Transient Diabetes Insipidus of Pregnancy and its Relationship to Preeclamptic Toxemia

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Polyuria and polydipsia are an infrequent occurrence during pregnancy. The physiological osmoregulatory adaptations of pregnancy include decreased thresholds for both thirst and arginine vasopressin secretion and an increased metabolic clearance rate of AVP. The combined effects of these changes may serve to unmask subclinical diabetes insipidus, either central or nephrogenic. The exarcerbation of diabetes insipidus during pregnancy may result from both increased vasopressinase activity and a diminished renal responsiveness to AVP.

The association of a transient form of diabetes insipidus with preeclampsia is a rare phenomenon. When described, it usually has been in the context of coexistent acute fatty liver of pregnancy or liver function abnormality [1,2]. In this setting, AVP resistance has been mainly attributed to excess vasopressinase due to decreased hepatic catabolism of the enzyme. Possibly, however, diabetes insipidus may be part of the spectrum of preeclampsia.

In this report we present a patient who developed transient diabetes insipidus during pregnancy. The relationship of this entity to preeclampsia is discussed.

Patient Description

A 29 year old primigravid woman was admitted in the 24th week of pregnancy with extreme elevation of blood pressure (up to 200/130 mmHg) and polyuria. Her past medical history was unremarkable. Blood pressure readings on routine antenatal care up to the point of admission were 110/70 mmHg. On the day of admission, the patient complained of a severe headache and increased thirst and had noticed a large increase in urinary output. On examination, reflexes were judged to be normal and uterine size corresponded to the period of gestation (confirmed by ultrasound). Fundoscopy was normal. A dipstick urine test was negative for protein. Laboratory data were as follows: hemoglobin 11.5 g/dl, white blood cells 15,900/µl, sodium 135 mEq/L, potassium 3.5 mEq/L, glucose 96 mg/dl, urea 12 mg/dl, creatinine 0.7 mg/dl, uric acid 4.0 mg/dl, albumin 2.9 g/dl, aspartate aminotransferase 25 IU/L and alanine aminotransferase 15 IU/L. Urinary output was 7 L/day with a urine osmolality of 190 mOsm/kg. Following an overnight water deprivation test, Uosm increased to 246 mOsm/kg and after intranasal desmopressin (1-desamino-8-D-arginine vasopressin) to 460 mOsm/kg.

Computed tomography of the brain showed normal appearance. A psychiatric evaluation revealed no signs of compulsive obsessive behavior. Intravenous hydrallazine and magnesium were administered. Blood pressure, however, proved difficult to control with values ranging around 160/100 mmHg. On the fourth day after admission, serum uric acid increased to 6.2 mg/dl, AST was 35 IU/L and lactate dehydrogenase 577 IU/L. Proteinuria was 720 mg/day. Since these laboratory parameters were compatible with preeclamptic toxemia and uncontrolled hypertension, it was decided to perform a cesarean section. A 600 g infant was delivered, and Apgar score at 1 and 10 minutes was 7 and 9 respectively. Postoperatively, blood pressure was controlled with atenolol and sustained-release nifedipine. Urinary output for several days postpartum was around 4 L/day and gradually decreased to 1.5 L/day 2 weeks after delivery, without DDAVP treatment. A random Uosm at this time was 506 mOsm/kg.

Comment

Normal gestation is characterized by a decrease in body tonicity to a nadir of plasma osmolality; approximately 10 mosm/kg below non-pregnant levels early in pregnancy. This physiological adaptation is brought about by decreased osmotic thresholds to both thirst and the release of AVP. As a result, water intake is stimulated and due to the non-suppression of AVP at the usual level of body tonicity, the ingested water is retained. Pregnancy is therefore typified by increased intravascular volume. However, volume-sensing AVP release mechanisms adjust as pregnancy progresses so that each new volume status is sensed as normal. In parallel, the metabolic clearance of AVP increases due to the production of vasopressinase (cystine aminopeptidase) by the placenta. DDAVP, an AVP analogue, is resistant to the action of vasopressinase [3].

Our patient presented towards the end of the second trimester of pregnancy with markedly elevated blood pressure, polydipsia and polyuria. Hypertension is the *sina qua non* of preeclamptic toxemia. Proteinuria may be absent in up to 20% of cases. Within the next 4 days after admission, other classical parameters of preeclamptic toxemia appeared – namely,

AVP = arginine vasopressin

Uosm = urine osmolality
AST = aspartate aminotransferase

DDAVP = 1-desamino-8-D-arginine vasopressin

increased serum urate, mildly elevated liver enzymes and proteinuria.

The interesting aspect of this case is that transient polyuria appeared at the same time as the raised blood pressure. Our patient had never previously experienced polydipsia and/or polyuria. Psychiatric consultation essentially ruled out the possibility of psychogenic water drinking. There was a minimal increase in Uosm following overnight water deprivation. Treatment with DDAVP resulted in a reduction of urine volume and an increase in Uosm. At 2 weeks postpartum, the polyuria had completely regressed. These data are consistent with a transient central diabetes insipidus that developed during pregnancy. Etiologically, two scenarios are plausible. The first is latent (partial) diabetes insipidus that was unmasked by pregnancy, and the second, transient diabetes insipidus as part of preeclamptic toxemia. In both situations, excess vasopressinase activity is probably responsible for the development of diabetes insipidus. As mentioned above, DDAVP retains its antidiuretic action due to the fact that, unlike naturally occurring AVP, it is resistant to vasopressinase.

With regard to the first possibility, we are unable to definitely rule out partial diabetes insipidus in our patient. Although a CT of the brain was of normal appearance, the imaging modality of choice is magnetic resonance imaging. In pregnancy as well as in diabetes insipidus, the posterior pituitary hyper-signal image generally disappears, reflecting reduced AVP storage. However, in most cases of diabetes insipidus during pregnancy, this abnormality usually reverts to normal in the postpartum period. It would require measurement of AVP levels during a water deprivation test to definitely exclude partial diabetes insipidus in our patient.

The second possibility seems to us the more likely. As seen in our case, transient diabetes insipidus of pregnancy is frequently accompanied by preeclamptic toxemia. In particular, it has been associated with acute fatty liver of pregnancy or other liver involvement (raised transaminases), themselves manifestations of preeclamptic toxemia. An attractive hypothesis linking diabetes insipidus of pregnancy to preeclamptic toxemia was put forward by Gordge et al. [4]. These authors argued that the association might be explained if the products of AVP degradation by vasopressinase maintained pressor activity while losing antidiuretic activity. They therefore measured both V1 and V2 receptor-stimulating activity of vasopressinase-degraded AVP in the blood of healthy women between week 34 and the end of pregnancy. There was no significant retention of V1, relative to V2, receptor-mediated activity. Nevertheless, the association of diabetes insipidus of pregnancy and preeclamptic toxemia, although rare, does exist. The fact that as with other manifestations of preeclamptic toxemia, the diabetic insipidus of pregnancy usually completely regresses in the postpartum period, points to it as being part of the spectrum of preeclamptic toxemia.

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