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Case Report

Case Report: Managing Acute Porphyria during Acute Leukemia

L Montes[1*], A Caulier[1], P Morel[1], M Joris[1], J Schmidt[2], JP Marolleau[1], B Galmiche[3], D Lebon[1]

[1]Hematology Department, CHU Amiens, France

[2]Inter Medicine Department, CHU Amiens, France

[3]Biochemistry Department, CHU Amiens, France

***Corresponding authors**: L Montes, Hematology Department, CHU Amiens, France

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Abstract

Porphyria are rare, mostly genetic diseases, affecting heme biosynthesis and its association with acute leukemia aggravates its management. Heme is an essential metabolite for aerobic conditions. Its metabolism is disturbed by many favoured factors like fast, hypoglycaemia, drugs, and leukemic cells themselves. This case will discuss therapeutic options and heme profilactic perfusions in order to not undermanaged leukemia.

Keywords: Leukemia; Porphyria; Heme; Genetic; Givosiran

Introduction

Porphyria are rare, mostly genetic diseases, affecting heme biosynthesis. One can distinguish between acute porphyria (1 case per 0.75 million live births; systemic symptoms include headache, confusion, abdominal pain, and tachycardia) and cutaneous porphyria (photosensitivity, vesicles, and bullous peeling; this entity will not be discussed here) [1,2]. Acute porphyria could interfere into leukemia management because of disability, patient suffer, organ damage, drugs that aggravate porphyrin accumulation. Moreover, leukemic cells could induce porphyrin accumulation in patients not diagnosed from acute porphyria. Leukemic cells could also interfere in heme biosynthesis, mostly in acute lymphoid leukemia (ALL), as also described in some solid organ cancer [3,4].

Case Report

We report on a 38-year-old male patient presenting with cervical lymph nodes, pancytopenia, and a circulating blast percentage of 37%. We diagnosed acute leukaemia with both myeloid and T lymphoid lineages. The patient's medical history included hepatitis A in childhood and acute intermittent porphyria proven by the presence of a heterozygous mutation in exon 12 of the gene coding for hydroxymethylbilane synthase. The patient started a 7-day course of induction treatment with steroids, followed by chemotherapy with the antimetabolite and alkylating agent's clofarabine, cytarabine, and cyclophosphamide (porphyria inducer drugs). During the induction phase, the patient experienced an episode of acute porphyria, with neurologic symptoms (headache, confusion, and altered consciousness) and abdominal pain. The diagnosis was straightforward, with urine aminolevulinic acid (ALA) and porphobilinogen (PBG) levels of 502 µmol/L and 55 µmol/L, respectively (normal reference values: <38 µmol/L and <9 µmol/L). The patient experienced three other episodes of acute porphyria during consolidation chemotherapy. We then combined heme arginate infusion with symptomatic treatments (hydration with intravenous glucose solution, analgesia, and antinausea drugs) to reduce the crisis. The patient discontinued all medications that could potentially induce an episode of porphyria. Faced with the poor prognosis for leukaemia, our patient was conditioned (using thiotepa, busulfan, and fludarabine) for hematopoietic stem cell transplantation. He received cyclosporine, mycophenolate

mofetil (both authorized by specialist porphyria centres) and cyclophosphamide (not recommended by specialist porphyria centres), to prevent graft-versus-host syndrome. After consulting a porphyria centre, we decided to infuse prophylactic heme during the transplantation, one per week. Despite our precautions, the patient developed another acute episode of porphyria on post-transplantation day 5 but with less severe symptoms. He sadly died from septic shock on post-transplantation day 35 due to medullar insufficiency. Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

Discussion

Heme is an essential metabolite for aerobic conditions because it serves as a cofactor for haemoproteins like haemoglobin, myoglobin, cytochrome p450, and mitochondrial cytochromes. Heme is synthetized by bone marrow erythroblasts (accounting for 80% of the production) and hepatocytes (20%) in eight steps, using eight different enzymes [1,5,6]. Mutations in any of these enzymes can lead to the loss of catalytic activity, the accumulation of protein precursors, and thus porphyria [7]. One can distinguish between four subtypes of acute porphyria (Table 1). Around 5% of patients with acute porphyria experience recurrent episodes (i.e. more than four per year). Several risk factors have been described, including hormone-related factors, antibiotics, analgesics, anticonvulsants, septic conditions, alcohol consumption, and fasting. The presence of atypical symptoms can complicate the diagnosis of acute porphyria. The most commonly described symptoms are abdominal pain (with no clinical or radiologic abnormalities), nausea, vomiting, confusion, arterial tension, tachycardia, and convulsions. A change in the colour of the urine (to red brown, due to porphobilinogen oxidation) is highly specific. With regard to laboratory variables, hyponatremia and liver damage are frequent. A lab analysis of urine ALA and PBG levels will confirm the diagnosis. Porphyrin accumulates in 85% of episodes of acute porphyria crisis and remains present for several months after the episode. A definitive diagnosis requires genetic testing; a genetic variant will be identified in 95% of cases of acute porphyria [8]. The management of episodes of acute porphyria includes the eviction of triggering/susceptibility factors, hydration with intravenous glucose solution, symptomatic medications (analgesics and antinausea agents), and heme infusions (to reduce ALA production via negative feedback). The latter infusions might reduce the duration and intensity of acute episodes. Although there is no consensus on the value of prophylactic, repeated, heme infusions, this approach is often used in recurrent and disabling cases and appears to be effective with regard to symptoms and quality of life [7]. In a study performed in England (in 1999) and Wales (in 2012), Rees et al. observed a symptom reduction in 15 out of 22 (67%) patients suffering from acute, recurrent porphyria (12 episodes per year) after the administration of heme arginate (median number of doses: 52) [9]. In contrast, Gouya et al.'s 30-year follow-up study in France (published in 2018) of 602 patients, suffering from acute intermittent porphyria refuted the benefit of heme use; the researcher observed acted that repeated heme infusions induce oxidative stress, which can over produce ALAS1 activity [10]. With the development of an RNA targeting the ALAS gene (givosiran from Alnylam Pharmaceuticals), gene therapy offers a new opportunity to treat this disease. The ENVISION Phase III double-blind multicentre study is comparing RNA administration versus placebo over six months. Ninety-four patients have been included in the study so far. The annual number of episodes was 3.2 in the givosiran group versus 12.5 in the placebo group, which corresponds to a risk reduction of 74% ($p < 0.001$) [11]. An analysis of the secondary criteria demonstrated that heme arginate infusion was associated with less intense episodes and had an acceptable toxicity profile. On the basis of these results, givosiran was approved for the treatment of acute porphyria by the US Food Drug Administration (in November 2019) and the European Medicines Agency) (in March 2020). Ventura et al.'s recently published intermediate analysis (after 24 months of follow-up) confirmed givosiran efficacy in reducing the number of episodes. A health quality analysis evidenced a lower level of opioid use and better quality of life [12]. Our patient presented acute intermittent porphyria and experienced several episodes during his leukaemia treatment; this was probably triggered or favoured by a number of different factors (chemotherapy, antibiotics, sepsis, etc).Moreover, some studies reported that leukemic cells have an implication in heme biosynthesis dysregulation, and could elevate porphyrin level, even in patients not suffering from genetic acute porphyria. Since, leukemia is itself acute porphyria trigger [3] Heme perfusions helped to limit the intensity of the symptoms but did not prevent the acute episodes. We recommend prophylactic heme infusions to support intensive treatment in patient suffering from acute intermittent porphyria and hematologic malignancies. Further studies are required to improve knowledge (Figure 1).

	Acute intermittent porphyria	Variegate porphyria	Hereditary coproporphyria	Porphyria due to delta- ALA dehydratase deficiency
Enzyme affected	Hydroxymethylbilane synthase	Protoporphyrinogen oxidase	Coproporphyrinogen oxidase	ALA dehydratase
Transmission	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal recessive
Visceral symptoms	+++	+	+	+++
Cutaneous symptoms	None	In 10-60% of cases	In 5-10% of cases	None
Incidence	0.13 per million live births	0.08 per million live births	0.02 per million live births	<0.01 per million live births

Table 1: subtypes of acute porphyria.

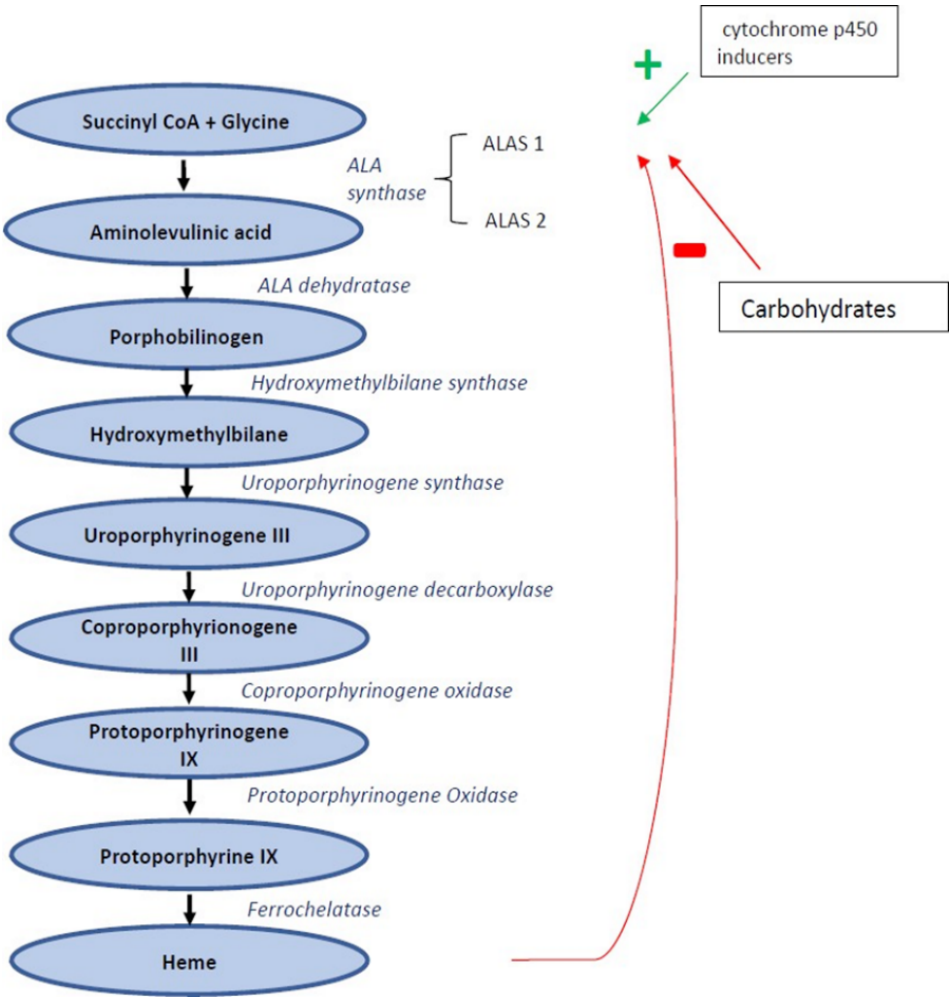

Figure 1: Heme biosynthesis.

Conclusion

In conclusion, acute porphyria is not an easy diagnosis. Various treatment and drugs (chemotherapy, antibiotics, antinausea agents, etc.) favour the onset of acute episodes of porphyria. Heme infusion is one option to reduce the severity of the episode's symptoms, although its prophylactic use is subject to debate. RNA therapy might be a valuable option in the future.

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