Daniela von Ah Lopes1, Marcelo Araújo do Valle[2], Jéfferson Taguti [3], Regina Celli Thomé Castro Taguti[4], Gustavo Navarro Betônico[5], Fabiana Clemente Medeiros [6]

Acute intermittent porphyria: case report and review of literature

Porfiria aguda intermitente: relato de caso e revisão da literatura

1. Physician from the Intensive Care Unit of the Hospital IAMADA - Presidente Prudente (SP), Brazil.
2. Physician from the Intensive Care Unit of the Hospital IAMADA - Presidente Prudente (SP), Brazil.
3. Physician from the Surgical Service of Hospital IAMADA – Presidente Prudente (SP), Brazil.
4. Physician from the Gastroenterology Service of Hospital IAMADA – Presidente Prudente (SP), Brazil.
5. Physician from the Intensive Care Unit of the Hospital IAMADA - Presidente Prudente (SP), Brazil.
6. Nutritionist from the Nutrition and Diet Service and from the Multidisciplinary Team of Nutritional Therapy of the Hospital IAMADA - Presidente Prudente (SP), Brazil.

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Author for correspondence:
Daniela von Ah Lopes
Rua Bandeirante René Nobre, 652
Bairro Jardim Bongiovani.
CEP 19050-430 Presidente Prudente (SP), Brasil.
Phone: 018 – 3908 7542
E-mail: dolgado@itelefonica.com.b

ABSTRACT

Acute intermittent porphyria is an unusual pathology with potentially severe consequences when not early detected. Among the possible causes of porphyric crises decrease of caloric intake has been described. A case of acute intermittent porphyria in the late postoperative period of a bariatric surgery performed for treatment of obesity is reported. A review of the diagnostic aspects and management of this pathology in the intensive care unit follows. A 31 year old woman was admitted in the intensive care unit three weeks after a bariatric surgery, with decreased level of consciousness and respiratory distress. The patient evolved with psychomotor agitation, mental confusion, abdominal pain and proximal tetraparesis. Diagnosis investigation disclosed severe hyponatremia (92mEq/L), hypomagnesemia, hypophosfatemia and hypocalcemia and cloudy urine without hematuria. Acute porphyria was suspected and the urine test detected high delta amino-levulinic acid and porphobilinogen. Treatment consisted of a correction of electrolyte disturbances and high carbohydrate intake. Hematin and heme arginate were not used, due to the difficulty to acquire the medication. After 8 months the patient progressed with full recovery of muscle strength and a clinical improvement. Acute intermittent porphyria has signs and symptoms common to several clinical, neurological, psychiatric and gastroenterological pathologies, which complicate diagnosis. Therefore, acute intermittent porphyria should be included in the differential diagnosis of neurological, psychiatric and gastroenterological alterations when results of all other exams are normal. Attention must be given to patients undergoing surgery mainly bariatric that, in addition to procedure stress, substantially limit the total caloric intake, potentially triggering crises. Review of literature did not disclose any report of acute intermittent porphyria crisis induced by bariatric surgery.

Keywords: Porphyria, acute intermittent/diagnosis; Hyponatremia; Bariatric surgery

INTRODUCTION

Acute intermittent porphyria (AIP) a rare autosomal dominant metabolic disorder resulting from a disorder in the hepatic pathway of heme biosynthesis caused by decrease of the porphobilinogen desaminase enzyme levels (PBG-D). It is characterized by generally intermittent signs and symptoms including abdominal pain, nausea, vomit, constipation or diarrhea, abdominal bloating, adynamic ileus, urinary retention or incontinence, tachycardia, sudoresis, tremor, fever, peripheral neuropathy, hydroelectrolitic and psychiatric disorders (Chart 1). Many factors can trigger an

AIP crisis, among them are noteworthy hypocaloric and low-carbohydrate diets. Regarding treatment of morbid obesity, it must highlighted that all surgical procedures (restrictive, disabsortive or mixed) may cause an AIP crisis because of the diet restriction to which patients are submitted at postoperative. Abdominal pain is the most characteristic symptom and generally the earliest, being diffuse and possibly accompanied by nausea and vomit. This clinical setting is common at postoperative period of abdominal surgeries, however in the case of AIP, pain is often very intense and does not respond to typical analgesics that, when used, may worsen the crisis. Furthermore, other signs and symptoms such as muscle weakness, mental confusion and hallucinations may orient towards a diagnosis according to the clinical context. To include AIP in the differential diagnosis of neurological, psychiatric and gastroenterological acute disturbances, when all other exams are normal, contributes to increased diagnostic accuracy as well as to adequate treatment.

Chart 1. Frequent signs and symptoms of acute porphyria[5]

Signs and symptoms	Estimated incidence (%)
Gastrointestinal	
Abdominal pain	85–95
Vomit	43–88
Intestinal constipation	48–84
Diarrhea	5–12
Neurological	
Unspecific algic symptoms	50–70
Paresia	42–68
Respiratory paralysis	9–20
Psychiatric symptoms	40–58
Seizure	10–20
Cardiovascular	
Tachicardia	28, 64–85
Systemic arterial hypertension	36–55

Based on a series of patients with symptomatic acute intermittent porphyria[5]

Source: Translated and adapted from : Anderson KE, Bloomer JR, Bonkovsky HL, Kushner JP, Pierach CA, Pimstone NR, Desnick RJ. Recommendations for the diagnosis and treatment of the acute porphyrias. Ann Intern Med. 2005;142(6):439-50. Erratum in: Ann Intern Med. 2005;143(4):316.

Diagnosis is based upon high urinary output of porphyrin precursors: delta-aminolevulinic acid (ALA) and porphobilinogene (PBG). Macroscopically, accumulation of these precursors excreted in urine may change its color after exposure to the sun, from yellowish to dark red or brown, occasionally even to a purple tinge. In laboratory tests, a very high value of PGB in the 24 h urine is a diagnosis of acute porphyria. Symptoms of AIP crises are treated with drugs considered safe, interruption of porphyrogenic medication, supply of a high glucose intake and use of hematin or heme arginate according to severity of the condition.

The case below is worthy of report as the clinical presentation of acute intermittent porphyria due to restrictive diet at late postoperative period of bariatric surgery was not found in literature.

CASE REPORT

A patient of the female gender, 31 years old, white, was admitted to the intensive care unit of the Hospital Iamada, in Presidente Prudente (SP) with a condition of low level of consciousness and respiratory distress for the last 12 hours. She had been admitted to the hospital seven days earlier with intense abdominal and back pain associated with nausea, vomit and inappetence. In the ward she evolved with psychomotor agitation, mental confusion and hallucinations. At physical exam she presented with torpor, confusion, responding to verbal requests, dehydration (++/4+), tachycardia (136 bpm) tachypnea (36irpm), hypertension (180x100mmHg) with bloated, flaccid abdomen, presence of hydroaerial sounds, diffuse pain to superficial and deep palpation, with palpable, not pulsatile, painful mass in the hypogastrium. There was proximal tetraparesis with muscle tone maintained, delayed tendinous reflexes, plantar cutaneous flexion reflex, and mydriatic pupilas although isochoric and photo-reactive.

There was a previous history of bariatric surgery (gastroplasty with intestinal by-pass) three weeks earlier that had no intercurrence in early postoperative period without other previous history or co-morbidity factors. After vesical catheterization upon admission to the ICU, 2000 ml of dark red urine were obtained. In view of the condition's severity, support measures with oxygen mask and volemic replacement were undertaken. Laboratory tests then showed severe hyponatremia (92 mEq/L) with hypomagnesemia (0.4 mEq/L), hypophosphatemia (1.7 mg/dL) and hypocalcaemia (0.86mmol/L). Other exams such as potassium, creatinine, blood test, amylase, rheumatic and thyroid functional studies had normal results. Serum levels of hepatic transaminases were discreetly increased; urine had a dark yellow color and cloudy aspect, however with no hematuria at urine test; C-reactive protein (CRP) was slightly increased; protein electrophoresis had no chang-

es; hemoculture and uroculture were negative. Image exams (chest, abdomen and intestinal transit x-ray; abdominal ultrasound; abdomen and lumbar spine computed tomography scan; nuclear magnetic resonance of the cranium) without alterations. High digestive tract endoscopy disclosed presence of ulcerated lesions in the efferent loop with no signs of bleeding. Correction of hyponatremia was begun at safe ratey with 3% saline, and sodium normalized after 5 days (Figure 1).

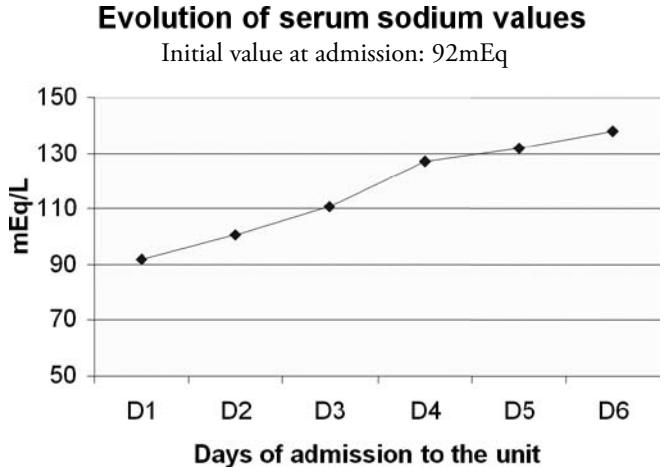

Figure 1 – Rate of hyponatremia correction.

Based upon clinical findings and of those of complementary exams, the hypothesis of acute porphyria was raised three days after admission in the ICU. Then dosage of the delta aminnolevulinic acid and of porphobilinogen in 24h urine was carried out, with significant increases of both (delta aminnolevulinic acid: 15mg/24h, ref- 1.3 to 7.0 mg/24h; porphobilinogen 4.25 mg/24h, ref- 1.0 to 1.5 mg/24h). Once diagnosis was confirmed, treatment was immediately begun with a carbohydrate rich diet: enteral diet by gastrostomy in continuous drip, 60 ml/h in 20 hours, hypercaloric (2370 calories), hypoproteic (35.55 g of protein), with high lipid content (113.28 g of lipids) and rich in carbohydrates (302.41 g). A carbohydrate (100% oligosaccharides – maltodextrin) 72 g/day module was associated to complete the recommendations established for AIP (300 to 400 g/day), adding up to 374.41 g carbohydrates per day.

At the same time the patient nourished herself orally with small amounts following a protocol of nutritional guidance post gastroplasty with reduced quantities of sugar to avoid the dumping syndrome induced by the intestinal bypass performed in the bariatric surgery. A specific therapy with hematine or heme arginate could not be initiated because of the difficulty of obtaining these drugs in Brazil. The patient evolved with gradual clinical improvement and was discharged from the ICU after 15 days after admission, conscious, oriented, without signs of pontine or extrapontine myelynolisis, however still with diminished muscle strength. In the intensive care unit, nutritional conduct remained unchanged during the entire stay. After two weeks she was discharged from the hospital with the following dietotherapy: 1) orally: bland diet non-acid fruit juices and vitamins with semi-skimmed milk every 2 hours in an amount tolerated by the patient with decrease of simple carbohydrates to avoid the dumping syndrome; 2) by gastrostomy: hypercaloric industrial diet, nutritionally complete, ready for use and a made to order diet rich in carbohydrates of high glycemic index administered by intermittent gravity drip every 3 hours with a pause during the night. Nutritional follow-up was continued in a daycare unit until it became possible to withdraw nourishment by gastrostomy tube and oral ingestion of calorie, protein and vitamin supplements needed for the patient's clinical well-being. Full recovery of muscle strength occurred 8 months after the acute event.

DISCUSSION

Acute intermittent porphyria pertains to a group of at least eight distinct genetic diseases, in addition to acquired forms known as porphyrias. Estimated occurrence is 1 to 2 in every 100,000 persons, with the most common incidence in the Northern European countries such as England, Ireland and Sweden (where it reaches 1:10,000).[1] In bearers of psychiatric disease, literature cites a prevalence of up to 1:500.[2] AIP is the main porphyria, causing acute symptoms, that may be severe and with risk of life, but of short duration. Typically AIP crises take place after puberty and are more frequent in women than in men.[3]

Under normal conditions the enzyme deficiency is not sufficient to trigger crises. Other factors are needed to induce symptoms. As such, about 80% of bearers of deficiency from enzymatic activity never present any symptoms (called individuals with 'latent" AIP) and some of the others suffer only light occasional symptoms.[4] Environmental factors play an important role in the unleashing and course of this disease. Many drugs (barbiturics, anticonvulsants, calcium channel blockers, some sedatives, antibiotics, antifungals and hormones) may activate the symptoms as well as con-

sumption of large amounts of alcoholic drinks, tobacco or hypocaloric and low carbohydrate diets. Stress as a result of infection, another eventual concomitant disease, surgery or psychological disorder also may sometimes be involved in the genesis of a porphyries crisis. Abdominal pain is one of the most characteristic symptoms and usually the earliest. Often, it is very intense, diffusedly located in the abdomen and does not respond to typical analgesics, that when used, may worsen the crisis. Nausea, vomit, constipation, urine retention, arrhythmias, hyper or hypotension besides hydroelectrolytic disorder, notably hyponatremia may appear together with the pain.[1,5] This may be secondary to a series of factors such as diarrhea, vomit, low intake and especially excessive renal loss and inadequate secretion of anti-diuretic hormones (ADH), Symptoms of peripheral neuropathy include muscle weakness in the upper and lower limbs, changes in sensitivity and motor neuropathy with cranial nerve involvement may develop (leading to symptoms such as dylali, dysphagia, diplonia and facial paralysis). The most severe central nervous system impairment may lead to seizure and even to bulbar paralysis with respiratory failure and death. Psychiatric findings include hysteria, anxiety, apathy or depression, phobias, psychosis, agitation, delirium, sleepiness or coma. [1]

In the case reported, the patient presented all the principal signs and symptoms, as well as the most severe: very intense abdominal pain, severe hyponatremia, arterial hypotension, respiratory failure and psychiatric disorder. Probably, the main crisis triggering factor was the hypocaloric diet, poor in carbohydrates, imposed by the surgery, but other factors such as drugs used prior to specific diagnosis may have contributed to aggravate the process. We must keep in mind that numerous conditions and surgical procedures, that entail diet restrictions such as gastrectomies and intestinal surgeries may precipitate crises of AIP that are possibly under-diagnosed. Attention paid to conditions of abdominal pain in crises that do no agree with the expected clinical picture for a particular postoperative, as well as the accompanying symptoms, may contribute for an early diagnosis.

Symptoms manifested by the patient since admission to the hospital, when analyzed separately, may mimic various diseases of the digestive and neuropsychiatric systems. Thus, it is known that diagnosis of porphyria, even in patients with severe crises, usually is difficult and can only be achieved after months of follow-up and several crises.

The early diagnostic hypothesis of AIP may be possible when there is a family history of the disease or if there is a high level of suspicion. The first step for diagnosis of AIP is, during crises, urine dosing, of 2mn ALA and of PBG in 24 hours. In crises, the excreted quantity of both may be various times this value. Even without crises, the value of both may be high, which permits diagnosis of latent AIP in a next of kin of the bearer of symptomatic AIP.[4] Measurement of the PBG deaminase enzyme activity (or HMB synthase) in red blood cells is sufficient to confirm diagnosis of AIP in 95% of cases.[1] Definitive diagnosis, in patients with characteristic symptoms and higher dosage of ALA and PBG or in a first degree relative, is performed by survey for the mutant gene through a molecular genetic test, with a detection capacity of the mutant gene of over 98%. [1]

Differential diagnosis of AIP must include, in addition to the obvious neuropsychiatric pathologies and habitual causes of abdominal pains in crises, diseases that cause elevation of the delta-aminolevulinic acid. Highlighted are: intoxication by lead (saturnism) – that lead to a picture similar to that of porphyria, however of acquired origin – and hereditary thyrosinemia.

AIP crises may lead to severe complications such as respiratory arrest by bulbar involvement, quadriplegia and chronic naturopathic pain in the extremities, depression and even suicide due to psychiatric disorder.[1,6] Other complications, generally not cited are chronic arterial hypertension, renal failure – that may occur due to still unknown mechanisms - and hepatocarcinoma. [7-10]

Treatment of crises consists in reducing pain, nausea and vomit with drugs considered safe, interruption of porphyniogeneic medication (Chart 2) alcohol and tobacco, supply a high intake of glucose in a carbohydrate rich diet and hypertonic infusion of glucose, according to the symptom severity. Need to instate support measures, such as correction of hyponatremia, hypo/hypertension and ventilation support (bulbar paralysis) varies according to the condition's severity. Therapy with hematine (in the United States) or heme arginate (in Europe) when available, must be started as soon as possible. These drugs inhibit action of the first enzyme of the heme synthesis route, blocking production and accumulation of porphyrias. In the described case, this therapy could not be carried out because these drugs are not easily available in the Brazilian market. The patient presented good evolution only with withdrawal of porphyrinogeneic drugs and especially with the carbohydrate rich diet. It must be considered if treatment with hematine or heme arginate were available; the patient could have had a quicker

clinical improvement, shorter and lower cost hospital stay. Nevertheless, we were able to prove that an efficient therapy is possible even without such expensive and difficult to obtain medication. This does not exclude the need to use medication, but it provides an efficient alternative for beginning treatment until these drugs become available.

Chart 2. Safe and contraindicated drugs for bearers of acute porphyria [4,5,12]

Contraindicated	Safe
Valproic acid	Acetaminofen
Àlcohol	Narcotic analgesics
Barbiturics	Aspirine
Calciu channel blockers	Atropine
Carbamazepin	Betablockers
Carisoprodol	Bromides
Clonazepam (high doses)	Cimetidine
Danazol	Clorpromazine
Diclofenaco	Diazepam
Ergots	Erythropoetine
Estrogen	Streptomycin
Phenytoin	Phenothyazines
Griseofulvin	Gabapentine
Pyrazenamide	Glucocorticoids
Progesterone	Chloral hydrate
Rifampicin	Serotonin reuptake inhibitors (anti-depressants)
Sulphonamides	Insulin
	Penicllin and derivatives
	Ranitidine

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Currently with the help of the Brazilian Association for Porphyria (ABRAPO), founded in 2006, access to diagnosis and therapy has become less troublesome. [11]

With adequate care 60% of the acute crises have been prevented in patients previously symptomatic and 95% of those with asymptomatic AIP. Currently, the risk of dying from, an acute crisis is small, unless the AIP condition in not promptly diagnosed and exposition to causal factors persist, mortality ranges from about 10 to 40%. Although, many patients with AIP live a normal life and seldom have crises, other disease such as hypertension, chronic renal failure and hepatocarcinoma may afflict them and medical follow-up is recommended. About 10% of patients with AIP die of hepatocarcinoma.[4]

Prevention of new crises is as important as early diagnosis and treatment to avoid complications. For this purpose periodic medical follow-up is needed together with simple measures such as an adequate diet, avoidance of porphyrinogenic drugs, alcohol, tobacco, strenuous physical activities and stress. Because of the high suicide risk, psychiatric treatment is recommended, if there are signs of depression. Arterial pressure must be adequately monitored as prolonged hypertension hastens and increases risk of renal disease.[7] As there is a much greater risk of hepatocarcinoma, periodic exams such as routine screening for bearers of cirrhosis, should be performed. [8,9] In bearers with frequent use of hematine, periodic blood dosage of ferritin is recommended, as this drug has a high iron concentration and its use may lead to secondary hemochromatosis. It is important to test all relatives of those with porphyria to verify existence of the genetic defect and thus take precautions to avoid that they become affected by porphyria. Even relatives who never had symptoms should be tested, as the disease may remain latent in a significant portion of bearers.

CONCLUSION

Acute intermittent porphyria should be included in the differential diagnosis of neurological, psychiatric and gastroenterological alterations when results of all other exams are normal. Attention must be given to patients undergoing surgery mainly bariatric that, in addition to procedure stress, substantially limit the total caloric intake, potentially triggering crises.

RESUMO

Porfiria aguda intermitente é patologia incomum, com conseqüências potencialmente graves se não reconhecida precocemente. Dentre as possíveis causas de indução de crises de porfiria, a redução da ingestão calórica é descrita na literatura. Relatamos um caso de porfiria aguda intermitente no pós-operatório tardio de gastroplastia indicada para tratamento da obesidade, revisando aspectos do diagnóstico e tratamento da patologia na unidade de terapia intensiva. Paciente feminina, 31 anos, com história de gastroplastia há 3 semanas admitida na unidade de terapia intensiva com rebaixamento do nível de

consciência e desconforto respiratório. Evoluiu com agitação psicomotora, confusão mental, dor abdominal e tetraparesia proximal. Na investigação diagnóstica foi encontrado hiponatremia grave (92 mEq/L), hipomagnesemia, hipofosfatemia e hipocalcemia, urina turva, sem hematúria. Aventou-se hipótese de porfiria aguda, realizado dosagem do ácido delta-aminolevulínico e porfobilinogênio na urina de 24h, com elevação de ambos. Iniciado tratamento com dieta rica em carboidratos, sem utilizar hematina ou arginato de heme, devido à dificuldades no fornecimento destas medicações. Evoluiu com melhora clínica gradativa e recuperação completa da força muscular após 8 meses. A porfiria aguda intermitente possui sinais e sintomas comuns a muitas patologias clínicas e neuropsiquiátricas dificultando o diagnóstico, em especial quando estes se manifestam isoladamente. Assim, deve-se incluir a porfiria aguda intermitente no diagnóstico diferencial de distúrbios neurológicos, psiquiátricos e gastroenterológicos em crises, no qual todos os demais exames estejam normais. Atenção deve ser dada a pacientes submetidos à cirurgias, em especial cirurgia bariátrica que, além do estresse cirúrgico, limita substancialmente a ingesta calórica podendo desencadear crises. Não há descrito na literatura, até o momento, nenhum caso de porfiria aguda intermitente no pós-operatório de cirurgia bariátrica.

Descritores: Porfiria aguda intermitente/diagnóstico; Hiponatremia; Cirurgia bariátrica

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