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CASE REPORT

Gestational diabetes insipidus

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Abstract

Gestational diabetes insipidus is a very rare complication. However, undiagnosed and untreated may lead to serious complications in both mother and fetus. In this study, a case of 34-year-old female patient with diabetes insipidus associated with pregnancy was reported. We discussed process of diagnosis and treatment with particular emphasis on the monitoring of water-electrolyte imbalance during labor.

INTRODUCTION

In physiological pregnancy, especially in the second trimester, many changes in the water-electrolyte balance occur. They are related primarily to changes in renal function, which persist to the end of pregnancy and quite rapidly retreat after labor. During pregnancy, one can observe reduced blood osmolality to 270 mOsm/kg, decrease in concentration of sodium in blood which rarely exceeds 140 mEq/l. Increase in urinary sodium excretion due to progesterone activity, which inhibits renal reabsorption, is observed. Significantly increased activity of the renin-angiotensin-aldosterone system prevents hyponatremia. However, neither pressure increase nor hyperkalemia are reported, which is a result of inhibiting activity of progesterone on mineralocorticoid receptors in kidneys. During pregnancy, progressively increased secretion of angiotensin is reported (Aleksandrov *et al.* 2010; Ananthakrishnan 2009; Barbery *et al.* 2011; Burrow *et al.* 1981; Dürr 1987; Fjellestad-Paulsen *et al.* 1993; Foyouzi *et al.* 2004). At the end of pregnancy, it is about 20-fold higher as compared to the concentration reached during menstrual cycle. Angiotensin exerts diuretic effect with subsequent impairment of expression of aquaporin 1 (Valdes *et al.* 2001).

Vasopressin (antidiuretic hormone – ADH) is mainly responsible for urine concentration.

It is a neurohormone secreted by neurons located in the supraoptic and paraventricular nucleus of the hypothalamus (Foyouzi *et al.* 2004). Inadequate secretion of vasopressin, its excessive catabolism or receptors' resistance cause diabetes insipidus (Lindheimer & Davison 1995).

Gestational diabetes insipidus is a very rare complication of pregnancy. According to different authors, its incidence is estimated to be between 1/300 000 and 1/20 000 pregnancies (Ananthakrishnan 2009; Dürr 1987; Ranjbar *et al.* 2010). The disease is caused by excessive activity of vasopressinase, an enzyme which degrades arginine-vasopressin (AVP). It should be noted that vasopressinase does not degrade synthetic form of vasopressin, 1-deamino-8-vasopressin (dDAVP), allowing for its use in treatment (Fjellestad-Paulsen *et al.* 1993; Kita *et al.* 2012). Gestational diabetes insipidus may develop in the course of hepatic steatosis and hypertension. The charac-

teristic symptoms of diabetes insipidus include excretion of large amounts of urine with a low specific weight (polyuria) and excessive thirst (polydypsia), which are particularly severe in the third trimester of pregnancy. In laboratory tests, hyponatremia is reported. Although water-electrolyte imbalance regress after labor, undiagnosed disease may lead to serious complications in mother and fetus (Kalelioglu *et al.* 2007).

The objective of the study is to draw attention to the problems associated with water electrolyte imbalance in pregnant women. The problems relate to diagnosis, treatment during pregnancy and labor, as well as to monitoring of the treatment and complications of pregnancy.

CASE STUDY

A 34-year-old female patient (IJ) in the 23rd week of pregnancy, complained of dry mouth and thirst. This was her third pregnancy, the two previous proceeded normally and ended up with physiological labors of children of birth weight 3 960 g and 3 850 g. The patient had a history of psoriasis, which required no treatment. In this period of pregnancy, the patient drank approximately 3–4 liters of fluids per day, the volume of urine corresponded to fluid intake. Specific weight of the urine was 1.014 g/ml (reference values from 1010 to 1030 g/l). Blood glucose concentration in 75 g oral glucose tolerance test was within normal range: 79 mg/dl before and 126 mg/dl 2 hours after administration of glucose. The patient was consulted by a dentist, who excluded the pathology of the salivary glands (urolithiasis, hyperplasia). During ultrasound examination, normal volume of amniotic fluid and fetus weight at the level of 50th percentile, were reported. Over the next four weeks, the symptoms of polydipsia and polyuria underwent intensification. The patient drank a lot and excreted 4 to 7 liters of urine per day. She urinated and drank also at night and for this reason, she did not sleep well and was constantly tired. The specific weight of urine was significantly decreased, subsequent values remained at the level between 1.003 g/ml and 1.005 g/ml. The symptoms were so burdensome, that the patient was consulted with several doctors, who recommended the fluid balance evaluation (volume of urine during the day corresponded to the amount of fluids drunk) and the measurement of the concentration of sodium and potassium (within normal ranges). In the 35th week of pregnancy, with the diagnosis of diabetes insipidus of unexplained etiology, the patient was admitted to the Department of Endorinology in order to perform diagnostic tests. During hospitalization, polyuria to 6 050 ml per day was confirmed. Specific weight of urine was 1.000–1.003 g/ml, concentration of sodium and potassium in serum was 136 mmol/l and 3.91 mmol/l, respectively. Hyperglycemia, hypercalcemia, hypercalciuria as well as liver and kidney failure, urinary tract infection, were excluded as a cause of polyuria. Urinary sodium excretion was significantly reduced (<20.0 mmol/l) along with excretion of potassium within normal limits (76.57 mmol/24h). Moreover, very low urine osmolality of 102 mOsm/kg (normal: 700–1200), along with high serum osmolality during pregnancy estimated at 287 mOsm/kg (normal: 270–295) were reported. The results of hormonal tests (TSH – 1.549 μIU.ml, fT4 – 9.51 pmol/l, LH – 5.44 IU/l, FSH <0.10 IU/l, PRL – 170 ng/ml, cortisol at 8:00 – 30 μg/dl, DHEA-S – 117.6 μg/dl) confirmed normal function of the anterior pituitary gland. In MR of the *sella turcica*, which was performed without administration of contrast agents due to pregnancy, no abnormalities were detected.

A valid signal from the posterior pituitary gland and symmetric enlargement of adenohypophysis, associated with hyperplasia of lactotropic cells physiological for this period of pregnancy, were observed (Figure 1). Oral administration of desmopressin (Minirin, Ferring GmbH) at a dose of 2 × 60 mg caused a significant reduction in urine volume of up to 3 000 ml per day, increase in its specific weigh to 1.009 g/ml and osmolality to 277 mOsm/kg and a decrease in osmolality of serum to 279 mOsm/kg. Based on the clinical characteristics, laboratory test results, as well as the response to administration of desmopressin, diabetes insipidus most likely associated with pregnancy was diagnosed. Minirin at a dose of 60 μg 2 times per day was recommended. The patient was under the care of endocrine clinic and counseling for pregnant women. Immediately after administration of desmopressin an increase in blood pressure to 150/90–160/90 mmHg persisting for several days was reported. The patient was referred to the department of pathology of pregnancy. During hospitalization, the pressure normalized without administration of antihypertensive drugs. The patient drank approximately 3–4 liters of fluid per day, and excreted corresponding volumes of urine. The specific weight of urine was approximately 1.009 g/ml and such values persisted to the end of pregnancy. The clinical, cardiotocographic and ultrasound examinations reported normal development of pregnancy and fetal well-being. The volume of amniotic fluid was normal. During the 38th week of pregnancy, one decided to induce labor due to the large weight of fetus estimated at 4 200 g by ultrasound, and the limit values of blood pressure. Due to difficulties in estimation of fluid intake need (increased physical activity, hot day), it was established, that during labor the patient will drink without any restrictions and no intravenous fluids will be administered. Throughout the whole period of labor, one hour fluid balance was conducted and levels of sodium and potassium in blood were controlled. When the sodium concentration decreased to 129 nmol/l the patient was asked to reduce fluid intake. The subsequent sodium concentration was 135 nmol/l. The course of labor was normal, after 3 hours and 30 minutes she gave birth to alive daughter 4 190 g weight, 55 cm length, in general good condition

(10 points in Apgar scoring). The weight of placenta was 630 g. After labor, the treatment with Minirin was discontinued. Polydipsia and polyuria began to subside spontaneously. Fluid balance in the first day after labor: liquids taken 3600 ml/urine volume 3700/ml. The patient was discharged home on the fourth day after labor in general good condition. Fluid balance: taken 3500 ml/ excreted 3000 ml, sodium concentration – 142 mmol/l, potassium – 4.2 mmol/l, specific gravity of urine 1.003 g/ml, plasma osmolality 290 mOsm/kg H2O (normal: 270–295 mOsm/kg H2O), urine osmolality 164.0 mOsm/kg H2O (normal: 250–1300 mOsm/kg H2O). After labor, the patient suffered from lactation disorders, which were not observed after the two previous labors. During the first eight weeks, the child was fed naturally and artificially. The symptoms of polyuria and polydipsia subsided gradually. Normal results of additional tests were observed after three months: urinary specific weight and urine osmolality were 1.012 g/ml and 380 mOsm/kg H2O, respectively.

DISCUSSION

Diabetes insipidus associated with pregnancy is a very rare complication of pregnancy but untreated leads to serious and severe complications in mother (hypernatremia, eclampsia, liver failure, intravascular coagulation) and fetus (polyhydramnios, oligohydramnios, hypoxia) (Weinberg *et al.* 2011; Wiser *et al.* 2011). Such rare occurrence of diabetes insipidus and very few literature positions cause large diagnostic problems (de Pinho *et al.* 2010). In the above-described female patient, first symptoms appeared during the 26th week of pregnancy. Initially, it was difficult to recognize diabetes insipidus. From a characteristic triad of symptoms, increased thirst was characteristic. The patient drank up to 5 liters per day, and the specific gravity of urine remained constant at the lower limits of the reference values. Symptoms gradually worsened, but despite consultations with several doctors, diagnosis was established in the 35th week of pregnancy. The existence of many common symptoms characteristic for normal pregnancy and endocrine disorders greatly complicates the diagnosis of hormonal imbalance during this period. Frequent urination associated with the oppression of the uterus on the bladder, may obscure the excretion of large amounts of urine. As a result of increased fluid loss, reduced sodium reabsorption in the kidneys and insufficient fluid intake, increase of the osmotic pressure of blood and stimulation of the thirst center are reported, which is manifested clinically by excessive thirst. At the same time, excessive thirst and excretion of large amounts of urine may also result from impairment of renal or hormonal regulation of water-electrolyte balance. Diagnosis of diabetes insipidus and determination of its type during pregnancy may be difficult due to inability to conduct dehydration test, which is the standard in diagnosis. Reduced water supply can cause dehydration, hemoconcentration of pregnant women, leading to uterine-placental dysfunction, dangerous for both mother and fetus. In the discussed patient, besides characteristic clinical symptoms, the diagnosis of diabetes insipidus was supported by lack of hypokalemia, hypercalcemia and glycosuria as well as plasma osmolality above 285 mOsm/kg. Decreased ability to concentrate urine may be a result of renal tubular damage occurring in the course of infection. In the case described, no clinical signs of inflammation in the urinary tract was reported, additionally both urinalysis and urine culture did not indicate that diabetes insipidus was caused by infection. Renal failure was excluded based on the results of creatinine and urea, and liver failure was excluded based on the results of activity of transaminases. Increased activity of vasopressinases in women with hepatic steatosis, hepatitis and preeclampsia is explained by the decrease of their metabolism in the liver (Barbera *et al.* 2011). Production of vasopressinases is proportional to the weight of placenta. Diabetes insipidus associated with pregnancy was described in a patient with twin pregnancy (Ranjbar *et al.* 2010). In our patient, the weight of placenta was 630 g and perhaps it could be an important risk factor in the development of diabetes insipidus during pregnancy.

Diabetes insipidus may be at the first sign of the hypothalamus or pituitary gland damage. Hence, it is essential to evaluate the hypothalamus and pituitary gland using magnetic resonance, and if the symptoms do not resolve after labor, to conduct dehydration test (Katase *et al.* 2006). In our patient, clinical and biochemical symptoms of diabetes insipidus in the presence of normal images of the hypothalamic-pituitary

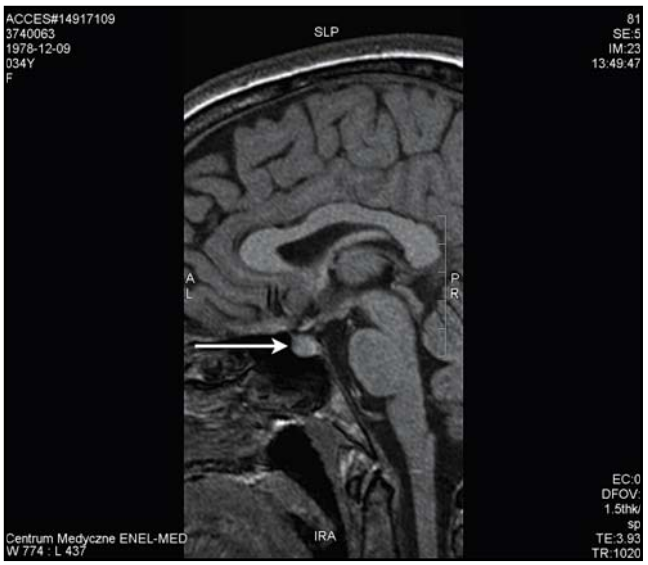

Fig. 1. The MR image in the sagital plane: the normal structure of the hypothalamus and pituitary gland, anterior lobe spherical (physiological enhancements related to pregnancy is marked with an arrow), posterior lobe of the normal signal (the optimal visible in the axial projection).

area allowed for the diagnosis of diabetes insipidus associated with pregnancy. The diagnosis was confirmed after the labor by the relief of symptoms (Gambito *et al.* 2012). A special care in women with diabetes insipidus requires the labor period due to reduction of fluid intake and an increased risk of electrolyte and hemodynamic abnormalities. In the literature, no reports on the conduction of labor are available. From our experience, the patient may be allowed to drink any amount of water, however heart rate, pressure, fluid balance and electrolyte concentration should be monitored very carefully. The tests should be performed at hourly intervals and, supportive treatment should be implemented, if necessary – in the described case, when the level of sodium decreased, limits of drinking were recommended. Effective treatment of diabetes insipidus associated with pregnancy is the administration of desmopressin (dDAVP), which is not degraded by placental enzymes and maintains its effect in blood for approximately 12 hours. The treatment should be initiated immediately after the diagnosis to avoid many serious complications (Aleksandrov *et al.* 2009; Maciejewski *et al.*. 2011). Desmopressin has no effect on uterine contractions and does not induce preterm labor (Robinson 1976), moreover administered in therapeutic concentrations does not pass through placenta (Ray *et al.* 2004) and is not excreted into breast milk (Burrow *et al.* 1981).

CONCLUSIONS

The occurrence of polydipsia and excretion of urine of low specific weight indicates the possible occurrence of diabetes insipidus. In this case, one should perform tests evaluating the functions of the kidneys, liver, water-electrolyte and carbohydrate balance and MR of the sella turcica. Diagnosis of diabetes insipidus associated with pregnancy requires the initiation of desmopressin administration, which is a safe drug during both pregnancy and breastfeeding.

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