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Hypertension and proteinuria in pregnancy: Preeclampsia, acute intermittent porphyria or both?

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ABSTRACT

We report a case of early onset recurrent preeclampsia in a patient with positive family history of preeclampsia and a newly discovered acute intermittent porphyria. A 28 years old patient was admitted to our Clinic, due to early onset of preeclampsia in her third pregnancy. She had refractory hypertension with tachycardia, facial flush, anxiety and difficulty in breathing. During hospitalization, she reported occurrence of opalescent orange to reddish morning urine, which turned dark after a while. The dipstick test revealed positive urobilinogen in the urine. The same sample of urine was tested for porphobilinogens in the urine (by the use of Ehrlich's reagent) which were found positive and also porphyrins which were found negative; therefore, her medication was switched to a beta blocker. She decided to terminate pregnancy and this was done in the next few days by the use of anesthetics that are approved for acute intermittent porphyria. At her check up one month after delivery, her blood pressure was stabilized and the coproporphyrine, porphobilinogen and porphyrins from single void urine were all negative. In the check up 2 months after delivery, proteinuria of 0.5 g/day was still present; however, it reached to normal range (1g/day) after six months. To our knowledge, this is the first case reported in the literature where superimposed preeclampsia occurs in a patient with newly discovered acute intermittent porphyria.

Implication for health policy/practice/research/medical education:
Preeclapmsia, as one of the main complications during pregnancy is discussed from a very rare angle. Reading this case is recommended for gynecologists, nephrologists and urologists.

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Background

Preeclampsia is defined as a substantial increase in blood pressure and occurence of proteinuria (> 0.3 g/24 hours) after 32nd gestation week. Very early onset of preeclampsia is defined as a change occurring before or during 20th gestation week. Very early onset of preeclampsia has been described as a consequence of antiphospholipid syndrome (1), partial mole (2), tryploidy (3) and only in one case, as an entity without known etiological or predisposing factor (4). We report a case of an early onset of recurrent preeclampsia in a patient with a positive family history of preeclampsia and a newly discovered acute intermittent porphyria.

Case presentation

A patient was admitted to the Department of Nephrology, Skopje, Macedonia, in December 2007, due to early onset of preeclampsia. She was 28 years old, in the 20th gestation week of her third pregnancy. Her first pregnancy, 6 years ago, ended by intrauterine death of the fetus. It was regularly controlled and she had supposedly normal blood pressure, but the histopathology of the placenta showed infarctions and calcifications. In the second pregnancy, her blood pressure rose to 180/130 mm Hg, during the 37th gestation week. She delivered by vaginal route; birth weight of the newborn was 2800 g. After delivery, her blood pressure was 150/100 mm Hg. antiphospholipid antibodies were negative. After the second pregnancy she was suffering from mild depression and anxiety. In her current pregnancy, blood pressure was normal until 18th gestation week, after which it rose to 150/100 mm Hg and therapy with methyldopa 500 mg/day was commenced. She was referred to the Clinic of Nephrolo-

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gy and the dose of Methyldopa was gradually increased up to 1500 mg/day without satisfactory control of blood pressure. The 24-hour blood pressure monitoring revealed average daily blood pressure of 142/104 mm Hg, night blood pressure 159/113 mm Hg and lab results showed high serum creatinine (241 micromols/ l) and a pathologic lipid profile. The patient had a positive family history of a mother and a sister with hypertension during pregnancy. Her physical exam revealed systolic murmur 2/6 with a maximum over the aortic valve. Office blood pressure at admission was 170/110 mm Hg and her BMI was 22.7. During hospitalization, ultrasound showed normal morphology of the kidneys. Doppler ultrasound of the uterine artery was pathological in 21st gestation week (resistance index - RI 0.78). Fetal growth parameters were adequate for 21st gestation week. The second 24-hour blood pressure monitoring revealed average daily blood pressure of 148/ 107 mm Hg. prothrombin, caolin-cefalin and thrombin time were within normal range. proteinuria of 0.5 g/ l (1 g/24 hours) emerged. Office blood pressure rose to 155/ 120 mm Hg, and nifedipine slow release 20 mg/day was added to the therapy. After four days, her blood pressure rose to 210/150 mm Hg, with tachycardia > 120 bpm, facial flush, anxiety and difficulty in breathing. The patient did not complain of any pain. Blood pressure was controlled to the level of 170/100 mm Hg by an increased dose of the same medications. Next morning, the patient reported occurrence of opalescent orange to reddish morning urine, which turned dark after a while. The dipstick test revealed positive urobilinogen in the urine. The same sample of urine was tested for porphobilinogens in the urine (by the use of Ehrlich's reagent) (5) which were positive and porphyrins in the urine, which were negative. She was diagnosed with acute intermittent porphyria and her medication was switched to a beta blocker (atenolol 100 mg/day) and an alpha blocker (doxazosin 1, 5 mg/day) after informing the patient for the risks for the fetus and obtaining the written consent from her. Diet high in carbohydrates was started.In the next days, her blood pressure was 120/90 mm Hg. Nevertheless, due to developments in her prior pregnancies and persistent changes in the Doppler of the uterine artery, she was informed that, because of the early onset of preeclampsia, it would be difficult to maintain control over blood pressure in the coming weeks. She decided to terminate pregnancy and this was done in the next few days by the use of anesthetics that are approved for acute intermittent porphyries. At her check up one month after delivery, her blood pressure was stabilized and the coproporphyrine, porhobilinogen and porphyrins from single void urine were all negative. Although proteinuria of 0.5 g/day was still present 2 months after delivery, it reached normal range (1 g/day) in six months follow up.

Discussion

Acute intermittent porphyria in pregnancy is rare and symptoms occur in a small percentage of patients. A study from Finland of 176 pregnancies in women with acute porphyria found symptoms indicative of porphyria in only 14 pregnancies (8%) (6). Acute intermittent porphyria is due to a combination of a genetic enzyme defect and acquired causes and approximately 80% of carriers of a gene mutation for acute intermittent porphyria remain asymptomatic, and others may have only one or a few acute attacks throughout life. Levels of ALA, porphobilinogen, and porphyrins in urine, serum, and faeces are normal in most asymptomatic carriers of autosomal dominant acute porphyrias (7). Yet, chronic complications may include hypertension and renal failure (8). Chronic hypertension in our patient, although not readily recognized, may be due to AIP discovered during her hospitalization. The patient denied other symptoms, but there was a positive history of depression and anxiety after her second pregnancy. The attack during her current pregnancy was most probably due to medications: the combination of calcium channel blockers and methyldopa, both used to control severe hypertension, and both well known to precipitate attacks of acute intermittent porphyria. The unusual features of the attack were due to neurovisceral symptoms which suggested increased catecholamine production and stimulation of the nervous system. The stimulation of the nervous system was proven in several studies, by an increased urinary excretion of catecholamines (9-11). Tachycardia has been observed in 64-85% of patients and hypertension in 36- 55% of the patients, and it may persist between attacks (10).The recurrence risk for preeclampsia in a subsequent pregnancy ranges from 7.5% to 65%, depending on sample size and severity of the disorder in the first pregnancy (12). So called 'placental preeclampsia', arising from poor placentation in the beginning of the pregnancy with a progressively hypoxic placenta, has high recurrence risk and a familiar componenent; if it progresses to maternal preclampsia it may be due to the interaction between a normal placenta and microvascular disease; nevertheless, there are mixed forms (13). Our patient had a mixed form of an early onset of preeclampsia, superimposed on chronic hypertension. Preeclampsia recurred in all of her pregnancies. Her family history for preeclampsia was strongly positive, with her mother and sister having the same condition during their pregnancies. Early changes in the doppler of the uterine artery, despite absence of intrauterine growth retardation, further confirmed the diagnosis of superimposed preeclampsia. This is the first case reported in the literature where superimposed preeclampsia occurs in a patient with newly discovered acute intermittent porphyria.

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Conflict of interest

None declared.

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