National Institute of Cardiology in Warsaw
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Summary of the doctoral dissertation

Assessment of structure and function of the heart and selected cardiovascular risk factors in patients with acute intermittent porphyria

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Background

Porphyrias are the group of metabolic disorders associated with impaired heme synthesis. Acute intermittent porphyria (AIP) is the most common acute hepatic porphyria in Poland. It is caused by the mutations in the gene encoding hydroxymethylbilane synthase, the third enzyme in the heme biosynthesis pathway. The clinical course of AIP can be various. About 90% of carriers of pathological variants in the HMBS gene do not present any porphyria-related symptoms throughout their lives. On the other hand, some patients suffer from recurrent exacerbations which require urgent treatment and lead to the complications in multiple organs. The most common symptoms of AIP include: abdominal pain, nausea, vomiting, paresis and mental disorders. They may be accompanied by tachycardia and elevated blood pressure. In rare cases AIP may lead to death due to respiratory muscle paralysis or cardiac arrhythmias. This applies particularly to the circumstances in which the disease was not diagnosed early enough or contraindicated drugs were used.

Scientific data published so far do not allow to clearly define changes in the cardiovascular system in people with AIP. They mainly consist of case reports and a few studies conducted on groups with a small number of patients. The following cardiac complications of acute porphyrias have been described: myocardial infarction, cardiomyopathies, takotsubo syndrome, pericardial calcifications. Foci of myocardial necrosis were observed in the autopsies. The only study assessing left ventricular systolic function revealed significantly lower ejection fraction (LVEF) in patients with AIP compared to the control group. The authors used Teichholz method, which is currently not recommended. All patients had the remission of AIP. Another article presented three cases of AIP exacerbation in whom decreased LVEF improved during treatment with heme arginate.

Some authors reported QT prolongation in AIP but data regarding this topic are limited and conflicting. The predisposition to arrhythmias in AIP has not yet been investigated with Holter ECG monitoring.

To the best of our knowledge, no studies comparing the concentrations of troponin, N-terminal pro-B-type natriuretic peptide (NT-proBNP) and left ventricular diastolic function in patients with AIP and in control groups have been conducted so far. Nor has the left ventricular systolic function been assessed with the currently recommended advanced techniques of echocardiography.

The pathophysiology of potential changes in the cardiovascular system in the course of AIP also remains unclear. There are premises that the toxicity of delta-aminolevulinic acid

(ALA), heme deficiency and/or damage to the autonomic nervous system may contribute to them. However, these hypotheses require confirmation in scientific research.

Aims

The aim of this study was to assess the structural and functional changes in the heart and to evaluate the prevalence of selected cardiovascular risk factors in patients with AIP.

Specific goals:

- assessment of cardiac morphology and function during AIP exacerbations and in the remission,
- assessment of the concentrations of myocardial injury (troponins) and heart failure (NT-proBNP) biomarkers during AIP exacerbations and in the remission,
- assessment of the prevalence of cardiac arrhythmias and electrocardiographic abnormalities (features of left ventricular hypertrophy, changes in depolarization and repolarization, including QT, QTc intervals) in patients with AIP,
- analysis of blood pressure profiles during the exacerbations and in the remission of AIP,
- assessment of selected cardiovascular risk factors, such as smoking, arterial hypertension, disorders of lipid and carbohydrate metabolism, chronic kidney disease in patients with AIP,
- assessment of the potential relations between clinical course of AIP, concentrations of heme precursors in urine and pathological changes in the cardiovascular system.

Material and methods

The study (no. 2.39/VII/18) was conducted at National Institute of Cardiology and Institute of Hematology and Transfusion Medicine in Warsaw during the period from April 2019 to March 2023. The protocol was approved by Local Bioethics Committee at National Institute of Cardiology.

It was a case-control study with follow-up of the subgroup of patients assessed during the exacerbations of AIP.

The studied group consisted of patients with overt AIP aged 18-65 (women and men), and the control group included people from the general population matched by age, sex and body mass index (BMI).

Inclusion criteria:

- acute intermittent porphyria (AIP) diagnosed by elevated concentrations of porphobilinogen (PBG) and ALA in urine and/or by genetic testing,

- at least one exacerbation of AIP requiring hospitalization in a lifetime.

Exclusion criteria: previous myocardial infarction, heart failure of established (other than porphyria) etiology, severe heart valve diseases, congenital heart defects, past or active myocarditis, pacemaker, thyrotoxicosis or hypothyroidism (unless treated adequately), chronic advanced lung diseases, no consent to participate in the study.

Procedures performed:

1. Anamnesis and physical examination
2. Laboratory tests
   a) complete blood count, concentrations of sodium, potassium, creatinine, glucose, glycated hemoglobin, lipid profile, troponin T (hsTnT), creatine kinase MB isoenzyme (CK-MB mass), NT-proBNP, C-reactive protein (hsCRP), cortisol, iron, ferritin, alanine aminotransferase (ALT) activity in serum,
   b) concentrations of metanephrine, normetanephrine, 3-methoxytyramine in plasma,
   c) concentrations of ALA and PBG in urine
3. Resting ECG examination
4. 24-hour Holter ECG monitoring
5. 24-hour blood pressure monitoring (ABPM)
   a) assessment of the average values of blood pressure during activity, at night and throughout the whole day
   b) assessment of diurnal blood pressure variability (nocturnal dipping)

6. Echocardiographic examinations performed according to the current recommendations of American Society of Echocardiography and European Association of Cardiovascular Imaging included assessment of the following parameters:

a) cardiac chambers size, wall thickness and left ventricular mass
b) systolic (global, segmental) and diastolic function of both ventricles with traditional methods, using tissue Doppler imaging and speckle tracking techniques
c) heart valves structure and function
d) pericardial effusion.

Patients assessed during the exacerbations of AIP were re-examined in the remission phase.

Results

A total of 144 people were enrolled to the study. The final analysis included 70 patients in the remission of AIP and 70 participants in the control group. The assessment in both phases of AIP was performed in 36 patients.

The mean age of the studied groups was 39.5 years (range 18 to 63 years), 80% were women. The median number of prior AIP exacerbations was 5, and the highest number was 276. In comparison to the control group patients with AIP more often reported dyspnea ($p=0.002$), arterial hypertension ($p=0.039$) and treatment with beta-blockers ($p=0.004$).

During the exacerbations of AIP a significant increase in the concentrations of NT-proBNP ($p<0.001$), hsCRP ($p=0.030$), metanephrine ($p=0.009$) and normetanephrine ($p<0.001$) in blood was observed. Conversely, sodium and potassium concentrations decreased ($p<0.001$). There were no significant differences in the values of troponin, CK-MB mass, cortisol and glomerular filtration rate (eGFR). The abnormal concentrations of NT-proBNP (> 125 pg/ml) were detected in 69.4% of patients during the exacerbations of AIP and in 35.7% of patients in the remission. In the acute phases of AIP the concentrations of NT-proBNP were correlated negatively with the concentrations of sodium and positively with the concentrations of cortisol in blood. In comparison to the control group patients with AIP had higher concentrations of NT-proBNP ($p<0.001$), troponin T ($p<0.001$), creatinine ($p<0.001$), potassium ($p=0.001$), normetanephrine ($p<0.001$), total cholesterol ($p<0.001$) and high-density lipoproteins (HDL) ($p<0.001$). The values of HDL and low-density lipoprotein (LDL) cholesterol correlated positively with the levels of PBG and ALA in urine.

During AIP exacerbations ST segment depression and/or T wave inversion and QT/QTc prolongation in ECG were more common than in the remission. Most of the changes resolved after treatment of the underlying disease. No significant differences in the ECG results were found between patients in the remission of AIP and the control group.

Holter ECG monitoring showed no influence of AIP on cardiac arrhythmias or atrioventricular conduction.

The acute phase of AIP was associated with a significant increase in the mean values of blood pressure: systolic (SBP) by 11.7 mmHg ($p<0.001$), diastolic (DBP) by 7 mmHg ($p<0.001$). They reached the threshold for the diagnosis of hypertension in 75% of patients. The correlations between changes in blood pressure and concentrations of normetanephrine in plasma were revealed. With the resolution of symptoms blood pressure decreased but it was significantly higher than in the control group ($p=0.009$ for SBP, $p=0.009$ for DBP). Chronic hypertension was diagnosed in 42 (60%) patients with AIP and in 23 (32.9%) participants in the control group. Independent factors associated with arterial hypertension were the increase in BMI and the history of paresis. The studied populations also differed in the 24-hour blood pressure profiles, mainly in a lower percentage of normal reduction of blood pressure during sleep ("dippers") among patients with AIP ($p<0.001$).

Echocardiography showed an increase in left ventricular mass ($p=0.003$) and relative wall thickness ($p=0.046$) in some patients hospitalized due to AIP symptoms. Sodium concentrations correlated negatively with these changes. Left ventricular systolic function expressed as LVEF and mitral annular systolic velocity in TDI was slightly higher during exacerbations. There were no significant differences in other parameters of left ventricular systolic or diastolic function. Patients with AIP had higher left ventricular mass indices and relative wall thickness when compared with the control group ($p<0.001$). Left ventricular ejection fraction, global longitudinal strain and mitral annular plane systolic excursion were lower in patients with AIP ($p<0.001$). Differences also concerned selected parameters of left ventricular diastolic function (E', E/e' ratio, flow propagation velocity, isovolumic relaxation time, left atrial volume index).

Based on the clinical symptoms and echocardiography 6 out of 70 (8.6%) patients were diagnosed with heart failure with preserved LVEF (HFpEF). Two patients had heart failure with mildly reduced LVEF (HFmrEF).

Conclusions

1. During acute intermittent porphyria (AIP) exacerbations there is an increase in the concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and catecholamines in blood. The concentrations of sodium and potassium decrease. In most patients the levels of markers of myocardial injury, such as troponin T and CK-MB mass, do not differ significantly between episodes of exacerbations and the remission of AIP.
2. Despite the remission phase patients with AIP have higher concentrations of troponin T and NT-proBNP than the population without this disease with comparable values of BMI and demographic characteristics.
3. During AIP exacerbations some patients experience an increase in left ventricular mass and wall thickness. In most cases the cardiac function do not change significantly. If some abnormalities occur, they may be dynamic and improve with treatment. Heart failure biomarkers (NT-proBNP) seem to be the promising tools for monitoring of patient's condition.
4. In patients with AIP left ventricular hypertrophy is more common than in people of the same sex, with similar age and BMI and they have worse systolic and diastolic function of the left ventricle.
5. Cardiac arrhythmias are rare in AIP. The abnormalities in myocardial repolarization, including prolongation of QT/QTc intervals, may occur during the exacerbations of this disease.
6. In comparison to the population with similar characteristics (age, sex, BMI) patients with AIP have higher systolic and diastolic blood pressure, and its daily profile is more often disturbed. During exacerbations of AIP blood pressure increases, probably due to the release of catecholamines.
7. Patients with AIP are more likely to have some cardiovascular risk factors, such as hypertension and renal dysfunction, whereas the differences in the concentrations of total cholesterol result mainly from the higher levels of high density lipoproteins (HDL).
8. The clinical course of AIP and the values of biochemical markers of its activity are related to some changes in the cardiovascular system.

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