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Review Article

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

Paolo Ventura [a,*], Maria Domenica Cappellini [b], Gianfranco Biolcati [c], Claudio Carmine Guida [d], Emilio Rocchi [a], and Gruppo Italiano Porfiria (GrIP) [1]

[a] Centre for Porphyrias, Division of Internal Medicine II, Department of Medical and Surgical Science — University of Modena and Reggio Emilia, Policlinico Hospital, Modena, Italy
[b] Department of Internal Medicine, IRCCS Cà Granda Foundation — Ospedale Maggiore Policlinico, Milan, Italy
[c] Centre for Porphyrias, Istituto Dermatologico S. Gallicano — Istituti Fisioterapici Ospitalieri, Rome, Italy
[d] Centro Interregionale di Riferimento per la prevenzione, la sorveglianza, la diagnosi e la terapia delle Porfirie — I.R.C.C.S. Casa Sollievo Sofferenza, San Giovanni Rotondo, (Foggia), Italy

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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

* Corresponding author at: Centre for Porphyrias and Diseases from Disturbances of Amino Acid Metabolism, Division of Internal Medicine 2, Department of Medical and Surgical Science for Children and Adults, University of Modena and Reggio Emilia, Policlinico Hospital of Modena, Largo del Pozzo 71, 41124 Modena, Italy. Tel.: +39 059 4225542; fax: +39 059 4224363.
E-mail address: paoloven@unimore.it (P. Ventura).
[1] M.D. Cappellini, G. Graziadei, E. Di Pierro, V. Brancaleoni, F. Granata (Department of Internal Medicine, IRCCS Cà Granda Foundation - Ospedale Maggiore Policlinico, Milan); P. Ventura, E. Rocchi, S. Marchini, A. Pietrangelo (Centre for Porphyrias and Diseases from Disturbances of Amino Acid Metabolism, Division of Internal Medicine 2, Department of Medical and Surgical Science for Children and Adults - Policlinico Hospital, Modena, Italy); G. Biolcati, A. Macrì, L. Barbieri, G. Lupia Palmieri, S. Iacopini, A. Pitisci, C. Aurizi, F. Sorge (Centre for Porphyrias, Istituto Dermatologico S. Gallicano- Istituti Fisioterapici Ospitalieri, Rome, Italy); C.C. Guida, M. Savino, F. Aucella, L. Di Mauro [Centro Interregionale di Riferimento per la prevenzione, la sorveglianza, la diagnosi e la terapia delle Porfirie- I.R.C.C.S. Casa Sollievo Sofferenza, San Giovanni Rotondo (Foggia), Italy].

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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