Review Article

Diabetes insipidus: the basic and clinical review

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ABSTRACT

Diabetes insipidus (DI) is a complex disease. DI is inability of the body to conserve water. Polydipsia and polyuria are the major manifestations of DI. DI has various variants including central diabetes insipidus (due to defect in ADH secretion), nephrogenic diabetes insipidus (due to defect in ADH receptors or urea receptors), gestational diabetes insipidus (due to catabolism of ADH by placental vasopressinase) and primary polydipsia (due to massive fluid intake). The cause of various variants of DI is either acquired or congenital. High plasma osmolality due to hypotonic urine excretion can be fatal because it can cause psychosis, lethargy, seizures, coma or even death. Polyuria and polydipsia help in the diagnosis of DI. Differential diagnosis of various variants of DI can be carried out on the basis of water deprivation test, MRI and other radiological techniques. The proper management of DI is the replenishment of water loss and correction of clinical presentations produced as a result of DI, major is hypernatremia. The best management for primary polydipsia is fluid restriction while fluid intake is used for adipsic diabetes insipidus. ADH replacement therapy is widely used to treat DI. DDAVP or desmopressin is mostly preferred ADH analogue because it has less side effects and resistant to placental vasopressinase.

Keywords: Diabetes, Desmopressin, Vasopressinase, Hypernatremia, MRI

INTRODUCTION

Diabetes Insipidus (DI) is a very complex and rare disease. The word “Diabetes Insipidus” is a combination of two words “Diabetes” and “Insipidus”. Diabetes is a word of Greek origin which means “siphon” and Insipidus is a word of Latin origin which means “without taste.”¹ DI is actually inability of body to conserve water due to pathophysiology of production of antidiuretic hormone (ADH) and its action.² ADH is produced by the neurons of supraoptic and paraventricular nuclei located in the hypothalamus. After the production ADH streamlines down along the hypothalmo-hypophyseal tract and is stored in posterior pituitary, which on proper stimulus from osmoreceptors, is released from its storage location.³ The production, storage and release of ADH are shown in Figure 1(a).⁴ Polydipsia, polyuria, hypernatremia, dehydration and severe thirst are most common manifestations of DI.¹,⁵-⁸ The incidence of DI in general population is about 3:100, 000.⁹

Types of diabetes insipidus (DI)

The Diabetes insipidus include following types¹⁰
1. Neurogenic diabetes insipidus
2. Nephrogenic diabetes insipidus
3. Gestational diabetes insipidus
4. Adipsic diabetes insipidus
5. Primary polydipsia
6. Dipsogenic diabetes insipidus
7. Psychogenic diabetes insipidus
Etiology

The congenital causes of NDI are the mutations of V2 receptor gene (X-linked), aquaporin-2 (AQP2) gene (autosomal-recessive) and urea transporter-B (UT-B) gene. The X-linked inheritance is most commonly observable condition in males and these patients do not respond to DDAVP or desmopressin. The acquired form of NDI is mainly due to lithium which is frequently used to treat bipolar disorders. The other drugs characterized as the causing agents of NDI are Amphotericin B, Colchicines, Gentamicin, Methoxyflurane and Demeclocycline. Acquired causes also include chronic renal failure, pyelonephritis, polycystic kidney disease, renal transplantation, obstructive uropathy, chronic renal medullary disease, chronic hypokalemia and chronic hypercalcemia. Low protein diets also downregulate the AQP2 protein.

Clinical Presentations

Due to the ADH insensitivity polyuria increases. The clinical presentation also includes nocturia. Osmotic diuresis, leading to hypernatremia, hyperchloremia, constipation and prerenal azotemia, can cause mental retardation, seizures and death.

Gestational diabetes insipidus

Gestational diabetes insipidus (GDI) is less frequently occurring type and only in pregnant women. The incidence of GDI is estimated to be 5:100,000 of pregnancies. Vasopressinase (enzyme) produced by placenta metabolizes the hormones of posterior pituitary both ADH and oxytocin.

Etiology

Placenta produces a Vasopressinase. Vasopressinase is a cysteine aminopeptidase and it degrades the ADH and oxytocin. When this cysteine peptidase is produced in large amount, it catabolizes almost 99% quantity of produced oxytocin and ADH leading to GDI.

Clinical Presentations

Polydipsia, polyuria and severe thirst are common presentations of GDI. The association of GDI with preeclampsia and HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count) is most commonly observed.

Adipsic diabetes insipidus

Adipsia is a disease in which there is an absence of thirst although body has dehydration and high plasma osmolality. Any lesion of thirst center in hypothalamus leads to the loss of thirst causing adipsia. Adipsia is often associated with CDI because the lesion of hypothalamus also affects the supraoptic and pavaventricular region (the
releasing sites of ADH). Hence, adipsia and CDI are collectively known as Adipsic diabetes insipidus (ADI). It is very rare disease. In the world only 200 cases have been reported till now.

Etiology

The main cause of ADI is the lesion of thirst center located in hypothalamus. Craniohypophyseomas affecting both thirst center and supraoptic and paraventricular region are important in causing the ADI.

Clinical presentations

Patients suffering from ADI present with lack of thirst sensation with high plasma osmolality and hypernatremia. High sodium level can cause various complications including lethargy, mental disturbances, disturbed acid-base balance and even death.

Primary polydipsia

Primary polydipsia (PP) is characterized by large amount of fluid intake. Large fluid intake leads to the low plasma osmolality and the production of ADH stops in response to low plasma osmolality. As a result of which the concentrating ability of kidneys fall down and person excretes large amount of dilute urine having low osmolality.

Depending upon the cause of PP, it has two sub-variants:

- **Dipsogenic diabetes insipidus**
  
  Dipsogenic diabetes Insipidus (DDI) is a sub-variety of PP and it is caused by the defect in person’s thirst center located in the hypothalamus. As a result of this defect, the thirst mechanism becomes overactive and person ingests large amount of fluid and discharges hypotonic urine.

- **Psychogenic diabetes insipidus**
  
  Psychogenic diabetes Insipidus (PDI) is also a sub-variety of PP. It is mainly caused by psychiatric disorders like schizophrenia. Such psychiatric disorders lead a person to increase fluid intake and person then excretes highly dilute urine.

Etiology

PP is mainly the large fluid intake. ADI is mainly caused due to the disturbance of thirst center while the psychiatric disorders and psychiatric medications are important in PDI. The side effects of psychiatric medications play an important role in PDI because these medications cause the dryness of mouth leading to high fluid intake. PP can also be due to some behavioral causes.

Clinical presentations

Hypotonic polyuria is common manifestation of PP. The other clinical presentations include polydipsia, intermittent hyponatremia and psychosis, the combination of these three is known as PIP syndrome. Hyponatremia can be fatal and cause death.

Differential diagnosis

According to the definition of DI, polyuria and hypotonic urine should be present. For the confirmation of polyuria, the urine output should be greater than 40ml/kg/24hrs. For the confirmation of DI urine osmolality should be <300 mOsm/kg. Polyuria can be confirmed by the history of patient. For differential diagnosis of various variants of DI, Water Deprivation Test is performed. In order to perform this test person should be sufficiently dehydrated to stimulate ADH production and measure the volume and osmolality with each discharge until the weight decreases by 3% or plasma sodium level reaches 145mmol/L. Now, treat with desmopressin or DDAVP. If the concentration of urine rises by 50% or more then person is suffering from CDI if it increases by <10% then the diagnosis is NDI. If the osmolality of urine increases more than 750 mOsm then the patient is suffering from either CDI or PP. PP can be distinguished from CDI by the ability of a person to concentrate urine in response to dehydration while this concentrating ability is absent in CDI patients. CDI can also be diagnosed with the help of MRI showing bright spot in sella turcica. MRI and other radiological techniques help in the conformation of ADI.

Management of diabetes insipidus

The proper management of DI involves the replenishment of water loss and correction of manifestations like hypernatremia produced as a result of DI. Thirst mechanism plays an important role in management of DI because water intake in response to thirst immediately corrects water loss but thirst mechanism is not much effective in unconscious patients and infants. Hypernatremia should not be corrected too quickly because it can cause cerebral edema, seizures and death. The rate at which hypernatremia is corrected should not be greater than 0.5mEq. The best management for psychogenic and dipsogenic DI is fluid restriction while adequate fluid intake is best proper management for adipsic diabetes insipidus.

Therapeutic approaches

**Neurogenic diabetes insipidus**

ADH replacement is best therapeutic approach for CDI. Pitressin is purified form of ADH given intramuscularly for treatment of CDI. But now-a-days it is not frequently used due to its side effects including angina, hypertension...
and abdominal cramping.\textsuperscript{59,60} The most preferred replacement therapy is DDAVP (1-desamino-8arginine vasopressin). It is also known as Desmopressin. It is preffered over pitressin and is resistant to placental vasopressinase.\textsuperscript{51,38,61,62} Chlorpropamide also decreases the Polyuria by upto 75\% and is used to treat the patients with mild CDI.\textsuperscript{63,64} The other drugs which are used for treatment of mild form of CDI are Carbamazepine and Clofibrate.\textsuperscript{59,60} Prostaglandin synthase inhibitors and thiazides are also used for treatment of CDI.\textsuperscript{65}

**Nephrogenic diabetes insipidus**

Patients of NDI do not respond to ADH and desmopressin. The best therapeutic approach is to remove the causing agent like lithium etc, if causative agent of NDI is of acquired form.\textsuperscript{11} Thiazides and amiloride are used for the treatment of lithium induced NDI.\textsuperscript{66-68} Prostaglandin synthase inhibitors are used because they increase the AQ2-2 channels at apical membrane by increasing intracellular cAMP level.\textsuperscript{69} The main side effect of these drugs is that they cause kidney damage and gastric problems.\textsuperscript{11,72,73} Recent studies have shown that long term treatment with thiazides can cause renal carcinoma.\textsuperscript{72} Another treatment of NDI is the release of trapped V\textsubscript{2} receptors from endoplasmic reticulum. This can be done with the help of chemicals known as nonpeptide chaperones.\textsuperscript{74,75} Recent studies have shown that gene therapy can be the better option for treatment of NDI but it is highly speculative.\textsuperscript{74} Recent investigations have revealed that statins also increase the expression of AQ2 in apical membrane.\textsuperscript{24}

**Gestational Diabetes Insipidus**

The best possible treatment of GDI is replacement of ADH by DDAVP.\textsuperscript{76} DDAVP or desmopressin is resistant to placental vasopressinase.\textsuperscript{76} DDAVP is frequently preferable because of its minute effect on maternal vascular tone but the recent studies have shown that the quantity of amniotic fluid may change.\textsuperscript{77,78} Another treatment of GDI is by hydrochlorothiazide but it is usually not preferred because of its side effects including neonatal hypoglycemia and neonatal DI.\textsuperscript{79}

**Adipsic diabetes insipidus**

DDAVP therapy is used to decrease the urine output in the patients of ADI. Moreover behavioral therapy is also required because the thirst mechanism fails to perform its function in patients of ADI.\textsuperscript{80}

**Primary polydipsia**

Clozapine is an effective drug because it reduces the water intake but it is generally not preferred because of its side effects. Therefore fluid restriction is best management.\textsuperscript{57}

**CONCLUSION**

Diabetes insipidus (DI) is not very common disease. Polyuria and polydipsia are common manifestations of DI due to inability of a person to conserve water. The cause of DI is either congenital or acquired. Water deprivation test and MRI are used for differential diagnosis. Water replenishment is best proper management of DI. Desmopressin or DDAVP is widely used ADH analogue in ADH replacement therapy to treat DI.

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