extremely uncommon circumstances: a) subjects affected by the very rare ALAd-P or by lead-poisoning, disorders characterized only by accumulation of ALA; b) subjects already treated with haem intravenous infusion (which may rapidly decrease ALA and PBG); c) in some cases of HCP and VP, where increases in ALA and PBG levels during APAs may be more transient; d) in cases of diseases with high urinary excretion of bilinogen (due to possible cross-reaction with p-dimethylaminobenzaldehyde) [86,96].

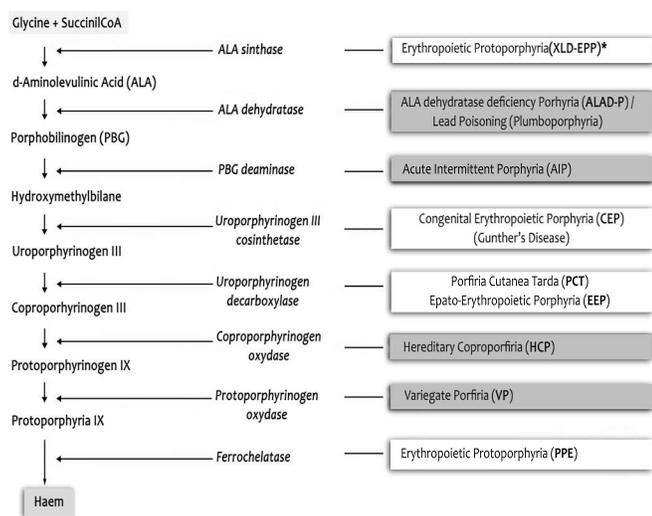
It should be recommended that all major medical facilities and emergency units are provided at least for in-house rapid determination of urinary PBG levels [also by using rapid ("bedside") test kits], because a significant delay in testing may be responsible for potential fatal consequences of delayed treatments. If urinary PBG levels are increased, further assessments [plasma, urine, and stool excretion patterns of porphyrin (and porphyrin-precursors); plasma fluorescence emission peak (after excitation at 410 nm); assessment of red blood cells enzymatic activity (ALA-dehydratase and PBG-deaminase); genetic testing] will determine the definite underlying kind of acute porphyria, although treatment (which is the same regardless of the type of acute porphyria, see below) should not be delayed, waiting for these results [2,4,15,77,93,97].

The Acute Porphyric Attack: the Treatment

The treatment of APAs is the same and irrespective of the kind of underlying acute porphyria (Figure 1). Identification and elimination of all possible trigger factors (for example drugs, infections, alcohol abuse) are mandatory [54,83,98]. In most cases, the patients with APA require hospitalizing and continuous monitoring of neurologic status, blood pressure, heart rate, fluid and electrolyte balance, muscle and tendon function and respiratory function. Symptoms (i.e., hypertension, vomiting, seizures) should be treated avoiding porphyrinogenic

drugs [14,54,77,83,98]. Non selective beta-blockers, as oral propranolol, are effective to treat hypertension and tachycardia [99], whereas opiates (meperidine) should be considered as mandatory in pain management during APA, being careful to prevent the opioid dependence in case of inappropriated prolonged administration [4,83].

Figure 1. Heme Biosynthesis and the Porphyrrias. The disorders in grey background are acute porphyrias.



*due to a gain of function enzymatic defect

Glucose down-regulates liver ALA-synthase (ALA-S1) and may help in reducing ALA and PBG overproduction, thus contributing to resolve the crisis [100,101]. In the absence of nausea or vomiting, it can be administrated orally, but, in most cases, it is used intravenously: the suggested regimen is 2-3 L of 10%-20% glucose (or dextrose) solution, infused by a central venous catheter over 24 h (100-125 mL/h). During the infusion, it is mandatory to monitor the patient's blood parameters, in order to avoid over hydration and electrolyte imbalance (especially hyponatremia) [4,77,83,102]. In consideration of the "glucose effect", all patients must avoid periods of starvation and/or severe diets or caloric restriction: after an APA, as soon as an adequate intake of carbohydrate (at least 300 g/day) should be assured [100].

Heme infusion is more rapid and effective than glucose in reducing ALA and PBG and should be administered immediately in case of severe painful attacks, electrolyte imbalance or neurological involvement. In case of significant neuropathic involvement, it has been reported that a delay in heme infusion may be responsible for a more severe nerve damage and a slower and possibly incomplete recovery of neuropathy [36,83,103].

The management of seizures complicating APAs is difficult,

since most drugs are contraindicated [45,54,104,105]; treatable causes of seizures, like severe hyponatremia or hypomagnesaemia should be always checked and corrected. Clonazepam may be used to treat seizures, although it's a potential hazard because in cultured chick embryo it induces cytochrome P450 and ALA synthase [106]; gabapentin is considered to be safe [107-109].

In most cases, heme infusion resolves the APAs in 2-4 days. In U.S. heme is available as lyophilized hematin (Panhematin®), to be reconstituted with sterile water [110]. In Europe, heme is available as heme arginate (Normosang®) solution, to be diluted in 5% glucose or saline. In both cases the recommended dose is 3 to 4 mg/kg IV once/day for 3-4 days [77, 83, 102, 110-112]. Hematin and heme arginate infusion may cause venous thrombosis and/or thrombophlebitis: these adverse events may be prevented by infusing heme together with serum albumin [83,102]. Patients affected by severe forms of acute porphyrias (namely, those presenting with severe and recurrent attacks) are considered at higher risk of permanent neurologic damage: for these patients liver transplantation may be an option. Liver transplantation leads to permanent cure of all acute porphyrias. On the contrary, patients with acute porphyrias should not serve as liver donors due to the well-documented risk of APAs in recipients [75,76,113-115]. The recent good results from different experimental gene-therapy programs depict new and very promising approaches to the treatment of acute porphyrias [116-118].

Conclusions

The neurological manifestations characterizing an APA may be extremely variable and misleading: for this reason, the correct diagnosis is still difficult. In every case of acute motor polyneuropathy or acute encephalopathy associated with abdominal pain, dysautonomia or mental symptoms it is mandatory to rule out a possible manifestation of acute porphyria: a delayed diagnosis and/or an inappropriate treatment of an acute porphyric attack may have a fatal outcome.

A complete recovery from severe APAs is quite possible, especially if the correct treatment is promptly started; in some cases, some neurological signs (foot and wrist drops, wasting of the intrinsic hand muscles or vary grade of sensory loss) may persist.

Urinalysis for non-porphyrin heme precursors (screening of urinary PBG seems to be cost-beneficial) should be performed at the symptomatic phase in any patient with acute polyneuropathy or encephalopathy accompanied by dysautonomia and/or pain. In order to the better understand the pathogenesis of neurological symptoms and to improve the therapeutic approach to APAs, further studies are still essential.

Conflict of Interest Statement

Matteo Marcacci, MD, Stefano Marchini, BD, PhD have no conflicts of interest to declare.

Paolo Ventura, MD, is a member of the advisory board for and has received funding for consultation, research, and lecturing from Orphan Europe Italy.

References

1. Puy H, Gouya L, Deybach JC. Porphyrias. *Lancet*. 2010, 375(9718): 924-937.
2. Kauppinen R. Porphyrias. *Lancet* 2005, 365(9455):241-52.
3. Anderson KE, Sassa S, Bishop DF, Desnick RJ. Disorders of heme biosynthesis: X-linked sideroblastic anemia and the porphyrias. In: Scriver CR, Beaudet A, Sly WS, Valle D, eds. *The metabolic and molecular basis of inherited diseases*. New York: McGraw-Hill, 2001, 2991-3062.
4. Ventura P. Le Porfirie. In: Brunetti P, Santeusano F, eds. *Trattato di Medicina Interna. Volume Malattie delle Ghiandole Endocrine, del Metabolismo e della Nutrizione*. Padova: Piccin Nuova Libreria, 2011, 931-52.
5. Heme proteins. *Adv Inorg Biochem*. 1988, 7: 1-271.
6. Ponka P. Cell biology of heme. *The American journal of the medical sciences*. 1999, 318: 241-256.
7. Kappas A, Sassa S, Galbraith RA. The porphyrias. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The metabolic basis of inherited diseases*. Volume 2. 7th ed. New York: McGraw-Hill, 1995, 2103-2195.
8. Ventura E, Rocchi E. Le Porfirie. In: Guarini G, Fiorelli G, Malliani A, Violi E, Volpe M, eds. *Teodori 2000 Trattato di Medicina Interna. Volume 2. 6th ed*. Roma: Società Editrice Universo, 2001, 2301-2334.
9. Crimlisk HL. The little imitator--porphyria: a neuropsychiatric disorder. *Journal of neurology, neurosurgery, and psychiatry*. 1997, 62: 319-328.
10. Shanley BC, Neethling AC, Percy VA, Carstens M. Neurochemical aspects of porphyria. Studies on the possible neurotoxicity of delta-aminolaevulinic acid. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde*. 1975, 49: 576-580.
11. Shanley BC, Percy VA, Neethling AC. Pathogenesis of neural manifestations in acute porphyria. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde*. 1977, 51: 458-460.
12. Meyer UA, Schuurmans MM, Lindberg RL. Acute porphyrias: pathogenesis of neurological manifestations. *Seminars in liver disease*. 1998, 18: 43-52.
13. Elder GH, Hift RJ, Meissner PN. The acute porphyrias. *Lancet*. 1997, 349: 1613-1617.
14. Ventura P, Cappellini MD, Rocchi E. The acute porphyrias: a diagnostic and therapeutic challenge in internal and emergency medicine. *Internal and emergency medicine*. 2009, 4: 297-308.
15. Ventura P, Cappellini MD, Biolcati G, Guida CC, Rocchi E et al. A challenging diagnosis for potential fatal diseases: recommendations for diagnosing acute porphyrias. *European journal of internal medicine*. 2014, 25: 497-505.
16. Pischik E, Bulyanitsa A, Kazakov V, Kauppinen R. Clinical features predictive of a poor prognosis in acute porphyria. *Journal of neurology*. 2004, 251: 1538-1541.
17. Pischik E, Kazakov V, Kauppinen R. Is screening for urinary porphobilinogen useful among patients with acute polyneuropathy or encephalopathy? *Journal of neurology*. 2008, 255: 974-979.
18. Bonkovsky HL, Maddukuri VC, Yazici C, Anderson KE, Bissell DM et al. Acute Porphyrias in the USA: Features of 108 Subjects from Porphyria Consortium. *The American journal of medicine*. 2014.
19. Stein JA, Tschudy DP. Acute intermittent porphyria. A clinical and biochemical study of 46 patients. *Medicine*. 1970, 49: 1-16.
20. Goldberg A. Acute intermittent porphyria: a study of 50 cases. *The Quarterly journal of medicine*. 1959, 28: 183-209.
21. Mustajoki P, Koskelo P. Hereditary hepatic porphyrias in Finland. *Acta medica Scandinavica*. 1976, 200: 171-178.
22. Hierons R. Changes in the nervous system in acute porphyria. *Brain : a journal of neurology* 1957, 80: 176-192.
23. Lithner F. Could attacks of abdominal pain in cases of acute intermittent porphyria be due to intestinal angina? *Journal of internal medicine*. 2000, 247: 407-409.
24. Gibson JB, Goldberg A. The neuropathology of acute porphyria. *The Journal of pathology and bacteriology*. 1956, 71: 495-509.
25. Suarez JI, Cohen ML, Larkin J, Kernich CA, Hricik DE et al. Acute intermittent porphyria: clinicopathologic correlation.

- Report of a case and review of the literature. *Neurology*. 1997, 48: 1678-1683.
26. Laiwah AC, Macphee GJ, Boyle P, Moore MR, Goldberg A. Autonomic neuropathy in acute intermittent porphyria. *Journal of neurology, neurosurgery, and psychiatry*. 1985, 48: 1025-1030.
27. Grundy D, Schemann M. Enteric nervous system. *Current opinion in gastroenterology*. 2006, 22: 102-110.
28. Cutler MG, Turner JM, Moore MR. A comparative study of the effects of delta-aminolaevulinic acid and the GABAA agonist, muscimol, in rat jejunal preparations. *Pharmacology & toxicology*. 1991, 69: 52-55.
29. Pischik E, Kauppinen R. Neurological manifestations of acute intermittent porphyria. *Cellular and molecular biology*. 2009, 55: 72-83.
30. McEneaney D, Hawkins S, Trimble E, Smye M. Porphyric neuropathy--a rare and often neglected differential diagnosis of Guillain-Barre syndrome. *Journal of the neurological sciences*. 1993, 114: 231-232.
31. Kochar DK, Pal M, Kochar SK, Vyas A, Kochar A et al. Acute intermittent porphyria presenting with neurological emergency: Review of six cases. *Neurology India*. 2007, 55: 413-415.
32. Ridley A. The neuropathy of acute intermittent porphyria. *The Quarterly journal of medicine*. 1969, 38: 307-333.
33. Kupferschmidt H, Bont A, Schnorf H, Landis T, Walter E et al. Transient cortical blindness and bioccipital brain lesions in two patients with acute intermittent porphyria. *Annals of internal medicine*. 1995, 123: 598-600.
34. Bhat JI, Qureshi UA, Bhat MA. Acute intermittent porphyria with transient cortical blindness. *Indian pediatrics*. 2010, 47: 977-978.
35. Kuo HC, Huang CC, Chu CC, Lee MJ, Chuang WL et al. Neurological complications of acute intermittent porphyria. *European neurology*. 2011, 66: 247-252.
36. Mustajoki P, Nordmann Y. Early administration of heme arginate for acute porphyric attacks. *Archives of internal medicine*. 1993, 153: 2004-2008.
37. Tyagi A, Chawla R, Sethi AK, Bhattacharya A. Respiratory failure in acute intermittent porphyria. *The Journal of the Association of Physicians of India*. 2002, 50: 443-445.
38. Wongthim S, Hemachudha T, Punthumchinda K. Respiratory insufficiency associated with acute hepatic porphyria. *Journal of the Medical Association of Thailand = Chotmaihet thangphaet*. 1989, 72: 655-659.
39. Greenspan GH, Block AJ. Respiratory insufficiency associated with acute intermittent porphyria. *South Med J* 1981, 74: 954-956,959.
40. Solinas C, Vajda FJ. Neurological complications of porphyria. *J Clin Neurosci* 2008, 15: 263-268.
41. Goren MB, Chen C. Acute intermittent porphyria with atypical neuropathy. *South Med J* 1991, 84: 668-669.
42. Sorensen AW, With TK. Persistent pareses after porphyric attacks. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde*. 1971, 101-103.
43. Scott L, Bean DW. Psychiatric manifestations of porphyria. *S D J Med* 1987, 40: 5-8.
44. Bautista O, Vazquez-Caubet JC, Zhivago EA, Dolores Saiz M. From metabolism to psychiatric symptoms: psychosis as a manifestation of acute intermittent porphyria. *The Journal of neuropsychiatry and clinical neurosciences*. 2014, 26: E30.
45. Magnussen CR, Doherty JM, Hess RA, Tschudy DP. Grand mal seizures and acute intermittent porphyria. The problem of differential diagnosis and treatment. *Neurology*. 1975, 25: 121-125.
46. 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.
47. Perlroth MG, Tschudy DP, Marver HS, Berard CW, Zeigel RF et al. Acute intermittent porphyria. New morphologic and biochemical findings. *The American journal of medicine*. 1966, 41: 149-162.
48. Yrjonen A, Pischik E, Mehtala S, Kauppinen R. A novel 19-bp deletion of exon 15 in the HMBS gene causing acute intermittent porphyria associating with rhabdomyolysis during an acute attack. *Clinical genetics*. 2008, 74: 396-398.
49. Nabin A, Thapa LJ, Paudel R, Rana PV. Acute intermittent porphyria with SIADH and fluctuating dysautonomia. *Kathmandu University medical journal*. 2012, 10: 96-99.
50. Lipschutz DE, Reiter JM. Acute intermittent porphyria with inappropriately elevated ADH secretion. *JAMA : the journal of the American Medical Association*. 1974, 230: 716-717.
51. Usalan C, Erdem Y, Altun B, Gursoy M, Celik I et al. Severe hyponatremia due to SIADH provoked by acute intermittent porphyria. *Clin Nephrol*. 1996, 45: 418.
52. Zhao B, Wei Q, Wang Y, Chen Y, Shang H. Posterior Revers-

- ible Encephalopathy Syndrome in Acute Intermittent Porphyria. *Pediatric neurology*. 2014.
53. Neal CR, Hunter AJ, Harper SJ, Soothill PW, Bates DO. Plasma from women with severe pre-eclampsia increases microvascular permeability in an animal model in vivo. *Clin Sci (Lond)* 2004, 107: 399-405.
54. Roveri G, Nascimbeni F, Rocchi E, Ventura P. Drugs and Acute Porphyrias: Reasons for a Hazardous Relationship. *Postgraduate Medicine*. 2014, 126: (In Press).
55. Jose J, Saravu K, Shastry BA, Jimmy B. Drug use in porphyria: a therapeutic dilemma. *Singapore medical journal*. 2008, 49: e272-e275.
56. Solinas C, Vajda FJ. Epilepsy and porphyria: new perspectives. *J Clin Neurosci*. 2004, 11: 356-61.
57. Reynolds NC, Jr. Epilepsy in porphyria. *Neurology*. 1996, 46: 1497-1498.
58. Kumar B. Acute intermittent porphyria presenting solely with psychosis: a case report and discussion. *Psychosomatics*. 2012, 53: 494-498.
59. Massey EW. Neuropsychiatric manifestations of porphyria. *J Clin Psychiatry*. 1980, 41: 208-213.
60. Ellenweig N, Schoenfeld N, Zemishlany Z. Acute intermittent porphyria: psychosis as the only clinical manifestation. *Isr J Psychiatry Relat Sci*. 2006, 43: 52-56.
61. Shanley BC, Joubert SM. The redox state of the liver in symptomatic porphyria. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde*. 1972, 46: 772-774.
62. Rocchi E, Ventura P, Ronzoni A, Rosa MC, Gozzi C et al. Pro-oxidant and antioxidant factors in acute intermittent porphyria: family studies. *Journal of inherited metabolic disease*. 2004, 27: 251-266.
63. Frith D, Yeung K, Thrush S, Hunt BJ, Hubbard JG. Lead poisoning--a differential diagnosis for abdominal pain. *Lancet*. 2005, 366: 2146.
64. Warren MJ, Cooper JB, Wood SP, Shoolingin-Jordan PM. Lead poisoning, haem synthesis and 5-aminolaevulinic acid dehydratase. *Trends Biochem Sci*. 1998, 23: 217-221.
65. Beard D. Plumbo porphyria. A difficult diagnosis. *Occup Health (Lond)*. 1993, 45: 25.
66. Sniderman King L, Trahms C, Scott CR. Tyrosinemia Type I. In: Pagon RA, Adam MP, Ardinger HH, Bird TD, Dolan CR, Fong CT, et al. eds. *GeneReviews(R)*. Seattle (WA), 1993.
67. Sassa S, Kappas A. Hereditary tyrosinemia and the heme biosynthetic pathway. Profound inhibition of delta-aminolevulinic acid dehydratase activity by succinylacetone. *The Journal of clinical investigation*. 1983, 71: 625-634.
68. Sassa S. ALAD porphyria. *Seminars in liver disease*. 1998, 18: 95-101.
69. Ribak CE, Harris AB, Vaughn JE, Roberts E. Inhibitory, GABAergic nerve terminals decrease at sites of focal epilepsy. *Science*. 1979, 205: 211-214.
70. Bonkowsky HL, Schady W. Neurologic manifestations of acute porphyria. *Seminars in liver disease*. 1982, 2: 108-124.
71. De Matteis F, Zetterlund P, Wetterberg L. Brain 5-aminolaevulinate synthase. Developmental aspects and evidence for regulatory role. *The Biochemical journal*. 1981, 196: 811-817.
72. Garg MK, Mohapatro AK, Dugal JS, Singh AP. Cortical blindness in acute intermittent porphyria. *The Journal of the Association of Physicians of India*. 1999, 47: 727-729.
73. Alhaider AA, Lei SZ, Wilcox GL. Spinal 5-HT3 receptor-mediated antinociception: possible release of GABA. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 1991, 11: 1881-1888.
74. Felitsyn N, McLeod C, Shroads AL, Stacpoole PW, Notterpek L. The heme precursor delta-aminolevulinic acid blocks peripheral myelin formation. *Journal of neurochemistry*. 2008, 106: 2068-2079.
75. Soonawalla ZF, Orug T, Badminton MN, Elder GH, Rhodes JM et al. Liver transplantation as a cure for acute intermittent porphyria. *Lancet*. 2004, 363: 705-706.
76. Singal AK, Parker C, Bowden C, Thapar M, Liu L, et al. Liver transplantation in the management of porphyria. *Hepatology*. 2014.
77. Anderson KE, Bloomer JR, Bonkowsky HL, Kushner JP, Pierach CA et al. Recommendations for the diagnosis and treatment of the acute porphyrias. *Annals of internal medicine*. 2005, 142: 439-450.
78. European Porphyria Initiative. In.
79. Bonkowsky HL, Barnard GF. Diagnosis of porphyric syndromes: a practical approach in the era of molecular biology. *Seminars in liver disease*. 1998, 18: 57-65.
80. de Rooij WM, Edixhoven A, Wilson JH. Porphyria: a diagnostic approach. In: Kadish KM, Smith KM, Guillard R, eds. *The porphyrin handbook*. St Louis: Elsevier. 2003, 211-245.
81. Tran TP, Leduc K, Savard M, Dupre N, Rivest D et al. Acute

- porphyria presenting as epilepsia partialis continua. Case reports in neurology. 2013, 5: 116-124.
82. Bottomley SS, Bonkowsky HL, Kreimer-Birnbaum M. The diagnosis of acute intermittent porphyria. Usefulness and limitations of the erythrocyte uroporphyrinogen I synthase assay. *Am J Clin Pathol.* 1981, 76: 133-139.
83. Elder GH, Hift RJ. Treatment of acute porphyria. *Hosp Med.* 2001, 62: 422-425.
84. Bissell DM. Laboratory evaluation in porphyria. *Seminars in liver disease.* 1982, 2: 100-107.
85. Lamon J, With TK, Redeker AG. The Hoesch test: bedside screening for urinary porphobilinogen in patients with suspected porphyria. *Clinical chemistry.* 1974, 20: 1438-1440.
86. Thunell S, Harper P, Brock A, Petersen NE. Porphyrins, porphyrin metabolism and porphyrias. II. Diagnosis and monitoring in the acute porphyrias. *Scandinavian journal of clinical and laboratory investigation.* 2000, 60: 541-559.
87. Andersson C, Thunell S, Floderus Y, Forsell C, Lundin G et al. Diagnosis of acute intermittent porphyria in northern Sweden: an evaluation of mutation analysis and biochemical methods. *Journal of internal medicine.* 1995, 237: 301-308.
88. Henderson MJ. Thin-layer chromatography of free porphyrins for diagnosis of porphyria. *Clinical chemistry.* 1989, 35: 1043-1044.
89. Hift RJ. The diagnosis of porphyria. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde.* 1999, 89: 611-614.
90. Lai CK, Lam CW, Chan YW. High-performance thin-layer chromatography of free porphyrins for diagnosis of porphyria. *Clinical chemistry.* 1994, 40: 2026-2029.
91. Sardh E, Andersson DE, Henrichson A, Harper P. Porphyrin precursors and porphyrins in three patients with acute intermittent porphyria and end-stage renal disease under different therapy regimes. *Cellular and molecular biology.* 2009, 55: 66-71.
92. Sardh E, Harper P, Andersson DE, Floderus Y. Plasma porphobilinogen as a sensitive biomarker to monitor the clinical and therapeutic course of acute intermittent porphyria attacks. *European journal of internal medicine.* 2009, 20: 201-207.
93. Sandberg S, Elder GH. Diagnosing acute porphyrias. *Clinical chemistry.* 2004, 50: 803-805.
94. With TK. Simple and rapid screening for acute porphyria--'porphobilinogen' and Hoesch test. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde.* 1971: 229-230.
95. Deacon AC, Peters TJ. Identification of acute porphyria: evaluation of a commercial screening test for urinary porphobilinogen. *Annals of clinical biochemistry.* 1998, 35 (Pt 6): 726-732.
96. McEwen J, Paterson C. Drugs and false-positive screening tests for porphyria. *British medical journal.* 1972, 1: 421.
97. Walsh DS, Beard JS, James WD. Fluorescent spectrophotometric analysis in the evaluation of porphyria. *JAMA : the journal of the American Medical Association.* 1994, 272: 1580-1581.
98. Kauppinen R. Management of the acute porphyrias. *Photodermatology, photoimmunology & photomedicine.* 1998, 14: 48-51.
99. Beattie AD, Moore MR, Goldberg A, Ward RL. Acute intermittent porphyria: response of tachycardia and hypertension to propranolol. *British medical journal.* 1973, 3: 257-260.
100. Doss M, Verspohl F. The "glucose effect" in acute hepatic porphyrias and in experimental porphyria. *Klin Wochenschr.* 1981, 59: 727-735.
101. Handschin C, Lin J, Rhee J, Peyer AK, Chin S et al. Nutritional regulation of hepatic heme biosynthesis and porphyria through PGC-1alpha. *Cell* 2005, 122: 505-515.
102. Stein P, Badminton M, Barth J, Rees D, Stewart MF, British, et al. Best practice guidelines on clinical management of acute attacks of porphyria and their complications. *Annals of clinical biochemistry.* 2013, 50: 217-223.
103. Sorensen AW, With TK. Persistent pareses after porphyric attacks. *Acta medica Scandinavica.* 1971, 190: 219-222.
104. Bonkowsky HL, Tschudy DP, Collins A, Doherty J, Bossenmaier I, Cardinal R, et al. Repression of the overproduction of porphyrin precursors in acute intermittent porphyria by intravenous infusions of hematin. *Proceedings of the National Academy of Sciences of the United States of America.* 1971, 68: 2725-2729.
105. Larson AW, Wasserstrom WR, Felsher BF, Chih JC. Post-traumatic epilepsy and acute intermittent porphyria: effects of phenytoin, carbamazepine, and clonazepam. *Neurology.* 1978, 28: 824-828.
106. Bonkowsky HL, Sinclair PR, Emery S, Sinclair JF. Seizure management in acute hepatic porphyria: risks of valproate and clonazepam. *Neurology.* 1980, 30: 588-592.

107. Pandey CK, Singh N, Bose N, Sahay S. Gabapentin and propofol for treatment of status epilepticus in acute intermittent porphyria. *Journal of postgraduate medicine*. 2003, 49: 285.
108. Zadra M, Grandi R, Erli LC, Mirabile D, Brambilla A. Treatment of seizures in acute intermittent porphyria: safety and efficacy of gabapentin. *Seizure*. 1998, 7: 415-416.
109. Bhatia R, Vibha D, Srivastava MV, Prasad K, Tripathi M et al. Use of propofol anesthesia and adjunctive treatment with levetiracetam and gabapentin in managing status epilepticus in a patient of acute intermittent porphyria. *Epilepsia*. 2008, 49: 934-936.
110. Anderson KE, Bonkovsky HL, Bloomer JR, Shedlofsky SI. Reconstitution of hematin for intravenous infusion. *Annals of internal medicine*. 2006, 144: 537-538.
111. Loftin EB, 3rd. Hematin therapy in acute porphyria. *JAMA : the journal of the American Medical Association*. 1985, 254: 613.
112. Pierach CA. Haem and porphyria attacks. *Lancet*. 1989, 2: 213-214.
113. Dar FS, Asai K, Haque AR, Cherian T, Rela M et al. Liver transplantation for acute intermittent porphyria: a viable treatment? *Hepatobiliary & pancreatic diseases international* : HBPD INT. 2010, 9: 93-96.
114. Seth AK, Badminton MN, Mirza D, Russell S, Elias E. Liver transplantation for porphyria: who, when, and how? *Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society*. 2007, 13: 1219-1227.
115. Dowman JK, Gunson BK, Bramhall S, Badminton MN, Newsome PN. Liver transplantation from donors with acute intermittent porphyria. *Annals of internal medicine*. 2011, 154: 571-572.
116. Yasuda M, Gan L, Chen B, Kadirvel S, Yu C, Phillips JD, et al. RNAi-mediated silencing of hepatic *Alas1* effectively prevents and treats the induced acute attacks in acute intermittent porphyria mice. *Proceedings of the National Academy of Sciences of the United States of America*. 2014, 111: 7777-7782.
117. Project EC. Augmenting PBGD expression in the liver as a novel gene therapy for acute intermittent porphyria (AIPgene). *Human gene therapy Clinical development*. 2014, 25: 61-63.
118. Paneda A, Lopez-Franco E, Kaeppel C, Unzu C, Gil-Royo AG, D'Avola D, et al. Safety and liver transduction efficacy of rAAV5-cohPBGD in nonhuman primates: a potential therapy for acute intermittent porphyria. *Human gene therapy*. 2013, 24: 1007-1017.