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ABSTRACT

Introduction*: Acute intermittent porphyria (AIP) is the most common and the most severe form of acute hepatic porphyria.* ***Case report:*** *Patient, 39 years old, was admitted to the Emergency Department because of abdominal pain. Abdominal pain started 5 days before the admission. The diagnostic research in his hospital showed presence of a stone in the right kidney, and the patient was transported to the other Clinical Centre, where a common urine test showed: high values of delta - aminolevulinic acid and porphobilinogen. The patient was transported to our Clinical Centre.*

At the admission, abdominal pain decreased, but the patient had a hypertensive crisis with a headache, tearing eyes, swelling, anxiety.Common laboratory tests were in reference range, except creatinine, CRP, arterial blood gas analysis, urine test. The hypertensive crisis was treated by beta blockers and diuretics in maximal doses, but without a positive effect, so we decided to try with Glyceryl trinitrate intravenously. Control blood pressure was 170/100mmHg.…130/80mmHg. ***Discussion:*** *Porphyria can be a diagnostic problem, because one of the manifestations can be abdominal pain.* ***Conclusions:*** *Comorbidities can be critical in the therapy of life threating conditions.*

Keywords*: porphyria, abdominal pain, hypertensive crisis*

SAŽETAK

Uvod*: Akutna intermitentna porfirija je najcesca i najopasnija forma akutne hepaticne porfirije.* ***Prikaz slucaja****: Pacijent, star 39 godina, hospitalizovan u Urgentnom Centru zbog bola u trbuhu. Bol u trbuhu se javio 5 dana pre prijema. Bol je bio difuzan, ostar, pracen gubitkom apetita, mucninom i povracanjem. Dijagnostickim pretragama dokazano je prisustvo kamena u desnom bubregu i pacijent je transportovan u drugu bolnicu, gde je uobicajenim laboratorijskim analizama dokazano povecanje vredosti delta amnilevulinske kiseline i porfobilinogena. Pacijent je preveden u nasu ustanovu.*

Na prijemu se bol u trbuhu smanjio, ali je pacijent imao hipertrenzivnu krizu pracenu glavoboljom, suzavim ocima, preznojavanjem i anksioznoscu. Uobicajene laboratorijske analize su bile u referentnom opsegu osim kreatinina, CRP, gasnih analiza, nalaza urina. Za hipertenzivnu krizu smo koristili diuretike i beta blokatore u maksimalnim dozama, ali bez adekvatnog efekta, pa smo probali sa upotrebom Gliceril trinitrata intravenozno. Kontrolne vrednosti krvnog pritiska su bile 170/100mmHg.…130/80mmHg. ***Diskusija****: Porfirija moze biti dijagnosticki problem, jer jedna od manifestacija moze biti bol u trbuhu.* ***Zakljucak****: Komorbiditeti mogu biti od vazni u terapiji zivotno ugrozavajucih stanja.*

Ključne reči: *porfirija, bol u trbuhu, hipertenzivna kriza*

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INTRODUCTION

Acute intermittent porphyria (AIP) is the most common and the most severe form of acute hepatic porphyria. It is an autosomal dominant inborn error characterized by a decreased activity (less than 50% (1)) of porphobilinogen (PBG) deaminase (also known as hydroxymethylbilane synthase or uroporphyrinogen I synthetase), leading to increased levels of the hem precursors, namely aminolevulinic acid (ALA) and PBG (2).

It can be activated by drugs (barbiturates, sulfonamide antibiotics, anti-seizure drugs, rifampicin, metoclopramide and alcohol), hormones (in women, it may occur after ovulation and during the last part of the menstrual cycle when progesterone levels are high), dietary changes (as an effort to lose weight) (3), as well as infections, surgery, and stressful situations. Sometimes, the activating factors can not be identified (1).The risk for developing chronic renal disease and liver cancer (hepatocellular carcinoma) is increased in AIP (4).

AIP manifests after puberty, especially in women (due to hormonal influences). The symptoms usually come as discrete intermittent attacks which develop over two or more days, that are sometimes life-threatening. They are due to the effects on the visceral, peripheral, autonomic and central nervous systems (5). Abdominal pain, neurological dysfunction and psychiatric disturbances form the classic triad of AIP. Abdominal pain, which is associated with nausea, can be severe and occurs in most cases (90%) (2,6). Presentation like respiratory failure necessitates admission to the intensive care unit. Other symptoms may include (7):

- nausea
- vomiting
- constipation
- pain in the back, arms and legs
- muscle weakness (due to the effects on nerves supplying the muscles)
- urinary retention
- palpitation (due to a rapid heart rate and often accompanied by an increased blood pressure)
- confusion, hallucinations and seizures
- peripheral polyneuropathy, primarily motor with flaccid paresis of the proximal musculature, with or without autonomic involvement

Because this disease is rare and can mimic a host of other more common conditions, its presence is often not suspected (8). On the other hand, the diagnosis of AIP and other types of porphyria is sometimes made incorrectly in patients who do not have porphyria at all, particularly if laboratory tests are improperly done or misinterpreted. The finding of increased levels of ALA and PBG in urine establishes that one of the acute porphyrias is present (2), but some studies have shown that acute attacks are more reflected by plasma PBG than plasma ALA or urinary PBG and ALA (9). The avoidance of precipitating factors and the use of hem preparations and intravenous dextrose form the basis of management (6,10).

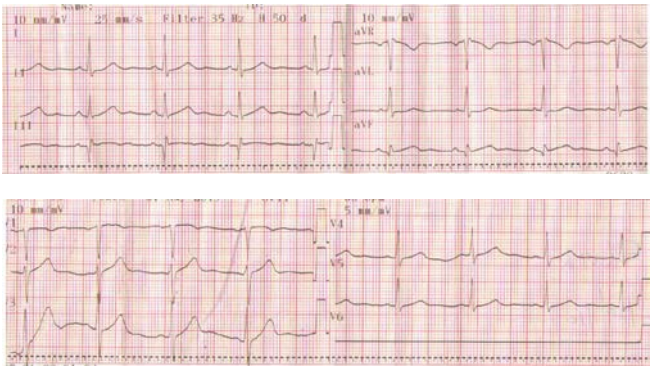
CASE REPORT

Patient, 39 years old was admitted do the Emergency Department because of abdominal pain. In previous history, he did not have any hereditary illness, he is a smoker (40 cigarettes per day). Six months earlier, he had had a surgical intervention after which he experienced similar abdominal pain.

Abdominal pain started 5 days before the admission. The pain was diffuse, sharp, followed by loss of appetite, nausea, vomiting. The diagnostic research in his hospital showed presence of a stone in the right kidney, and the patient was transported to the other Clinical Centre. The common urine test showed: higher values of delta - aminolevulinic acid and porphobilinogen. The patient was transported to our Clinical Centre.

At the admission, abdominal pain decreased in intensity, but the patient had a headache, tearing eyes, swelling, anxiety. He was afebrile, with rhythmic heart beats, referent breathing sounds, diffuse abdominal pain without a peritoneal reaction. Legs were without edema. Blood pressure was 220/120mmHg. Electrocardiogram (Figure 1): sinus rhythm, 80 beats per minute, Q wave in III. Abdominal echo was without any abnormalities. The common laboratory tests were in reference range, except creatinine, CRP, arterial blood gas analysis, urine test (Table 1.)

Figure 1. Electrocardiogram



The diagnosis was a hypertensive crisis. Acute intermittent porphyria. Abdominal pain. A surgeon observed the patient for abdominal pain, and Ranitidine was administrated. We were limited in using drugs for the hypertensive crisis. We used Furosemide and Metoprolol intravenously, in maximal doses but without a positive effect. In absence of other safe drugs for the hypertensive crisis in the patients with porphyria, we decided to try with Glyceryl trinitrate intravenously. The control value of blood pressure was 170/100mmHg ….130/80mmHg. The therapy was followed by a slow intravenous administration of glucose.

Table 1. Laboratory tests

Analysis		Value	Reference value
arterial blood gas analysis	pH	7.46	7.35-7.45
	pCO2 (kPa)	5.2	4.66-6.38
	pO2(kPa)	10.5	11.4-14.36
	Na^+ (mmol/L)	132	132
	K^+ (mmol/L)	3.8	3.4-4.5
	Ca^{2+} (mmol/L)	1.04	1.15-1.35
	Hematocrit (%)	48	35-51
	$HCO3^-$ (mmol/L)	27.7	18-23
	SpO2 (%)	96	95-98
CRP (mg/L)		21.2	0.0-5.0
Creatinine (umol/L)		114	49-106
Urine test	Leukocytes	15-20	<0
	Erythrocytes	2-3	<0
	Ketones	++	<0

Explanatory notes: CRP- C reactive protein; K^+ – potassium; Na^+ – sodium; Ca^{2+} – calcium; $HCO3^-$- bicarbonate, SpO2-oxygen saturation, pO2- arterial oxygen tension pCO2-arterial carbon dioxide tension

DISCUSSION

The word "porphyria" is derived from the Greek word *porphuros*, which means red or purple. The porphyrias are the group of rare metabolic disorders arising from the reduced activity of enzymes in the hem biosynthetic pathway. These deficiencies disrupt the normal hem production, with symptoms especially prominent when the increased hem is required. The porphyrin precursors, overproduced in response to the synthetic pathway blockages, accumulate in the body, cause diverse pathologic changes, and become the basis for diagnostic tests (11).

A specific enzyme catalyzes each step of the hem biosynthetic pathway. Eight enzymes are involved in the synthesis of hem and, except for the first enzyme (δ-aminolevulinate synthase), the low activity of any of these can disrupt the normal pathway, especially when a stimulus occurs to increase the hem production. The suboptimal activity of any one of these seven enzymes, due to either a defective gene or a toxic chemical effect, results in the overproduction and accumulation of the preceding intermediates, known as porphyrins or the porphyrin precursors. Although these intermediates have no known useful physiologic function, they act as highly reactive oxidants, and deficiencies of seven enzymes are linked to specific types of porphyria (12).

Clinical manifestations are variable. The symptoms may vary considerably in the same patient during different episodes, as well as among the patients with the same porphyria subtype. Because the clinical course can vary from acute, self-limiting attacks to attacks that result in chronic or progressive deficits, the attacks may mimic many other psychiatric or medical disorders, making the potential for a misdiagnosis great (8).

In our case, the patient had abdominal pain which was evaluated for acute abdomen. The common laboratory tests confirmed acute intermittent porphyria, but acute abdomen couldn't be excluded immediately. The administration of some drugs in the patients with porphyria can be dangerous. Unfortunately, the information for most drugs is insufficient to allow them to be classified as definitely harmful or safe.

Pantoprazole is recommended to be used with caution, as other agents in this class. H2 receptor antagonists (Ranitidine and Famotidine) are considered to be safer, even though certain studies proposed that they can be used with caution (13). We decided to use Ranitidine intravenously.

After the admission, the patient had the hypertensive crisis. Hypertension is common in patients with AIP, but the hypertensive crisis is rare. Most antihypertensive drugs are unsafe because they can precipitate attack or they are porphyrinogenic (14). Safe antihypertensive drugs are limited to beta adrenergic blockers (15). Diuretics can be used too (Furosemide, Hydrochlorthiazide). There are contradictory reports about the safety of calcium channels blockers, especially Almodipine (16). The use of Nifedipine is unsafe or it can be used with extreme caution. In some cases, using these drugs in maximal doses can precipitate attack. ACE inhibitor, such as Enalapril is unsafe because it greatly increases the porphyrin accumulation, while Captopril, Lisinopril, Losartan slightly increase. (17)

The administration of glucose and the hem therapy is the basis of treatment, but some studies have shown that

glucoseis not sufficient to achieve the clinical and biochemical remission in more serious attacks in contrast to the hem therapy (9).

In our case, after the administration of beta blockers and diuretics, blood pressure was still high. Of available drugs, Glyceryl trinitrate was alternative, as the drug whose safety has not been proved, but it can probably be used. After its administration, blood pressure was lower, and the patient didn't have any adverse effects, as well as after Ranitidine use.

Porphyria is a rare condition, and clinical trials about it are insufficient. This is one case more which justifies the use of Glyceryl trinitrate and Rantidine in patients with porphyria.

CONCLUSION

Comorbidities can be critical in the therapy of life treating conditions.

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