Use of intrathecal drug infusion pump with combined morphine and bupivacaine medication for the treatment of abdominal pain due to Acute Intermittent Porphyria (AIP)

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Abstract: Porphyrias consist of nine genetic disorders, acquired or congenital, resulting from failures in the biosynthesis process of the heme group, resulting in the accumulation of metabolic intermediates in the human body, causing toxicity. We describe a case of a 32-years-old Woman presented with severe and continual abdominal pain, presenting a visual analog scale (VAS) score of 9-10, described by the patient as the worst pain she has ever felt in her life, colic type in the mesogastric area and that radiated throughout the entire abdomen for six months. Due to the presented condition, she underwent appendectomy and cholecystectomy procedures, being later diagnosed with acute intermittent porphyria (AIP). It is important to highlight that some manifestations resulting from AIP are similar to Acute Abdomen. This is a clinical condition characterized by sudden or progressive abdominal pain, which usually requires an emergency surgical procedure to resolve the condition. The diagnosis of AIP is quite complex, and it can easily cause misdiagnoses, as in the present case report, in which the patient was mistakenly submitted to appendectomy and cholecystectomy procedures, due to the symptom of severe abdominal pain, which could lead to exposure her to iatrogenic damage.

Keywords: Acute intermittent porphyria; Abdominal pain; Morphine; Bupivacaine.

1. Introduction

Porphyrias consist of nine genetic disorders, acquired or congenital, resulting from failures in the biosynthesis process of the heme group, resulting in the accumulation of metabolic intermediates in the human body, causing toxicity [1]. The heme group is indispensable for the performance of oxidation-reduction reactions, in addition to being essential for the functionality of several enzymes and proteins related to energy metabolism. Thus, porphyrias are conditions that contribute to increased production of products from heme synthesis, such as 5-aminolevulinic acid (ALA), porphobilinogen (PBG) and
porphyrins [2], which are present in blood, urine and feces. There is also the possibility of pathological deposition in tissues and organs [3]. Porphyrias can be classified as hepatic or erythropoietic, depending on whether porphyrins accumulate in the liver or bone marrow, or acute and cutaneous, depending on the clinical features of the disease [4,5].

In most countries, such as the United States, a genetic prevalence of porphyria is estimated in the order of 1/10.000 individuals, while the manifestation of the aforementioned disease, in the USA, is approximately 5/100.000 inhabitants, with no indication of seasonal predominance in the incidence of porphyria [6]. Patients affected by this condition may present, as symptoms, neurological dysfunctions (neuropathies, alterations in the level of consciousness, seizures and behavioral abnormalities), neurovisceral alterations (gastrointestinal symptoms) and cutaneous manifestations (cutaneous photosensitivity and hemolysis) [1].

Acute intermittent porphyria (AIP), a hepatic form of porphyria and the most common form of porphyria, is an autosomal dominant and hereditary disease caused by successive mutations in the hydroxymethylbilane synthase (HMB-synthase) gene, responsible for the conversion of porphobilinogen to hydroxymethylbilane within the heme biosynthesis pathway, culminating in the accumulation of substrates, such as PBG and delta-aminolevulinic acid, in the liver [4]. Despite the aforementioned pattern of inheritance, 90% of heterozygous individuals do not present typical signs of AIP, with a predominance of females [8]. It is known that the manifestation of the disease is related to factors such as hypocaloric diet, use of drugs (oral contraceptives, steroid hormones, antibiotics, antiepileptics and calcium channel blockers), recurrent infections, alcohol consumption and smoking [5].

AIP can trigger, especially in moments of crisis, neurological manifestations (hyperesthesia, motor neuropathies, bulbar palsy, dysphagia, dysarthria, dysphonia and convulsions), psychiatric aspects (hallucinations, psychosis and delirium); cardiovascular conditions (arrhythmias, hypertension, tachycardia and hemodynamic instability), endocrine aspects (hyponatremia and hyperthyroidism); gastrointestinal manifestations (disproportionate abdominal pain, constipation, abdominal distension, symptoms present in more than 80% of the cases of the disease in question), urological issues (dark urine, due to the degradation of PBG to porphobilinogen, as well as urinary retention and incontinence), and kidney problems (nephropathy and chronic kidney dysfunction) [7,8].

Regarding abdominal pain, this symptom can lead to the diagnosis of an eventual situation of AIP as Acute Abdomen, and the need for surgical intervention may be mistakenly considered [7]. Some manifestations of the disease may erroneously indicate the suspicion of diverticulitis, appendicitis, neurodegenerative diseases and encephalitis [8]. Thus, guidelines are constantly published by health entities, with the purpose of helping to indicate the best course of action to be followed by the medical team [3], for example, the need to observe the existence of a history of abdominal crises and the identification of other typical symptoms of AIP in the patient, especially neurological [7].

An acute attack of AIP represents a fatal risk for the patient affected by the disease. Therapeutic intervention, in these cases, needs to occur quickly, notably from the removal of all potentiating factors to the manifestation of the condition and the infusion of intravenous heme, aiming to reduce PBG levels and contribute to clinical improvement. For symptomatic treatment, the administration of morphine is recommended for short-term relief of discomfort, in addition to bupivacaine, for the treatment of chronic pain arising from AIP [9]. The therapy can be performed through the use of an intrathecal drug infusion pump, which can be definitively implanted in the patient, requiring a prior assessment [5].

Thus, the present work aims to analyze Acute Intermittent Porphyria, a relatively rare disease that can be misdiagnosed, from the analysis of the diagnosis and treatment of a rare clinical case and investigates the effectiveness of the combined administration of drugs, especially morphine and bupivacaine, such as morphine and bupivacaine, from
the infusion of the aforementioned drugs through the use of an intrathecal drug infusion pump.

2. Case Report

A 32-years-old Woman presented with severe and continual abdominal pain, presenting a visual analog scale (VAS) score of 9-10, described by the patient as the worst pain she has ever felt in her life, colic type in the mesogastric area and that radiated throughout the entire abdomen for six months. Due to the presented condition, she underwent appendectomy and cholecystectomy procedures, being later diagnosed with AIP. The patient underwent therapy with immunomodulators and use of morphine through an infusion pump at a dose of 100mg/day for three months.

In a context of severe abdominal pain, the patient was admitted, and she received a five-day course of epidural morphine injections via epidural catheter. The installation of the aforementioned drug device was successful, and she had a good evolution of her health condition after one week, presenting a VAS score of 2-3. After one month, the patient’s pain score increased, which is why the dose of morphine injected into the patient was also increased, without showing any improvement. Due to the unsatisfactory results, it was decided to start a therapy using the morphine-bupivacaine combination. After six months of beginning the last-mentioned treatment, the patient presented a relevant improvement of symptoms, reducing the VAS score to 2-1.

3. Discussion and conclusions

Acute Intermittent Porphyria, also known as Swedish porphyria, pyrroloporphyria or intermittent acute porphyria, was first described by the Dutch physician Stokvis in 1889 [9,10,13]. It is an uncommon genetic disease of autosomal dominant inheritance caused by hydroxymethylbilane synthase (HMBS) deficiency. In patients with AIP, there is an increase in the regulation of ALA synthase-1 (ALAS1), the liver’s first heme synthesis pathway, resulting in increased production and accumulation of delta-aminolevulinic acid and porphobilinogen in organs and tissues of the human body [17] and may cause gastrointestinal, neurological, psychological, endocrine and urological symptoms [16]. It is estimated that the incidence of AIP cases in Europe is approximately 1/20.000 individuals [11], while the prevalence of symptomatic cases of AIP in most countries is only 5.4 per million per year [12]. Thus, despite the possibility of hereditary transmission, genetic investigation helps to identify the patient’s mutation and contributes to the identification of family members who may be potentially at risk of the disease.

Studies show that several factors can contribute to the expression of AIP. This disease becomes more evident when the demand for heme group increases in the liver, through some substances, such as phenytoin, nifedipine, ketamine [14], chloroquine [16], barbiturates, sulfonamides and hydantoins; hormones, like progesterone, and habits, such as smoking, alcohol consumption and stress. In addition, patients diagnosed with AIP are contraindicated to adopt ketogenic diets or low carbohydrate intake, situations in which there’s a tendency for a higher intake of fats, which can lead to an overload of the liver [14]. AIP has been more commonly reported in women [13] who use contraceptives or who are in the puberty period, which suggests the role of sex hormones, such as progesterone, in acting as inducers of the clinical manifestation of the disease [14,15].

Regarding the frequent gastrointestinal symptoms resulting from AIP, as reported in the present case, it consists of severe abdominal pain, with a VAS score equal to or greater than 7 [17] and is related to autonomic nerve dysfunction [8]. The stress caused by pain can contribute to increase the production of ALAS1 [2] by neuroendocrine reactions, resulting in a worsening of the symptom [17]. That symptom is present in more than 80% of cases and may be associated with nausea, constipation, abdominal distension, muscle weakness, lack of appetite and paralytic ileus [8]. The delay in starting treatment in a
context of acute crises increases the chances of developing liver diseases and hepatocellular carcinoma [12].

Studies show that the neurological manifestations resulting from AIP occur due to the fact that excess ALA impairs the function of gamma-ammoniobutyric acid (GABA), leading to impairment of the central nervous system. Peripheral neuropathy is a common neurological manifestation in cases of AIP, caused by ALA neurotoxicity [10]. Patients may experience seizures, mental disturbance, peripheral neuropathy, and even respiratory paralysis, if acute crisis treatment is delayed. Furthermore, a variety of psychiatric symptoms, such as depression, anxiety, insomnia, psychosis and schizophrenia, can occur during an acute illness crisis [17].

In addition, it is often possible to observe other aspects in patients with AIP, such as cardiovascular conditions (tachycardia, arrhythmias, hypertensive crises, which may progress to hemodynamic instability), endocrine manifestations (hyponatremia, hypothyroidism, cholesterol and low-density lipoprotein elevations). - LDL), urological issues (characteristic deep red port wine colored urine and urinary incontinence) and kidney problems (nephropathy and chronic kidney dysfunction) [8, 17].

It is important to highlight that some manifestations resulting from AIP are similar to Acute Abdomen. This is a clinical condition characterized by sudden or progressive abdominal pain, which usually requires an emergency surgical procedure to resolve the condition. The diagnosis of AIP is quite complex, and it can easily cause misdiagnoses, as in the present case report, in which the patient was mistakenly submitted to appendectomy and cholecystectomy procedures, due to the symptom of severe abdominal pain, which could lead to exposure her to iatrogenic damage [15]. In fact, symptoms like intense and diffuse abdominal pain can indicate several conditions, so the AIP can often be misdiagnosed. Thus, as a way to avoid delaying or harming the patient’s recovery, the health professional needs to be aware of the maximum information extracted from the patient’s family history, in addition to the need to improve the subject in the curriculum of medical schools [12].

In a context of extreme difficulty in the clinical diagnosis of AIP, health professionals can also use laboratory procedures (urinary exams), such as the Watson–Schwartz test, which consists of a simple and effective experiment for the detection of AIP, which aims to locate PBG in the patient’s urine. In the aforementioned screening test, a certain amount of urine is mixed with an equal amount of Ehrlich reagent. In the presence of PBG, there will be the formation of porphobilinogen-Ehrlich complex. Subsequently, chloroform is added, which causes the PBG to become highlighted by the red color and migrate to the upper aqueous layer of the compartment [14]. As patients with AIP expel large amounts of PBG in the urine during episodes of acute attacks, studies show that false-negative results of AIP are uncommon in these cases [12].

The management of patients diagnosed with AIP should include treatment of acute attacks of the disease, long-term monitoring of their health condition and treatment of eventual complications, such as chronic kidney disease [16,17]. In this context, one of the conventional and most effective therapies is the use of intravenous heme. This procedure provides exogenous heme to the patient’s body, contributing to the inhibition of ALAS1 enzyme transcription, the consequent reduction in the exaggerated production of ALA AND PBG and to the improvement of the patient’s general clinical condition in approximately 4 days (19), being very effective in combating symptoms resulting from AIP, such as seizures, neuropathies and psychosis [17]. However, studies demonstrate that successive treatments with exogenous heme increase the risk of liver fibrosis (18). Anti-inflammatory drugs are commonly used by health teams as the first attempt to alleviate the effects of pain caused by AIP, especially in mild cases. However, in situations of acute crises, as in the present case, opioid analgesics, such as morphine, prove to be safe and effective drugs for the treatment of AIP, contributing to the relief of pain within 3 to 5 days of treatment. The use of opioids in the treatment of IAP can cause side effects such as constipation, itching, convulsions, vomiting and bradypnea. Dependence on patients with AIP
is a situation that deserves attention by health authorities. However, studies show the occurrence of few cases of opioid addiction in patients with AIP [17,18,19]. In addition to morphine, the patient described in the present case report also underwent synergistic treatment with bupivacaine, an amide-type local anesthetic. Bupivacaine has positive results in longer operative contexts (more than 40 minutes in duration) and with a lower association of analgesics. This is because bupivacaine prevented peripheral nerve sensitization, resulting in postoperative pain reduction [24]. Furthermore, the literature describes that prescribing bupivacaine is safe to attempt to alleviate chronic pain from AIP [25, 26]. However, studies have shown that bupivacaine is not efficient in reducing short-term pain [27]. Furthermore, there is no evidence capable of demonstrating the efficacy of the routine use of bupivacaine or any advantage of this drug when compared to other local anesthetics [23,24].

The administration of these drugs has several routes of application, including subcutaneous, intravitreal and intrathecal delivery [20]. In cases of treatment of chronic pain, the use of the intrathecal route is shown to be quite efficient, in which the medication is injected directly into the cerebrospinal fluid [21]. As it is an invasive infusion modality, it is necessary that the patient’s condition is evaluated and that the feasibility of installing the device is recognized [5]. Studies have shown that the combination of interthecal application of morphine and bupivacaine contributed to the achievement of positive results in an attempt to avoid pain in several scenarios, such as in the recovery of patients after gynecological surgeries [22], in addition to contributing to an antinociceptive effect in cancer patients [23], although the literature has not yet commented on the effectiveness of synergistic application of morphine and bupivacaine in inhibiting pain symptoms resulting from AIP. Caution is required in the application of such substances, as the interthecal application of bupivacaine can induce the emergence of hemodynamic disorders, such as hypotension, which may worsen in elderly patients, while the disproportionate interthecal application of morphine can result in nausea and depression of the respiratory system [22].

Thus, it is observed that the isolated use of morphine was not enough to alleviate the symptoms of abdominal pain of the patient, resulting in a she was later medicated with a synergistic intrathecal infusion of morphine and bupivacaine, showing significant improvement after 6 months of treatment, featuring an EVA scale from 9-10 to 1-2. It was observed that the synergistic effect of the use of the infusion of morphine associated with bupivacaine for the control of chronic pain in ABP was more effective, despite the lack of scientific evidence about the effectiveness of synergistic interthecal application of morphine and bupivacaine to alleviate the symptoms of abdominal pain in cases of AIP.

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References


