19-YEAR-OLD FEMALE WITH ABDOMINAL PAIN

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ABSTRACT

Porphyria is a group of at least 8 diseases that differ greatly between them. Common feature of these diseases is the accumulation in the body of porphyrins or porphyrin precursors, due to defects of specific enzymes in the biosynthesis of heme. Many symptoms of porphyria are nonspecific and therefore the diagnosis is often delayed. Laboratory tests can confirm or exclude the diagnosis of porphyria. However, certain diagnosis requires demonstration of specific enzyme deficiency. The presented case demonstrates the difficulty in diagnosis of acute intermittent porphyria (AIP) in a young woman without a history of significant pathology.

Key words: abdominal pain, neurological deficit, porfobilinogen.

INTRODUCTION

AIP is part of the hepatic porphyria, so named because the liver is the place of porphyrins and precursors porphyrin overproduction and deposit. It is a rare disease (1-5/100.000 people in USA)(1)cause by genetic mutation of gene that encodes hidroximetilbilan (HMB) synthase (also known as the porfobilinogen (PBG) deaminase) (Figure 1), occurs frequently after puberty, more common in women than in men and is manifested by the fact that 80% of the AIP gene carriers remain asymptomatic or may have one or several episodes for life (2).

Evolving disease relapse with neurological manifestations mainly as described triad: abdominal pain, peripheral neuropathy and impaired mental status (3) but other symptoms may occur: nausea, vomiting, constipation, back, arms and legs pain, muscle weakness (due to the nerves serving the muscles), urinary retention, palpitations often accompanied by high blood pressure, confusion, hallucinations and seizures. Positive diagnosis include elevated level of PBG and d-aminolevulinic acid (ALA) in blood and urine (you can see the change in color of urine exposed to sunlight (Figure 2) and demonstrate gene mutation coding for HMB synthase (4). However, it is a disease difficult to diagnose for at least four reasons: abdominal pain is not associated with significant physical examination changes, neurological examination signs and symptoms are variable, laboratory tests often give false negative results and there is no well-defined diagnostic criteria for the diagnosis requiring sometimes enzyme level measurement (5).

While the mechanism of damage to the nervous system is unclear, it is describ a number of precipitating factors including: some drugs (Table 1), narcotics, alcohol, luteal phase of the menstrual cycle, stress, smoking and diet (6).

TABLE 1. *Forbidden drugs in porphyria.*

Aminoglutethimide	Barbiturates
Carbamazepine	Chloramphenicol
Clemastine	Clonidine
Co-trimoxazole	Danazol
Dapsone	Dihydralazine
Dimenhydrinate	Dipyrone
Ergot derivatives	Erythromycin
Etamsylate	Ethosuximide
Etomidate	Griseofulvin

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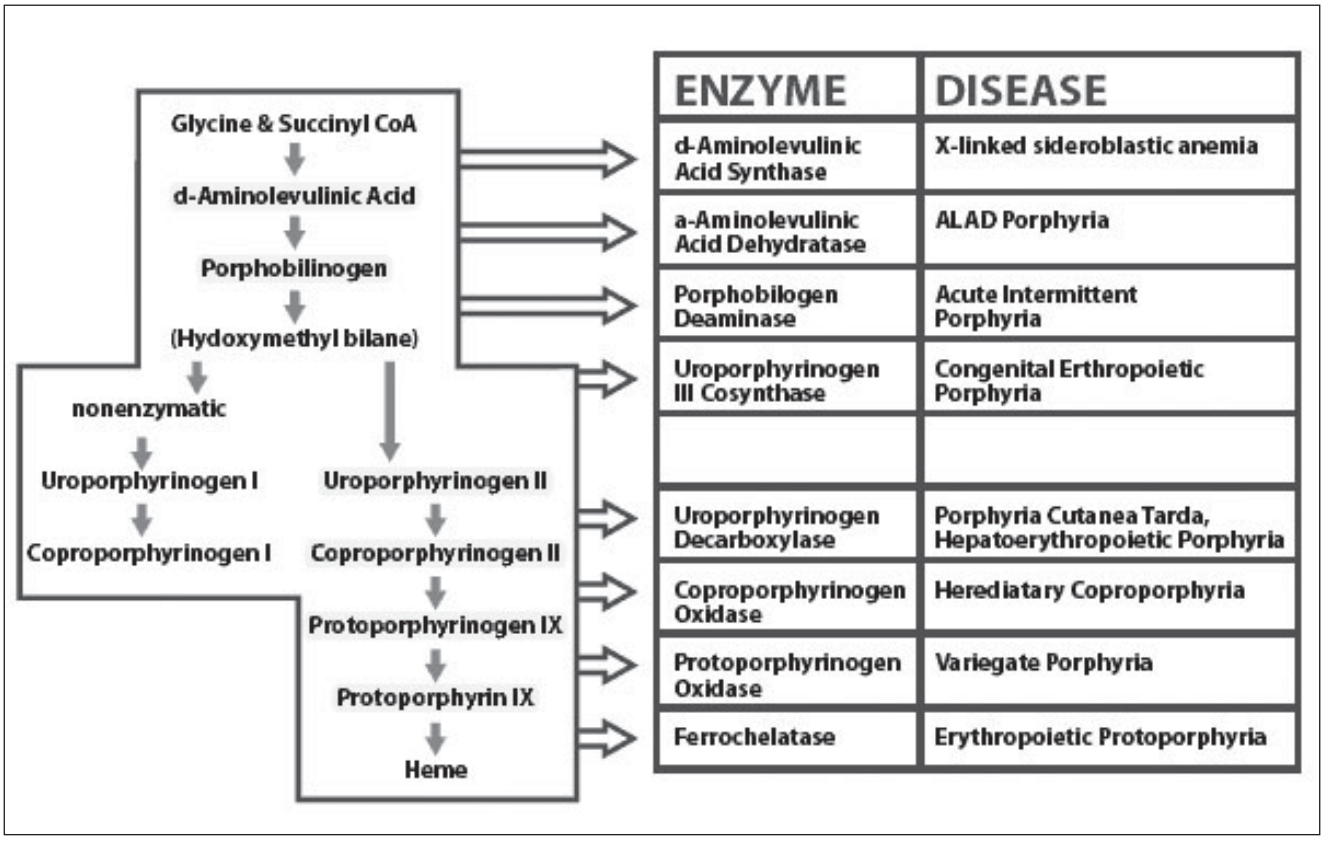

FIGURE 1. *Synthesis of porphyrins*

FIGURE 2. *Urine color change from sun exposure*

Ketoconazole systemic	Meprobamate
Mesuximide	Methyldopa
Methysergide	Nalidixic acid
Orphenadrine	Oxcarbazepine
Oxtriphyl	Phenylbutazone
Phenytoin	Primidone
Progestogens	Pyrazinamide
Pyrazolone	Sulphonamides

To assist in the diagnosis of this disease as quickly as you can use the following diagnostic algorithm (Figure 3) (7):

CASE PRESENTATION

AA, female, 19 years old, urban states, mother of two children without a significant pathological history was presented to the emergency room of the emergency hospital with mediocre general state accusing predominant diffuse abdominal pain in right iliac fossa, accompanied by nausea and bilious vomiting and no bowel movements.

Of patient history reports that symptoms began 9-10 days ago, so that was present at the emergency room of several hospitals where he was diagnosed with urinary tract infection and treated appropriately, without favorable evolution, so that shows to emergency room where deciding admission for specialist investigation and treatment.

General clinical examination is normal except that the abdomen is slightly distended by volume, symmetrical, mobile with breathing, spontaneously painful to diffusely palpation with predominant in right lower quadrant and mild draft defense at this level. Digital rectal exam is normal with no feces in rectal ampulla.

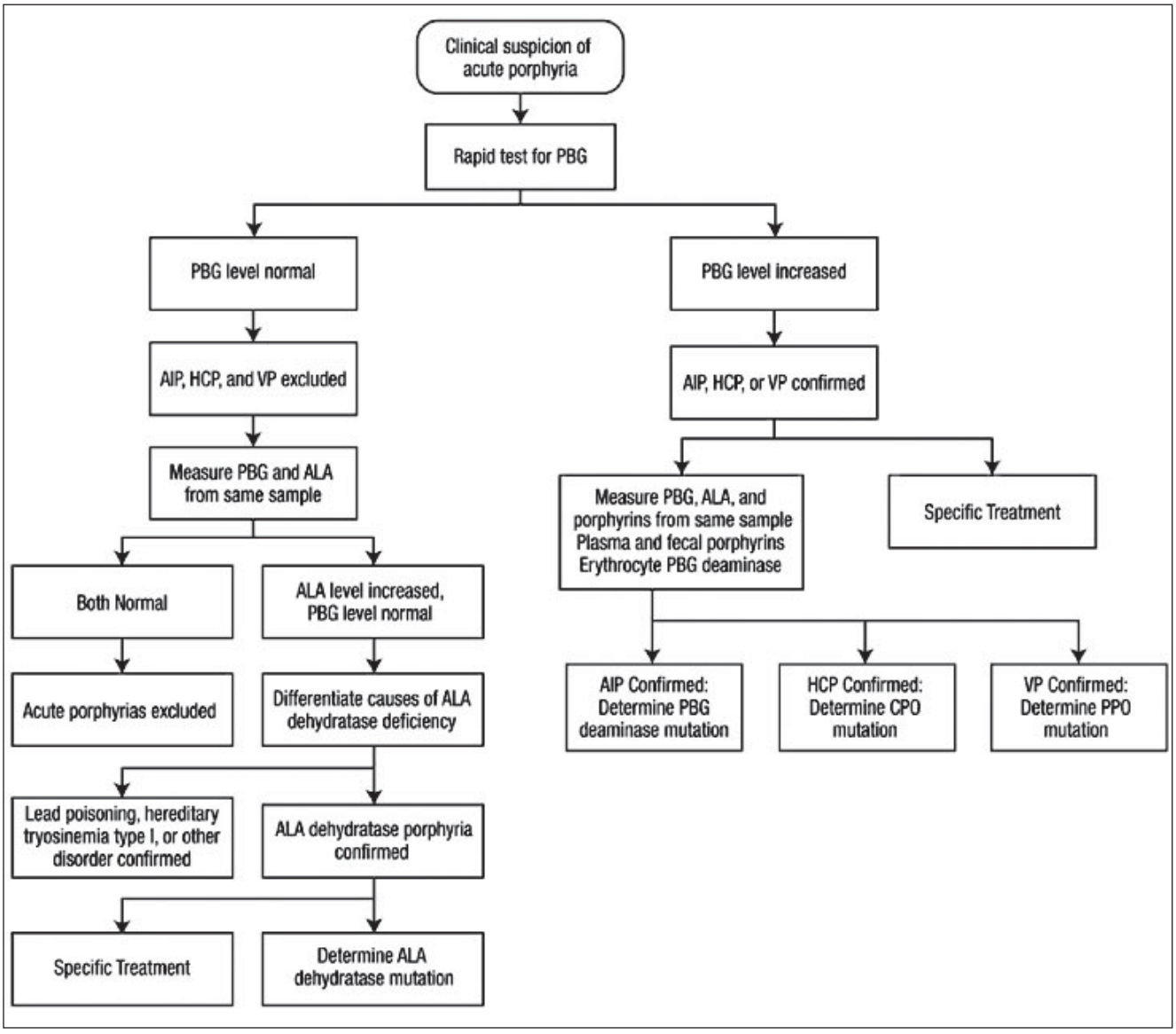

FIGURE 3. *Algorithm for the diagnosis of AIP*

Common laboratory tests show leukocytosis.

Abdominal ultrasound shows no pathological changes.

Before taking therapeutics measures it must made remarks about abdominal pain. Abdominal pain, the main symptom for which the patient presents to the emergency room has several possible causes can be classified into:

- pain with origin in the abdomen,
- pain irradiated from a extraabdominal source,
- pain due to metabolic and
- pain due to neurological/psychiatric (8).

Pain with origin in the abdomen has several mechanisms. Pain due to inflammation of the parietal peritoneum is continuous, vague and is located directly over the inflamed area, its exact location is possible because it is transmitted through somatic nerves innervating the parietal peritoneum. Pain intensity is dependent on the type and amount of foreign substance to which they are exposed peritoneal surface by time. Peritoneal inflammation pain is invariably pronounced to pressure or tension changes of peritoneum, if produced by palpation or movement, as in coughing or sneezing. Another characteristic feature of peritoneal irritation is reflex tonic spasm of the abdominal muscles located in the region involved. Tonic muscle strength that accompanies inflammation spam peritoneal inflammatory process depends on the location, how they develop and nervous system integrity(9). Obstruction of hollow abdominal viscera pain is classically described as intermittent and colicky. However, the lack of a cramp should not mislead because distension of hollow viscera can cause continuous pain, occasionally exacerbated. Although not as well located as the parietal peritoneum inflammation pain,

some generalizations can be made useful. If there vascular disorders sometimes misconception that abdominal pain associated with vascular disorders is sudden and terrible. Pain embolism or thrombosis or the superior mesenteric artery due to an impending rupture of an abdominal aortic aneurysm surely is severe and diffuse. Frequently, patients with superior mesenteric artery occlusion has only diffuse pain continues, gentle, for 2 or 3 days before the collapse of vascular or peritoneal findings of this inflammation. Early and insignificant discomfort is caused by hyperperistalsis rather than peritoneal inflammation. Of course, lack of sensitivity and stiffness in the presence of diffuse and continue pain to a patient's vascular disease is probably characteristic of superior mesenteric artery occlusion. Abdominal pain with radiation to the sacral region, flank and genitals will always indicate the possible presence of an abdominal aortic aneurysm and will persist over a period of several days before the occurrence of rupture and collapse. Pain with origin in the abdominal wall is usually constant and persistent. Movement, prolonged standing, and pressure accentuate the discomfort and muscle spasms. Simultaneous involvement of other parts of the body muscles usually help differentiate myositis of abdominal wall by a intraabdominal process that can cause pain in the same region. History of pain and its characteristics, including it's accompanied by nausea, bilious vomiting and no bowel transit, local examination of the abdomen associated with leukocytosis advocates for a cause with origin in the abdomen (10).

This is why, although the patient is stable in terms of vital functions, deciding surgery for suspected acute appendicitis and exploratory laparoscopy practice. In support of this decision is that abdominal ultrasound shows no pathological changes. During surgery no macroscopyc pathological lesions are seen only stain appearance of the liver surface and the moderately distended transverse colon and descending and several loops of small intestine. Postoperatively, the patient shows favorable trend and given that no organic lesions were detected intraoperatively. Patients respond favorably after administration of opioids and painful symptoms diminish in intensity.

Although patient accuse localized abdominal pain accompanied by gastrointestinal symptoms associated with leukocytosis, which would be called for an abdominal infectious process, exploratory laparoscopy cause abdominal excluded as the source of the patient's symptoms. Returning to the diagnostic algorithm once excluded the cause of the abdominal pain is going to further investigate the origin of the patient's symptoms.

Irradiated abdominal pain in chest, spinal cord or genitals can be a difficult diagnostic problem because the upper region of the abdominal cavity diseases such as acute cholecystitis or perforated ulcers are frequently associated with intrathoracic complications. Therefore it must consider the possibility of thoracic disease in a patient with abdominal pain, especially if it is located in the upper abdomen (11).

During the *neurological* causes sensory nerves damage can cause pain who has burning character and is usually limited to the territory of a peripheral nerve distribution. Normal stimulus such as touch or temperature changes can be converted to this type of pain, which is also present in a patient at rest. Although pain may be precipitated by gentle palpation, stiffness of abdominal muscles is absent and breathing are not disturbed. Abdominal distension is something uncommon, and the pain is not related to food consumption. Pain arising from the spinal nerves or roots appears and disappears suddenly and is the lancinant type. Can be caused by herpes zoster, favored by arthritis, tumors, nucleus pulposus herniation, diabetes or syphilis. Again, it is not associated with food intake, abdominal distension or changes in breathing. Severe muscle spasms, such as in gastric crises or tabes dorsalis is common, but is comforted and is accentuated by abdominal palpation. Pain gets worse by moving the column and is limited to a few dermatomes. Hyperaesthesia is very common (12).

Psychogenic pain is not conform to a pattern found in any of the causes listed in the previous classification. In this case, the mechanism is difficult to define. The most common problem is young or adolescent hysteria, complaining of abdominal pain and ovulation or any other natural phenomenon that causes mild abdominal discomfort can sometimes be perceived as an abdominal catastrophe. Psychogenic pain varies in type and location but usually not related to meals. At first, it is often deeply accentuated at night. Nausea and vomiting are rarely observed although occasionally patients report these symptoms. Spasm is rarely induced in abdominal muscles and, if present, it do not persistent, especially if the patient's attention may be distracted. Persistent localized tenderness is rare, and if present, muscle spasm in the area is inconsistent and often absent. Limiting depth of breathing is the most common respiratory abnormality, but is part of the feeling of suffocation and drowning, being a part of the state of anxiety. Occurs in the absence of immobilization of thoracic or change in respiratory rate (13).

Metabolic origin of pain can always simulate any other intra-abdominal disease. This can be activated several mechanisms and differential diagnosis prob-

lem is not often solved. In specific situations, such as hyperlipidemia, metabolic disease itself may be accompanied by abdominal process such as pancreatitis. Pain is not specific to uremia or diabetes and pain sensitivity change frequently in location and intensity. Diabetic acidosis can be precipitated by acute appendicitis or intestinal obstruction, so if prompt resolution of abdominal pain does not result in correction of metabolic disturbance, a subsidiary body problem must be strongly suspected. In this case, the pain of porphyria as the saturnine is usually difficult to distinguish from that of intestinal obstruction as severe hyperperistalsis, is an important feature of both (14).

In light of those presenting it is requested the internal medicine consult to elucidate the diagnosis mentioning the fact that after installing the urinary catheter the urine turn to pink-red appearance. Therefore urine sample is collected for bacteriological and biochemical dosage mentioning porphyrin precursors and porphyrins, obtaining PBG = 89mg/24hours. The is suspected diagnosis of AIP and is releasing the following recommendations: hygienic-dietary regime (eliminating smoking, self-medication, alcohol and caffeine), avoid intense effort, will remain in evidence of metabolic and nutrition department.

At home, after discharge, patients experience numbness, dizziness, proximal muscle deficit, unable to maintain standing, muscle pain for which is presenting to the emergency room.

General clinical examination highlights: severe general condition, afebrile, stetacustic lung without rales, blood pressure 110/60mmHg, heart rate 85bpm, rhythmic without abdominal pain, present bowel transis and diuresis. Imaging is performed routinely and it shows the following changes.

Abdominal ultrasound highlights renal microcalculus without any changes.

Chest X-ray shows no evolutionary pleuropulmmonare injuries.

Abdominal X-ray not show pneumomediastinum images, but hidroaeric level at left hypochondrium with importance air distension at this level.

Neurological consultation is required which states: no signs of meningeal irritation, without affecting the cranial nerves, muscle pain on palpation, muscular hypotonia, proximal dominant force down both brachial and crural, symmetrical tendon reflexes present in the upper limbs, absent rotulia reflexes, present ahilien reflexes without objective changes in superficial and deep sensitivity testing, can not examine coordination, awareness and self-directed temporal-spatial and allopsihic.

DIAGNOSIS

Positive diagnosis of AIP is supported on history, clinical examination and incrise of urine PBG values. To demonstrate the certainty of diagnosis it is indicate to demonstrate the mutation of gene encodes porfobilinogen deaminase.

Differential diagnoses include: diabetic ketoacidosis, polyarteritis nodosa, porphyria hereditary arsenic toxicity, lead toxicity, uremia, poliomyelitis, tabes dorsalis, manic depressive illness, abdominal disorders, other types of porphyria. Therefore it performs a series of laboratory tests to exclude these diagnoses and it performs brain CT scan, nerve conduction studies, needle electromyography examination refused by pacient, EEG, blood and urine determination of leaden and urine toxicology tests for: came out positive test for the benzodiazepines and came out negative test for amphetamines, barbiturates, cocaine, methadone, cannabis, opiates and phencyclidine. It is request for psychiatric examination for exclusion of psychiatric illness in this area and highlights: patient quiet, temporo-spatially oriented, anxiety in the context of hospitalization with transient episodes of psychomotor restlessness in the context of adjustment disorder. It is recommend psychological counseling and supervision.

Treatment of acute attacks of porphyria is trying decreased heme synthesis and reduced synthesis and production of porphyrin precursors. High doses of glucose can inhibit heme synthesis and are useful for the treatment of mild attacks. People who experience severe attacks, especially those with severe neurological symptoms require treatment with hematin. Pain control is best maintained with opiates. Laxatives should be taken to avoid exacerbating of constipation. Hematin is the only heme compound approved for treatment today. Heme arginase is a stable heme compound with low frequency of adverse effects. Heme requires prompt management to clinical benefits. Attacks of porphyria can cause irreversible neuronal damage. Heme therapy is initiated to prevent an episode of reaching critical stage of neuronal degeneration. Concentrations of urinary porphyrins are monitored to control the effectiveness of treatment. Acute seizures are treated with magnesium sulphate and diazepam. Lorazepam is the first choice drug for patients with porphyria. Gabapentin is used successfully in controlling seizures. It is important to control electrolyte imbalances. Hyponatremia can be corrected with an infusion of normal saline. Fluid restriction and diuretics may be necessary if the patient shows

signs of the syndrome of inappropriate secretion of ADH. Psychiatric symptoms are controlled with the use phenothiazines. This improves nausea, too. Acute hypertension is treated with suitable agents –beta blockers. In this case is administered hypertonic glucose solution, opioids, vitamins B1 and B6 and electrolyte rebalancing. Under treatment given the patient's clinical evolution is favorable without beeing neuro-psychological sequels and is releasing with the following recommendations: physiotherapy recovery, avoidance of precipitating factors of AIP and the prohibition of self-medication when symptoms appear (15).

Complications most powerful of AIP are: respiratory paralysis, respiratory failure and chronic renal failure. Complications and sequelae AIP diseases found in statistics include: seizures, proximal myopathy, neutrophilia, chloride levels low (plasma or serum), increased levels of thyroid hormone binding protein, abdominal pain, hypertension, systemic weakness, proximal muscle weakness, paralysis bulbar, sleep disturbances, papilledema, chest pain, peripheral motor neuropathy, peripheral demyelination, constipation, SIADH, acute confusional state, cranial nerve injury, postural hypotension, back pain, ileus, dysuria, high sodium levels (urine), peripheral sensory neuropathy, abnormal urine color 16)

Prognosis: AIP is extremely dangerous and can lead to death if not diagnosed and if they are given harmful drugs. The prognosis is usually good if the disease is recognized and if treatment and preventive measures are initiated before severe damage to occur to the nerves. Although symptoms usually disappear after a episode, some patients develop chronic pain. Nerve damage associated with muscle weakness may improve over a period of months or more after a severe episode. Mental symptoms may occur during attacks, but are not usually chronic.

DISCUSSION

The peculiarity of the case: patients without significant APP which in approximately 9-10 days presenting mediocre general state, accusing diffuse abdominal pain predominant in right iliac fossa, accompanied by nausea, bilious vomiting and lack of bowel transis, is presenting to the emergency room of several hospitals. The patient said no similar episodes in the past and it can not detect with certainty the precipitating factor triggering the AIP episode. After symptoms and clinical examination is initially diagnosed with urinary tract infection but the specific treatment no improves the health of the patient. Evolution is unfavorable, patients presenting acute abdominal syndrom and investigations requiring emergency hospitalization. After clinical and paraclinical evaluation is suspected the existence of acute appendicitis which is a surgical emergency, reason why is do laparoscopic intervention. Not be confirmed acute appendicitis, which why is reassess, the patient is stable in terms of vital functions. It goes on the assumption of a metabolic causes to explain the clinical state and the existence of a suspected episode of acute porphyria suggested by discoloration of urine exposed to light. Timing AIP diagnosis led to neurologic complications with presence of motor deficits. Not available hematin as a treatment of choice and therefore hypertonic glucose solution is administered to interfere with the synthesis of porphyrin precursors, which are asocieaza with vitaminoterapie, opioids and electrolyte rebalancing. Evolution is favorable without neuro-psychological sequels.

AIP is an autosomal dominant genetic disease and genetic screening is required to demonstrate porfobilinogen deaminase gene mutations that encode both the patient and the offspring as primary prophylaxis method. To avoid episodes of AIP patient must fit to follow the advice on avoiding certain medications, illicit drugs, alcohol, stress and smoking. Although 80% of AIP gene carriers are asymptomatic, in this case likely onset of symptoms following a precipitating factor. The disease is unfavorable with neurological complications, a sign of seriousness that requires special treatment with hematin not available in the hospital. Although the disease is severe with complications the clinical evolution is favorable due to given treatment.

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