Renal Tubulo-Interstitial Impairment in Acute Intermittent Porphyria and Variegate Porphyria

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Introduction

Porphyrias form a group of hereditary metabolic defects of haem biosynthesis, which are the manifestation of overproduction and accumulation of haem precursors – porphyrins. Acute intermittent porphyria is severe and the most often occured porphyria. Genetic defect affects gene for deaminase of porphobilinogen, which is situated on chromosome 11. Under the physiological conditions deamination of porphobilinogen is encoded by two structural genes. In acute intermittent porphyria one gene is defective. Only 50% of needed enzyme is produced, which is necessary for the deamination of porphobilinogen and for the formation of tetrapyrole. The final product of this metabolic pathway is haem (1, 2). Clinical attack of acute intermittent porphyria is occuring after the stimulation of δ-aminolevulinic acid and much more porphobilinogen is formed and accumulated in the body (3, 4).

Causes inducing attack of acute intermittent porphyria are: infection of upper respiratory tract, stress, starvation, use of various drugs (estrogenes, progesterone, contraceptive drugs, barbiturates, fibrates, statins, antifugal drugs, propaphenone, amiodarone, lidocaine, nifedipine, α-methyldopa, hydrolasine, ACE-inhibitors, sulfonamides, meprobamate, glutethimide, carbamazepine, allopurinol and others), (5).

Clinical signs of acute intermittent porphyria are: abdominal pain, hypertension, tachycardia, sweating, damage of motoric and sensitive nerves, paresis and plegia, seazures, muscle cramps, impairment of sensitivity, affection of autonomic nerve system, restlesness, insomnia and dark urine without haematuria. In addition characteristic signs of variegate porphyria are: increased skin fragility, photosensitivity, blisters, hyper-pigmentation, atrophic maculae on skin areas exposed to the sun (5).

Laboratory investigations of acute intermittent porphyria for diagnosis and during acute attack include the following parameters: urinary porphobilinogen, δ-aminolevulinic acid, uroporphyrin, coproporphyrin, serum potassium, sodium and magnesium (2).

Renal damage in acute intermittent porphyria is relatively rare except hypertension (6). Renal functional changes in acute intermittent porphyria show for the tubulo-interstitial nephropathy (7-10). Some of the patients suffering from chronic renal failure must be dialyzed (9, 10).

In the past the treatment of acute intermittent porphyria and variegate porphyria was often unsuccessful and many patients died during the acute attack (11). In the present time the therapeutic method of choice of these porphyrias is haem-arginate (Normosang). Daily dose of Normosang is 2-5 mg/kg and duration of the treatment is 4-5 days (5). That treatment influences the clinical signs of acute intermittent porphyrias and corrects the elevated urinary excretion of haem precursors (δ-aminolevulinic acid and porphobilinogen). Recovery from neurological disorders remains much slower. Additional therapy of patients suffering from acute intermittent porphyria is infusion of glucose and vitamins of B group (12, 13).

Patients and Methods

During 15 years 7 patients suffering from acute intermittent porphyria and 1 patient suffering from variegate porphyria were investigated. Among them were 6 women and 2 men, mean age was 40 ± 5 years. In these patients were repeatedly investigated urinary porphobilinogen using qualitative Watson-Schwartz test – modification of Ehrlich reaction (3), urinary δ-aminolevulinic acid and urinary coproporphyrin using spectrophotometric methods (14, 15). In all patients examination of kidney function in clinical remision of the disease was performed.

Results

The most important characteristic clinical signs of acute intermittent porphyria and variegate porphyria were shown in Table 1. Urinary porphobilinogen was present in all patients during acute attack (++++) and also in clinical remission (++). Mean values of urinary δ-aminolevulinic acid was 26.1±3.5 mg/L and urinary coproporphyrin was 0.180±0.02 mg/L. Results of examination of kidney function in both types of porphyria are shown in Table 2. Renal concentration ability was decreased in 6 patients and impairment of tubular excretory phase in isotopic renography was repeatedly observed in 6 patients.

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Table 1. Examination of kidney function in acute intermittent porphyria (IP), and variegate porphyria (VP)

Number of patients	Age (years)	Sex F	Sex M	First signs of the disease (year)	Clinical signs: Abdominal pain	Hypertension	Restlesness, seizure, neuropathy	Dark urine	Blister
IP 7	40 ± 5	6	1	29 ± 6	7	6	6	6	-
VP 1	52	-	1	35	1	1	1	1	1

F - female, M- male

Table 2. Examination of kidney function in acute intermittent porphyria (IP), and variegate porphyria (VP)

Number of patients	Protein-uria (g/24hr)	β_2-μG in urine (mg/L)	β-NAG in urine (μkat/L)	GFR (ml/s)	Leucocyt-uria (mil/24hr)	Bacteri-uria	Investigation of renal CA	Isotopic renography
IP 7	0.164 ± 0.02	0.087 ± 0.01	0.050 ± 0.01	1.49 ± 0.21	0 - 43	negative--10^3/ml	hyposthenuria (n=5) normal range (n=2)	impairment of tubular EP (n=5) normal range (n=2)
VP 1	0.160	0.120	0.095	1.40	2	negative	hyposthenuria	impairment of tubular EP

β_2-μG – β_2-microglobulin: normal range in urine < 0.370 mg/L
β-NAG – N-acetyl-β-D-glucosaminidase: normal range in urine < 0.110 μkat/L
CA – concentration ability, EP – excretory phase

Five patients during acute porphyric attacks were repeatedly treated by i.v. haem-arginate (Normosang, Leiras). In addition all patients were treated by phenothiazines, i.v. infusion of glucose, and by oral vitamins B_1 and B_6. All investigated patients survived and they are in a very good clinical condition.

Discussion

Acute intermittent porphyria is a very rare disease. The diagnosis of that disease is relatively difficult according to clinical signs when the acute abdominal pain is incorrectly interpreted (2, 5, 11). Presence of porphobilinogen in urine lead to the neurological and other investigation mainly to the cerebral and peripheral nervous systems (4, 5). Diagnosis of variegate porphyria in our patient was very early because the patient had the skin signs of the disease (blisters, hyper-pigmentation and the presence of atrophic maculae on skin areas exposed to the sun).

Recent therapy of acute intermittent porphyria and variegate porphyria during the acute attack by haem-arginate prevents of severe or mortal celebral complications. Neurological symptoms disappeared in our patient slowly despite of this therapy. In 4 patients lasted for a very long time (quadruparesis, paraparesis, polyneuropathy, etc.). In our patients during acute pophyric attack was administered infusion of haem-arginate in 5% glucose very early in outpatient department or during short hospitalization (2, 11, 12). In addition pheno-thiazines and vitamins B_1 and B_6 were administered in clinical remission.

Impairment of kidney function of both types of porphyria is known only in the recent years. Progression of renal tubulo-interstitial nephropathy is relatively slow despite of the fact that several patients were in chronic renal failure and underwent renal replacement therapy and renal transplantation (7-10). Renal function abnormalities in our 6 patients showed for chronic tubulo-interstitial nephropathy with hypertension but without clinical and laboratory progression.

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