PRIMEVIEW

DIABETES INSIPIDUS

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Diabetes insipidus (DI) is a form of polyuria–polydipsia syndrome characterized by excessive urination (polyuria) and excessive drinking (polydipsia), and comprises four types: central, nephrogenic, and gestational DI and primary polydipsia.

MECHANISMS

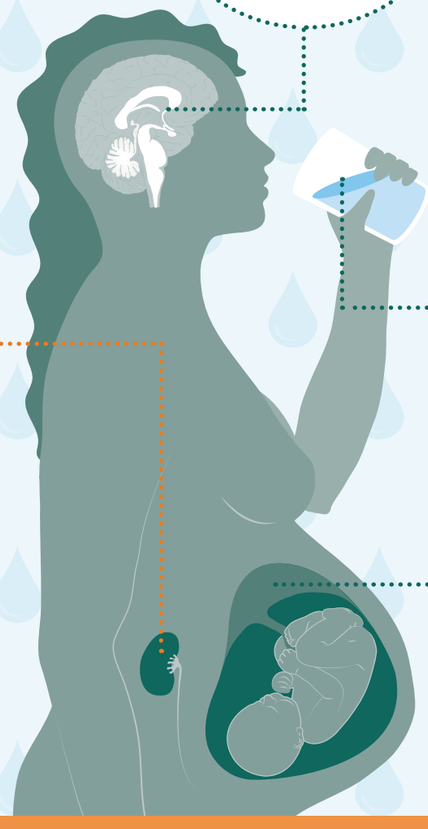
Arginine vasopressin (AVP) is a hormone that is released from the posterior pituitary gland to increase water and solute reabsorption by the kidneys into the blood

CENTRAL DI
Destruction of AVP-producing neurons in the pituitary gland or *AVP* mutations

These forms of DI result in reduced serum AVP due to deficient synthesis or pituitary release of AVP or increased AVP degradation

NEPHROGENIC DI
Decreased response to AVP or mutations in AVP receptor or water channel genes

This form of DI results in reduced sensitivity of the kidneys to the antidiuretic effects of physiological AVP levels



PRIMARY POLYDIPSIA
Excessive fluid intake physiologically suppresses AVP secretion

GESTATIONAL DI
Excessive activity of AVP-degrading placental vasopressinase

EPIDEMIOLOGY

DI is a rare disease with a global prevalence of ~1 in 25,000. Although precise prevalence data for DI forms are not available, central DI is most common. Risk factors for central DI include traumatic and non-traumatic damage to the AVP-producing neurons in the hypothalamus (such as tumour resection or tumours, respectively). Lithium treatment, hypercalcaemia and hypokalaemia are the most common risk factors for acquired nephrogenic DI. Gestational DI is more prevalent in multiple pregnancies. Primary polydipsia occurs in patients with neurodevelopmental or psychotic disorders and is becoming more prevalent in the general population owing to compulsive water drinking.

MANAGEMENT

The main goals of DI treatment are correcting pre-existing body water deficits and reducing ongoing water loss from excessive urination, while avoiding detrimental effects of overtreatment, such as hyponatraemia (low plasma sodium concentration). Fluid administration should balance replacing body water quickly enough to avoid brain damage owing to prolonged hyperosmolality, and providing enough water to avoid rapid changes in serum sodium concentration (which can lead to cerebral oedema and seizures). Oral consumption of hypotonic fluids (such as water or milk) should begin as soon as feasible. Desmospressin is the gold-standard pharmacological therapy to initiate antidiuresis. Treatment of acquired nephrogenic DI targets the underlying cause, whereas symptom amelioration is the focus in hereditary nephrogenic DI. Gestational DI can be safely treated with desmopressin, even during breastfeeding. Treatment of primary polydipsia involves behavioural interventions; desmopressin is not recommended due to high risk of hyponatraemia.

DIAGNOSIS

Excessive urination (>50 ml/kg body weight/24 h) and drinking (>3 l/day) suggest a diagnosis of DI. Identifying the type of DI is more difficult and requires additional testing, typically an indirect water deprivation test, but this has low diagnostic accuracy. This test is not recommended in pregnant women owing to a high risk of dehydration; instead, comprehensive laboratory tests are undertaken to confirm gestational DI. Once the type of DI is established, the underlying pathology must be identified; for example, gadolinium-enhanced brain MRI is used to check for disruption of the hypothalamic or pituitary anatomy.

OUTLOOK

The rarity of DI has resulted in neglect of these conditions in medical education curricula and research. Improved understanding of the aetiology of idiopathic forms of central DI and the genes underlying some cases of hereditary nephrogenic DI is needed. Safer, less onerous alternatives to the indirect water deprivation test are needed; the hypertonic saline infusion test plus copeptin measurement has higher diagnostic accuracy and has been proposed to replace the water deprivation test. Treatment of central DI is usually straightforward, whereas treatment of nephrogenic DI is more challenging because correcting defective AVP-receptor-mediated signalling or water channel mislocalization is currently unfeasible, although pharmacological bypass of these defects may hold promise.

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