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Review Article

A challenging diagnosis for potential fatal diseases: Recommendations for diagnosing acute porphyrias

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ABSTRACT

Acute porphyrias are a heterogeneous group of metabolic disorders resulting from a variable catalytic defect of four enzymes out of the eight involved in the haem biosynthesis pathway; they are rare and mostly inherited diseases, but in some circumstances, the metabolic disturbance may be acquired. Many different environmental factors or pathological conditions (such as drugs, calorie restriction, hormones, infections, or alcohol abuse) often play a key role in triggering the clinical exacerbation (acute porphyric attack) of these diseases that may often mimic many other more common acute medical and neuropsychiatric conditions and whose delayed diagnosis and treatment may be fatal. In order to obtain an accurate diagnosis of acute porphyria, the knowledge and the use of appropriate diagnostic tools are mandatory, even in order to provide as soon as possible the more effective treatment and to prevent the use of potentially unsafe drugs, which can severely precipitate these diseases, especially in the presence of life-threatening symptoms.
In this paper, we provide some recommendations for the diagnostic steps of acute porphyrias by reviewing literature and referring to clinical experience of the board members of the Gruppo Italiano Porfiria (GrIP).

1. Introduction

Acute porphyrias are metabolic disorders of haem biosynthesis characterized by the possible onset of recurrent acute attacks of non-specific but very severe and potentially life-threatening neurovisceral symptoms (acute porphyric attacks) [1–4]. They are rare and mostly inherited diseases, but in some circumstances, the metabolic alteration responsible for the disturbance may be acquired [5]. Moreover, many different environmental factors or pathological conditions (such as drugs, calorie restriction, hormones, infections, or alcohol abuse) often play a key role in triggering the clinical exacerbation of these diseases [6]. Currently, although the specific enzymes and many of their corresponding genetic defects have been identified, some aspects involved in the pathogenesis of these diseases remain ill-defined and the diagnosis of these disorders still represents a formidable diagnostic challenge for clinicians. Acute porphyrias are often misdiagnosed diseases due to their multiform clinical manifestations, which can mimic many other (and more common) diseases. For this reason, many different specialists – such as surgeons, psychiatrists, gastroenterologists, neurologists or emergency physicians – may be variably involved in diagnosing and managing these diseases [1,5].

As clinical features alone are not so specific and suitable either to confirm a diagnosis of acute porphyric attack or to distinguish between the different forms of acute porphyrias, the knowledge and the correct interpretation of the appropriate tests are mandatory for accurately diagnosing and managing these diseases [3,7–10]. A delayed diagnosis and an inappropriate treatment of an acute porphyric attack may be fatal; the availability of infusion-stable haem preparations (haem arginate in Europe and haematin in USA) has significantly improved the treatment outcome of acute porphyric attacks, so the knowledge about the diagnosis and the management of these diseases may be

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relevant, especially for physicians working in internal medicine and emergency units [11–14].

To date, well defined diagnostic algorithms of these rare disorders are lacking, despite the availability of sensitive and specific biochemical tests [7,15]. In this review, we provide updated recommendations for diagnosing acute porphyrias on the basis of literature reviews and clinical experience of a panel of Italian physicians (board members of the Gruppo Italiano Porfiria, GrIP) with proven long-time expertise in the clinical management of patients with porphyrias.

1.1. The GrIP panel

The experience about misdiagnosis, delayed diagnosis and/or inappropriate treatment of acute porphyrias in Italy has induced a group of Italian physicians and laboratory specialists to set up a national board, named Gruppo Italiano Porfiria (GrIP). The board is formed by physicians with long-lasting proven experience in diagnosis of porphyrias and in clinical management of porphyric patients, and it represents specialties including internal medicine, genetics, gastroenterology and hepatology, haematology, nephrology and dermatology. The GrIP was founded in 2011 with the aim of sharing the experience of four different Italian centres having expertise and scientific interest in metabolic diseases resulting from a disturbance of haem metabolism as well as discussing and formulating updated recommendations for diagnosing and treating porphyrias, which are addressed to Italian colleagues. All four Italian centres participating in the panel are working within the European Porphyria Network (EpNet: www.porphyria-europe.com) and they currently undergo its quality control tests, as well they also operate in strict connection with porphyric patient associations (Associazione Italiana Malati di Porfiria, AMAPO, www.amapo.it), often attending the GrIP's meetings.

2. Acute porphyrias

The metabolic pathway of haem synthesis proceeds through eight different complex biochemical reactions, catalysed in turn by specific enzymes located in cytosol or mitochondria: two amino acid-like compounds (succinyl-coenzyme A and glycine) are progressively converted into the complex tetrapyrrole ring of protoporphyrin IX that, after complexation with an atom of Fe^{2++}, leads to haem synthesis (Fig. 1). Disturbance in the activity of each one of these enzymes causes accumulation of different patterns of precursors, whose biological effects are responsible for different kinds of diseases (generally known as porphyrias) [4,16–18]. Four different "porphyrias" may present with recurrent attacks of neurovisceral symptoms (neurovisceral crisis or acute porphyric attack) and they are classically defined as "acute porphyrias" (or also "acute hepatic porphyrias", as the enzyme defects are mostly located in the liver) [6]. The by far most common form of these disorders is acute intermittent porphyria (AIP) [9,10,18]. Acute attacks of AIP are clinically more severe, even though they are formally indistinguishable from those of less common conditions: variegate porphyria (VP) [5,19–22], hereditary coproporphyria (HCP) [5,23,24], and of the extremely rare porphyria due to ALA dehydratase deficiency (ALAD-P) [25]. Quite similar acute clinical manifestations may also occur in case of lead poisoning (a condition also referred as *plumboporphyria*), which can be considered a typical example of acquired disturbance of haem metabolism due to a blockade of ALA dehydratase by lead [26,27]. The main clinical and biochemical features of the above-mentioned acute porphyrias are summarized in Table 1.

An accurate epidemiological assessment of acute porphyrias is difficult, due their low clinical penetrance (the proportion of patients who develop overt clinical form of these diseases is thought to be less than 20% of carriers of the enzymatic defect). Information about morbidity of acute porphyrias is mostly derived from the clinical experience of specialist porphyria centres [2,18,28], and from some systematic studies concerning individual porphyrias from different countries [21,29–38]. According to a recent prospective survey [39], the incidence of AIP seems to be remarkably the same in all European countries (ranging from 0.11 to 0.22 per year per million, with an overall incidence of 0.12), with the exception of Sweden, where the incidence of about four-fold higher (0.51 per year per million) is explained by a founder effect [34]; for VP (about half that of AIP) and HCP (0.2 per year per 10 millions) the incidence in Europe is lower. In this survey, the calculated overall prevalence of AIP in Europe (including Sweden) is about 5.9 per million inhabitants, significantly lower with respect to previous estimates (from10–20 per million to 101 per million) [2,18,28,29], where probably all subjects with AIP, even those who have never had symptoms, have been included. Similar considerations are valid for the calculated European prevalence of VP (3.2 cases for million inhabitants) [39]. To this regard, some Finnish retrospective studies have showed that in the last 50 years the number of AIP patients experiencing acute attacks declined with time and this trend seemed to have continued subsequently [35,40]; similarly, a decrease in acute attacks in VP has been noted in South Africa [41]. Thus, this observed lower prevalence may be consistent with a decreasing incidence of new acute attacks over the past decades, which may be explained by improvement in diagnosis, treatment, family screening and preventive counselling.

In old surveys, mortality during an acute attack has been reported to be as high as 50–60% [42]. With modern treatment, however, an acute attack of porphyria is only rarely lethal. Nevertheless, an American report found that the mortality rate was three times higher among patients with AIP, as compared to the general population and the major cause of this increase in mortality was symptoms associated with the porphyric attack itself [43].

3. Diagnosing acute porphyrias

Here we highlight the basic clinical steps for diagnosing an acute porphyria, from the diagnosis of an acute porphyric attack to the definition of the specific kind of acute porphyria responsible for it.

3.1. Step 1 — diagnosis of acute porphyric attack

3.1.1. Diagnosing an acute porphyric attack — clinical features

The diagnosis of acute porphyria should be considered in any patient presenting with symptoms that are prevalent in these conditions, that is, in particular, abdominal pain, especially if a first clinical evaluation is not suggestive of other possible causes (Table 2). A diagnostic suspicion may be provided by urine darkening (red tint varying from port wine to diluted strawberry sap) on standing in sunlight (half an hour is enough), as an effect of spontaneous polymerization of urinary porphobilinogen (PBG) to uroporphyrins and other pigments (such an effect being typically enhanced by sun exposure) [44,45].

The cardinal sign of an acute porphyria is the acute porphyric attack, whose clinical features are characterized by great variability; even if other symptoms may occasionally occur, the most common complaint is a severe abdominal pain, usually excruciating, mimicking an "acute abdomen" and prompting immediate attention (Table 2). It is generally accompanied by nausea and vomiting, and by neurological and psychiatric symptoms [ranging from depression and apathy to (more frequently in our experience) extreme agitation or psychosis with hallucinations] [46–49]. Back pain extending to or involving proximal limbs is also frequently observed, together with signs of vegetative dysfunction (hypertension with postural hypotension, tachycardia and constipation) [1,3,5,6,50,51]. An acute attack may be preceded by a period of different-grade behavioural changes such as anxiety, irritability, restlessness and insomnia, and it may evolve rapidly into symptoms of severe autonomic and acute motor and sensory neuropathy. Muscular weakness, in particular proximal motor neuropathy (resembling Guillain–Barre syndrome), is quite common. It can progress to general paralysis, leading to severe respiratory impairment up to death from cardiorespiratory arrest [52–54]. Hyponatremia and hypomagnesemia may occur as a result of dehydration, nephrotoxicity or inappropriate antidiuretic hormone secretion

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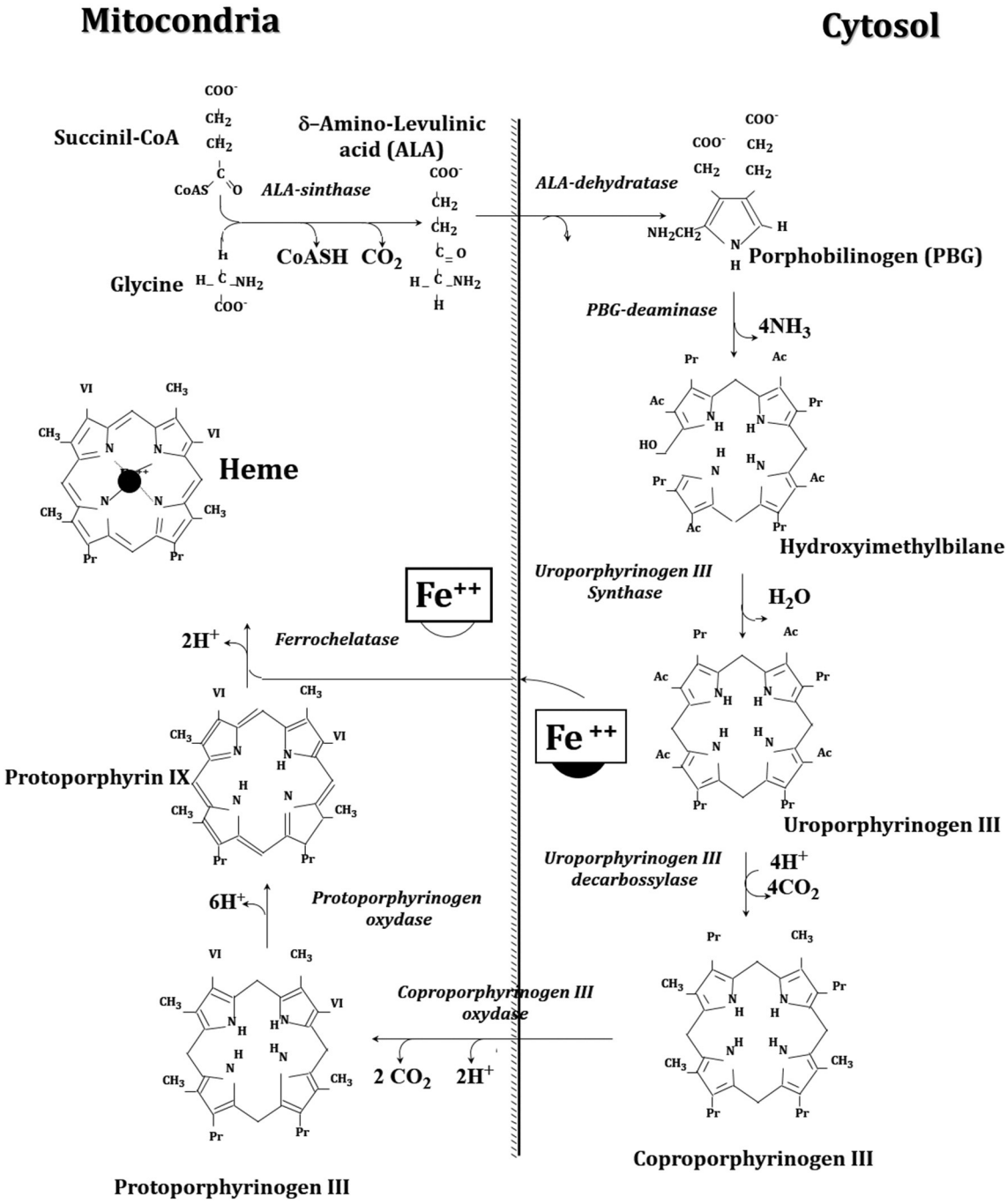

Fig. 1. Biosynthesis of Haem (modified from: Pomka P., Blood, 1997).

[55,56]. These water/electrolyte disorders may contribute to neurological and psychiatric symptoms of the acute porphyric attack [46,54].

Although even a single specific symptom should lead to consider the diagnosis, additional features in a patient with abdominal pain or other compatible symptoms may contribute to increase the diagnostic suspicion (dark/reddish urine; new-onset hypertension; hyponatremia; proximal muscle weakness; recent use of drugs known to exacerbate porphyria; recent calorie restriction diets; alcohol abuse). Age at clinical onset may also be relevant: in contrast to the ALA-D deficiency porphyria, which is reported to start in early infancy, clinical symptoms of AIP, HCP, and VP have never been reported before puberty [25]. HCP and VP are also cutaneous porphyrias: in these cases, skin fragility and bullous eruptions may be relevant presenting symptoms. Even though AIP may be characterized by more frequent and severe neurovisceral symptoms, the acute neurological presentation does not differ qualitatively among the different forms of acute porphyria, including lead poisoning [6,20,23,57]. It must be noted that universal signs or symptoms do not exist, and in up to 5%–10% of patients the disease may not occur with the most widespread and shared features (such as abdominal pain). Family history may be relevant in case of symptomatic relatives, but it may also be inconclusive as acute porphyrias are diseases characterized by highly incomplete penetrance and most carriers of the trait in affected families may remain life-long asymptomatic. On the other hand, it is recommended to test immediately patients with abdominal pain or other suggestive findings and a family history of acute porphyria [15,58].

When a patient known to be affected by acute porphyria shows symptoms of a possible acute attack, the obvious question is whether

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Table 1
Main clinical and biochemical features of acute porphyrias.
(in bold the most characteristic biochemical features for each kind of acute porphyria).

Disease	Clinical features	Plasma fluorescence	Erythrocyte	Urine	Stool
Acute intermittent porphyria (AIP)	-Acute neurovisceral attacks, neuropathy, or both -No skin lesions	Emission peak at wavelength of 618 ± 2 nm*	–	**Increased urinary levels of ALA and PBG (PBG > ALA)** (higher during acute attacks) **-Increased urinary porphyrins** (URO >> COPRO)**	-Normal
Hereditary coproporphyria (HCP)	-Acute neurovisceral attacks, neuropathy, or both -Blister skin lesions and skin fragility (in 30% of patients)	Emission peak at wavelength of 618 ± 2 nm*	–	-Increased urinary levels of ALA and **PBG** (**PBG** > **ALA**) mostly only during acute attacks **-Increased urinary porphyrins (URO and COPRO)**	**-Increased faecal porphyrins** (COPRO ≫ PROTO, with Copro III prevalence)
Variegate porphyria (VP)	-Acute neurovisceral attacks in 20–30% patients (50% with blisters or skin lesions)	**Emission peak at wavelength of 626 ± 2 nm**	–	-Increased urinary levels of ALA and **PBG** (**PBG** > **ALA**) mostly only during acute attacks **-Increased urinary porphyrins (COPRO prevalence)**	**-Increased faecal porphyrins (PROTO >> COPRO, with Copro III prevalence)**
ALA dehydratase deficiency porphyria (ALAD-P)	-Acute neurovisceral attacks, neuropathy, or both -No skin lesions	Emission peak at wavelength of 618 ± 2 nm*	**-High Total erythrocyte protoporphyrins (High ZnPP)**	**-Increased urinary levels of ALA (ALA >> PBG)** -Increased urinary porphyrins (COPRO; prevalence of COPRO III)	-Normal
Lead Poisoning (plumboporphyria)	-Acute neurovisceral attacks, neuropathy, or both **-Lead exposition (incidental, professional)** **-Microcytic anaemia**	Emission peak at wavelength of 635 nm	**-High total erythrocyte protoporphyrins (High ZnPP)**	**-Biochemical features resembling ALAD-P (see above) (prevalence of Copro I)** **-High level of lead in serum and urine**	-Normal

Abbreviations: ALA = delta amino-levulinic acid; PBG = Porphobilinogen; URO = Uroporphyrins; COPRO = Coproporphyrins; PROTO = Protoporphyrins; ZnPP = Zinc Protoporhyrins. *described in literature, but not frequent; **sometimes COPRO may be prevalent.
References: Ventura E. and Rocchi E., in: Le Porfirie; in: Teodori 2000. Trattato di Medicina Interna (2000); Hindmarsh JT. Clin Chim Acta. 2003; 333:203-7; Deacon A.C. and Elder G.H. J Clin Pathol. 2001. 7:500-7. EPI/Epnet (http://www.porphyria-europe.com).

these are due to its disease or not: not all symptoms in porphyric patients are due to porphyria; moreover, patients with acute porphyrias may be suffering from other (and more common) diseases. Table 3 summarizes some of the most common pathological conditions whose differential diagnosis should include an acute porphyric attack.

Due to their non-specificity, the clinical features alone are not sufficient either to confirm a diagnosis of acute porphyric attack or to differentiate between the various forms of acute porphyria. For this reason, an immediate (we recommend at the onset of acute phase of the disease) assessment and interpretation of some appropriate laboratory biochemical tests (i.e. determination and quantification of porphyrins and non-porphyrin precursor patterns in biological samples) are mandatory for an accurate diagnosis, and hence for starting an appropriate treatment [5,7,8,13,59].

Table 2
Frequency of signs and symptoms in acute porphyric attack.
NB more symptoms may be present contemporary.

Signs/symptoms	%
Abdominal pain	95–97
Tachycardia	65–80
Urine darkening	70–75
Peripheral motor neuropathy	40–60
Constipation	46–52
Nausea, vomiting	48–85
Mental changes/psychosis	10–40
Hypertension (diastolic > 85 mmHg)	38–64
Hyponatriemia (<120 mEq/L)	25–35
Hypo/areflexia	20–30
Back pain	20–30
Sensory neuropathy	20–28
Hypotension	15–22
Seizures	10–20
Chest pain	8–15
Coma	2–10

3.2. Diagnosing an acute porphyric attack — biochemical tests

According to current knowledge and consensus, an acute porphyric attack is invariably associated with an acute worsening of the metabolic imbalance which is characterized by an accumulation and a consequent increased urinary excretion of non-porphyrin precursors

Table 3
Differential diagnosis of acute porphyric attack — common clinical conditions mimicked by an acute porphyric attack.

Surgical Conditions Associated with acute abdomen
(Peritonitis, appendicitis, acute cholecystitis, pancreatitis, intestinal occlusion, etc.)
Dismetabolic/Disendocrine conditions
Acute hypoadrenalism (Addisonian crisis)
Acute hypoparathyroidism and hypocalcemic crisis
Pheocromocytoma
Neurolopsychiatric conditions
Guillain–Barre' syndrome
Emicrania
Acute psychotic attack
Delirium
Acute panic attack
Epilepsy
Acute myopathies
Cardiovascular conditions
Hypertensive crisis
Tachyarrhythmia
Haematological conditions
Acute haemolytic crisis
Acute drepanocytic crisis
Gastroenterological conditions
Acute gastroenteritis with vomiting

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[δ-aminolevulinic acid (ALA) and porphobilinogen (PBG)] [6,13,60,61]. So, in the evaluation of a patient suspected to have an acute porphyric attack, a fresh light-protected urine sample should be sent to a specialist laboratory for adequate assessment of ALA and PBG concentrations [to date, HPLC assays are the most accurate, but rapid, ion-exchange column tests (column-chromatographic screening tests) being available] (*first-line test*) [62–65]. In case of significant renal dysfunction, ALA and PBG levels should be measured in serum [66,67].

The Watson–Schwartz test, the Hoesch test or other Ehrlich's reagent-based tests (where the colourless pyrrole PBG forms a red-violet pigment after reaction with *p-dimethylaminobenzaldehyde*) may be used as a simple and rapid assay to test the presence of urinary PBG (qualitative test) [68,69]. Even for its low-cost (a kit for a single determination is sold at about 14 euros in Italy), this test may be considered a "first-line" guide to confirm (or to rule-out) a suspicion of acute porphyric attack in case of the most common acute porphyrias (AIP, PV and HCP) at or close at the time of clinical onset.

These assays may miss the diagnosis in some extremely uncommon circumstances: a) patients with the rare ALA-D porphyria or with lead-poisoning, two disorders being characterized by accumulation of ALA but not of PBG; b) subjects immediately treated with haem arginate (which rapidly decreases ALA and PBG); c) in some cases of HCP and VP, where increases in ALA and PBG levels may be more transient, as well the corresponding symptoms; d) in cases of high urinary bilinogen excretion (due to cross-reaction with *p*-dimethylaminobenzaldehyde) [45,70].

During an acute porphyric attack, especially in case of AIP, urinary ALA and PBG are generally very high, so that potential differences in reference ranges among different laboratories are of little relevance, as well the collection of urine samples for 24 h, which delays diagnosis. The classical 24-hour urine collection approach has been recently replaced by determinations of ALA and PBG on spot urine sample in which the values are normalized on gram (or mmoles) of urinary creatinine.

It should be recommended that all major medical facilities and emergency units are provided for in-house rapid determination at least of urinary PBG levels [preferably 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 testing (*see below*) will determine the definite disorder of haem metabolism, although treatment (which is the same regardless of the type of acute porphyria) should not be delayed, waiting for these results.

If only the ALA level is substantially increased, ALA-dehydratase porphyria and other causes of ALA-dehydratase deficiency, such as lead poisoning (*plumboporphyria*), should be taken into account before starting treatment [1,5,15,45,71,72]. (Fig. 2).

In our experience, urinary ALA and PBG values significantly decrease with clinical improvement and dramatically after therapy (especially after haem arginate infusion). Urinary ALA and PBG levels are generally less markedly increased in HCP and VP and they decrease more rapidly after an acute attack than in AIP, with excretion levels of ALA being often similar to that of PBG.

3.3. Step 2 — definition of the kind of acute porphyria (Table 2)

After diagnosing an acute porphyric attack, it is mandatory to define the kind of acute porphyria responsible for it.

AIP, VP, and HCP may be readily differentiated, especially if clinically overt, by a group of biochemical tests (Table 1), including the assessment

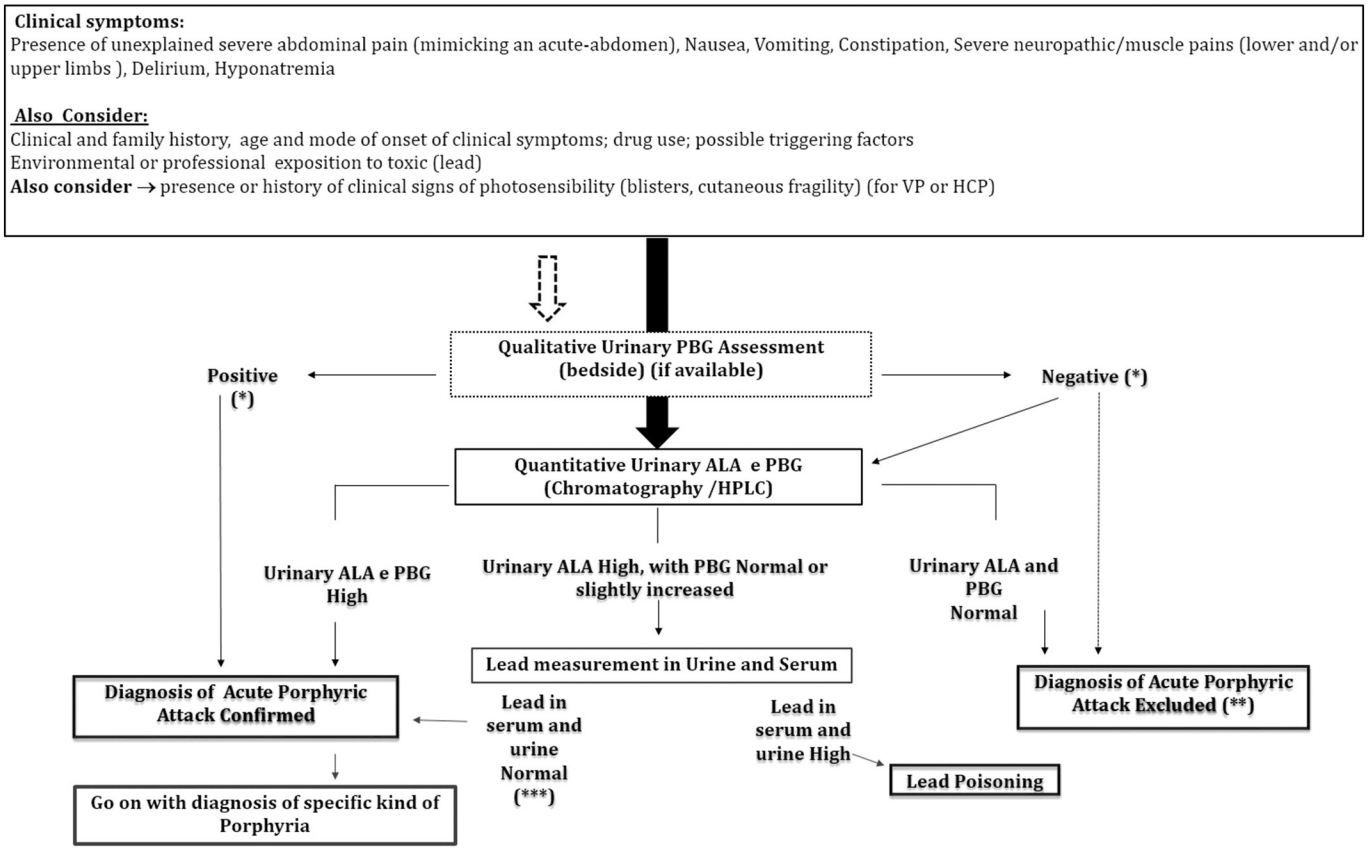

Fig. 2. Schematic algorithm for diagnosis of acute porphyric attack (APA); bedside qualitative test for urinary PBG is not everywhere available yet, so urinary PBG (and ALA) are often simultaneously measured (qualitatively and quantitatively) by using HPLC or column-chromatographic test in labs (see text) as first-line assays. *Considering the extreme rarity of ALA dehydratase-deficiency porphyria (ALAD-P, which is characterized mostly by a greater ALA increase), the positivity of the qualitative urinary PBG test together with compatible clinical features is greatly suggestive of diagnosis of acute porphyric attack. In case of negative bedside PBG test, the laboratory tests for ALA and PBG may be important to rule out conditions characterized only by ALA increase (lead poisoning, ALAD-P or tyrosinemia). **Consider other causes of clinical manifestations. ***Check for ALAD-P; rule out tyrosinemia.

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of urine, plasma, and faecal porphyrin patterns (this assay should be performed in samples collected distant from haem arginate therapy) and some fluorescence plasma patterns [15,24,45,63]. These tests may also be used to identify even more rare cases of dual porphyrias (conditions due to coexistence of deficiencies of 2 enzymes along the haem pathway) [73,74]. Their costs range from 15 euros for a plasma fluorescence scan, to about 40–60 euros for quantitative assessments of ALA/PBG or different fractions of porphyrins.

These tests still remain mandatory in the follow-up of the disease during symptom-free periods, in order to evaluate the efficacy of treatment and the risk of development of long-term organ complications (liver and kidney) associated with acute porphyrias [8]. Evaluation of specific enzyme activities (assessed on erythrocytes, fibroblasts or liver tissue) may also be useful in some cases [75–77].

In general, a marked increase in urinary and faecal total porphyrins and the relative pattern of the individual porphyrins (uro-, copro- and proto-porphyrins) (measured by spectrophotometer after separation by high-performance liquid chromatography or thin-layer chromatography) are of the greatest diagnostic importance [8,24,45,63,75].

We underline that the significance of these tests should be always critically considered in case of acutely ill patients, as they may be lacking in sensitivity and/or specificity. Urinary porphyrin levels, for example, can be increased as a result of many different non-porphyric conditions. Coproporphyrin is the predominant porphyrin in normal urine, but it is also partially excreted in bile. Minor liver dysfunction (or low-to-high grade of intra- or extrahepatic cholestatic diseases) may reduce biliary excretion, thus increasing the urinary coproporphyrin excretion [5,78–82].

3.3.1. ALA-D porphyria and lead intoxication (plumboporphyria)

Lead intoxication and the extremely rare ALA-dehydrase (ALA-D) deficiency porphyria are both due to a significant decrease in ALA-D activity (and the corresponding increase in ALA-S activity), with consequent massive ALA overproduction and urinary excretion, in the presence of normal (or slightly elevated) levels of urinary PBG [25]. Isolated urinary ALA increase may also arise from oral ALA ingestion, as in case of systemic ALA loading used during the photodynamic localization and treatment of a variety of malignant lesions or in hereditary tyrosinemia type I, which can lead to symptoms resembling acute porphyria [83,84]. Clinicians should confirm ALA-dehydratase porphyria or lead intoxication by using also enzymatic and molecular methods. Both conditions are also characterized by a significant increase in urinary excretion of coproporphyrin (both coproporhyrin I and coproporhyrin III isomers, with the prevalence of the latter), and increased levels of erythrocyte zinc protoporphyrin IX [3,5,25].

As ALA-D is a cytosolic enzyme, its activity may be assessed on liver tissue or erythrocytes. In symptomatic patients, ALA-D enzymatic activity is by far under 30% than normal, whereas in relative carriers (with no increase in urinary ALA excretion) it is about 50% compared to normal. The decreased activity of ALA-D can be restored by thiols and zinc ions in case of lead intoxication, but not in ALA-D deficiency porphyria [77]. Moreover, patients with lead intoxication usually present with sideroblastic and haemolytic anaemia and high levels of lead in serum and urine [18,72]. Coproporphyrin urinary excretion is usually very high in case of lead intoxication due to concurrent inhibition of copro-oxidase by lead. In case of lead poisoning, a plasma fluorescence emission peak at 635 nm has also been described [72,85,86]. Differentiation of ALA-D deficiency conditions from HCP and PV may be done considering the possible presence or history of photo cutaneous symptoms in both latter forms and typical increased faecal excretion of coproporphyrin in HCP and protoporphyrin in VP, respectively (see below). Only few studies are available on ALA-D gene, but they all show great heterogeneity in mutations responsible for this very rare disease [87].

3.3.2. Acute intermittent porphyria (AIP)

Besides the phenomenon of urine darkening (port wine to strawberry sap) on standing and/or typically enhanced by sun exposure (as result of polymerization of urinary PBG in excess to porphyrins and other pigments), which is more evident in case of AIP than in other acute porphyrias and besides the high levels of ALA and PBG (with PBG increase significantly higher than ALA increase), a fluorescence emission peak positive at 619 nm is highly suggestive of AIP diagnosis, even if this finding is not so frequent in our experience [67,88,89]. AIP diagnosis may be confirmed by typical increase in total porphyrin urinary excretion (with normal faecal porphyrin excretion) characterized by very high prevalence of uroporphyrins. Demonstration of reduced red cell activity of porphobilinogen-deaminase (PBGD, or hydroxylmethylbilane synthase, HMBS) (a value of 35–40% out of the normal range may be considered highly suggestive of AIP) may be also useful both for diagnostic confirmation and for family screening. In rare cases only the liver enzyme is deficient, making it necessary to perform enzymatic studies on liver biopsy samples [45,89–92].

Once biochemical studies have confirmed the diagnosis of AIP, DNA analysis (*Third-level assays*) can identify mutations in PBGD (or HBMS) gene [93–96]. To date, more than 200 different mutations (including deletions, insertions, missense and nonsense mutations) in PBGD (or HMBS) gene have been identified, even if it is not always possible to define a sharp phenotype-genotype relation [97–99]. Most mutations are family-specific with a few exceptions in northern Sweden, where a particular mutation has been transmitted over generations from a single founder [38,60,100].

Besides the further confirmation of the diagnosis, DNA analysis is important for rapid and accurate identification of asymptomatic carrier family members, together with counselling activities [94]. The risk of developing potentially acute and life-threatening fatal attacks even in asymptomatic carriers, when exposed to possible precipitating factors (drugs, alcohol abuse, etc.), makes it essential to exclude or to confirm the diagnosis of porphyria in all relatives, whenever it has been diagnosed in any family member. Every gene carrier should be timely informed about the nature of the disorder and counselled about exposures to avoid and measures to take if symptoms should appear, as well as about the probabilities of propagating potential dangerous mutations in new generations.

3.3.3. Hereditary coproporphyria (HCP)

HCP may be distinguished from AIP by the presence or history of photo cutaneous syndrome [23,57]. Besides urinary ALA and PBG elevation (whose levels are frequently normal if assessed far away from the acute attack), HCP is characterized by normal-to-slightly increased levels of urinary total porphyrins (with prevalence of coproporphyrins, especially coproporphyrin III isomers) and constant high faecal excretion of total porphyrins, with coproporphyrins largely prevailing over protoporphyrins. This issue may be useful in distinguishing it from VP, where faecal hyper excretion of porphyrins shows an inverse pattern (protoporphyrins ≫ coproporphyrins) (*see below*). In the rare congenital erythropoietic porphyria (CEP), faecal porphyrin pattern is similar to HCP, but the levels of faecal coproporphyrin are usually much higher and isomer I is prevalent [101]; moreover, in CEP photo cutaneous syndrome is quite more severe and there is no history of acute porphyric attacks. This very rare and severe cutaneous porphyria is also characterized by very high levels of porphyrins in erythrocytes [23,57,102].

Similar to AIP, also in HCP the catalytic capacity of PBGD (HBMS) enzyme may be compromised (probably as a consequence of inhibitory effect of porphyrins produced in excess), and a plasma fluorescence peak positive at 620 nm has been described [23].

The direct evaluation of copro-oxidase activity probably represents the more specific and sensible test for diagnosing HCP. As the enzyme is mitochondrial, this assessment should be performed on liver tissue (or in lymphocytes or fibroblasts). In clinical practice, due to the extreme complexity of this test (available only in highly specialized

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laboratories), the biochemical determination of faecal porphyrin pattern is considered highly reliable for confirmation of diagnosis and for identification of asymptomatic carriers of the diseases (first-degree relatives) [23,45].

Even for HCP, after identification and definition of copro-oxidase gene, DNA analysis is possible. Besides the role of this third-level assessment for diagnostic purposes (see above for AIP), genetic testing for HCP makes it possible to identify asymptomatic carriers with very poor biochemical abnormalities and to confirm great genetic heterogeneity for this disease [103].

3.3.4. Variegate porphyria (VP)

In VP the presence or history of photo cutaneous syndrome (extreme fragility and/or erythematous bullous dermatitis) may be the sole clinical picture for a long time. In case of history of neurovisceral crisis suggesting a VP, a typical plasma red fluorescence at 626 ± 2 nm is usually present, and it represents a quick and valuable diagnostic tool also for family studies [64]. In the active phase of disease, besides high urinary levels of ALA and PBG, VP is also characterized by high level of total urinary (coproporphyrin isomer III being largely prevalent) and faecal (protoporphyrins ≫ coproporphyrins) porphyrins. The typical faecal porphyrin pattern usually persists even during the remission phases of the disease, when the other biochemical abnormalities may be completely absent [64]. Similar to HCP, also in VP the catalytic capacity of PBGD (HBMS) enzyme is often compromised in subjects with a history of acute porphyric attacks [104]. The non-invasive assessment of proto-oxidase activity (in lymphocytes or fibroblasts) is suitable but technically difficult and it is performed only in highly specialized laboratories, mostly for research purposes or for large family studies aimed at identifying asymptomatic carriers of enzymatic abnormalities [104]. To date, DNA analysis is mostly performed for confirmation of diagnosis and for family studies: more than 100 different mutations of proto-oxidase gene have been identified. Even if most of these mutations are family-specific, the existence of a single diffuse mutation in South Africa transmitted over generations from a single founder is well-known [105–109]. As already observed for AIP or HCP, even in VP the research for a possible genotype–phenotype association has produced frustrating results, thus suggesting the importance of association with other factors (genetic, environmental or both) in clinical expression of this disease [21,110].

4. Conclusions

The diagnosis of an acute porphyric attack and/or acute (hepatic) porphyria is a challenging clue: acute porphyrias are rare diseases characterized by extreme variability in their clinical presentation. Nevertheless, because of their potential lethality, a prompt diagnosis is mandatory, and it should be taken into consideration in many different fields of medicine. An accurate diagnosis of acute porphyric attack requires the knowledge and use of the correct diagnostic tools, whose availability should be warranted in all laboratories associated with emergency units. An accurate diagnosis is mandatory to provide immediate proper therapeutic approach, in order to prevent the use of potentially unsafe drugs, usually precipitating the clinical picture, especially in the presence of life-threatening symptoms [111–114].

Diagnosis of individual porphyrias requires a correct analysis of porphyrins and porphyrin precursors in appropriate (urine, stools, blood) samples, often supported only in porphyria clinical specialist centres [1,3,45,59,63,115].

The correct identification of patients strongly suggests an in-depth study of their relatives (to date mostly by means of DNA assays), in order to identify potential disease carriers, who should be informed about their possible health risk when exposed to potential triggering factors.

Further information about porphyria laboratory diagnostics in Italy, for specialist counselling and GrIP activities will be soon available at www.gruppoitalianoporfiria.org.

Conflict of interest statement

Paolo Ventura has been involved as consultant in advisory boards and he has received research and travel grants from Orphan Europe Italy.

There are no other competing interests to declare for him and for all the other co-authors.

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