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REVIEW ARTICLE

Paediatric Diabetes Insipidus: A Review

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Abstract

Diabetes insipidus is a disease characterized by partial or total inability to concentrate urine due to a vasopressin secretion deficiency (central diabetes insipidus), a resistance to its action (nephrogenic diabetes insipidus) or an excessive consumption of water (primary polydipsia). The main signs and symptoms of the disease are polydipsia, polyuria, and nocturia; central diabetes insipidus has an insidious onset, whereas nephrogenic diabetes insipidus has a gradual onset. Because of the advances in clinical, laboratory, imaging techniques and molecular biology, the etiologic diagnosis of diabetes insipidus has improved, from 50% of patients with idiopathic diabetes insipidus to 10%-20% of patients; therefore, it has been achieved more timely treatments, resulting in reduction of the risk of sequelae. Accordingly, it is pivotal to rule out secondary causes of diabetes insipidus, such as drug consumption or metabolic disorders in patients with nephrogenic diabetes insipidus, brain tumors, encephalic trauma, infiltrative diseases, autoimmune disorders or central nervous system infections in case of patients suffering from central diabetes insipidus. Regarding treatment, it is recommended the use of desmopressin, an analogue of vasopressin, for the treatment of central diabetes insipidus, whereas water consumption, decrease of salt consumption and treatment with diuretic and non-steroidal anti inflammatory drugs are recommended for treatment of patients with nephrogenic diabetes insipidus.

Keywords: *Pediatrics, Diabetes insipidus, central, nephrogenic.*

Introduction

Diabetes insipidus was first described in the 18th century.[1] Diabetes is a Greek word meaning "siphon". It is derived from the verb diabaine, which means "to stand with legs apart, as in urination, or to go through. Insipidus is a Latin word meaning "without taste". In contrast to diabetes mellitus (DM), which involves the excretion of sweet urine, diabetes insipidus (DI) involves passing urine that is tasteless because of its relatively low sodium content.[2] DI is a rare, but serious disorder, that can be life threatening as it causes fluid imbalance that results in severe dehydration and electrolyte abnormalities.[3]

DI is characterized by polydipsia, polyuria, hypernatremia and dehydration.[2-5] There are different types of DI; the most common type is the neurological form, called central diabetes insipidus (CDI), which involves a deficiency of arginine vasopressin (AVP) or also known as antidiuretic hormone (ADH). CDI has several other names in literature. It is also known as pituitary, hypothalamic, neurohypophyseal or neurogenic DI. The second common type of DI is the nephrogenic diabetes insipidus (NDI), which is due to resistance of the renal tubules to ADH. NDI can be primary (idiopathic) or secondary, caused by drugs or chronic disorders, such as renal failure, sickle cell or polycystic kidney diseases.[6-11]

Epidemiology

The incidence of DI in general population is 3 in 100,000, with a higher incidence among males (60%).

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X-linked NDI is very rare, with AVPR2 gene mutations among males estimated to be 4 in 1,000,000.[3] The incidence of compulsive water drinker (CWD) is unknown, but it seems to be that there is a female predisposition (80%). Although, the CWD commonly presents in the third decade of life, cases have been described in patients from 8-18 years of age.[3]

Etiology

Deficiency of AVP secretion is referred to as central DI, pituitary DI, or neurohypophyseal DI. Destruction of para-ventricular and supra-optic nuclei of the posterior pituitary by a tumor or surgery results in decreased ADH secretion and CDI. Alternatively, CDI may be idiopathic or inherited as either autosomal dominant or autosomal recessive trait in the locus 20p13.[12-14]

About 50% of central DI cases are idiopathic.[13] It usually appears within 24 hours followed by a 2-3-week period of inappropriate antidiuresis. In a German study, only 8.7% of DI cases persisted for more than 3 months.[15]

Close follow up of patients diagnosed with idiopathic DI is necessary to detect slowly growing intracranial lesions. Other causes of central DI include infiltrative disorders (histiocytosis X, sarcoidosis), anorexia nervosa, infections such as viral meningitis toxoplasmosis, inflammatory conditions including lupus erythematosis, wegener's, and vascular lesions such as arteriovenous malformations or aneurysms. Among them, Neurosurgical procedures, tumors, traumatic brain injury, tumors, infiltrative lesions, and malformations are the most frequent causes of DI.

NDI can be secondary, which is more common, or primary. The acquired form can be secondary to drugs like lithium, amphotericin B, methicillin and rifampin or due to renal disorders. The congenital forms, which are less common but very severe and difficult to treat, are the X-linked, autosomal recessive and autosomal dominant forms.[10] Majority of cases of hereditary nephrogenic DI have X-linked inheritance.[16] Hypercalcemia causes defective urinary concentrating ability which is generally reversible with correction of the hypercalcemia and may be associated with reductions both in sodium chloride reabsorption on the thick ascending limb of the loop of Henle, thereby interfering with the countercurrent mechanism. Persistent severe hypokalemia can have similar effects in the collecting tubule and the thick ascending limb of the loop of Henle. A variety of renal diseases can give rise to nephrogenic DI. Apart from lithium multiple medications are associated with nephrogenic DI.[8]

Pathophysiology

Arginine vasopressin (ADH) is an antidiuretic hormone that is first synthesized in cell bodies of the nuclei in the hypothalamus and is transported for the hypothalamus through the neural component of the pituitary stalk and stored in the nerve terminals in the posterior pituitary. ADH is usually transported in the blood to the receptor sites on the baso-lateral surface of the collecting duct membrane. Activation of the ADH receptor increases cyclic adenosine monophosphate (cAMP) production through a G protein adenylate cyclase coupling, and stimulates protein kinase A; leading to increased recycling of the protein aquaporin in the plasma membrane, which enhances water entry into the cell from the lumen. Absence of ADH receptor does not allow the process to take place, causing inhibition of water intake and polyuria. Alternatively, defective or absent aquaporin impairs the process in the absence of normal arginine vasopressin receptor (AVPR2 or V2 receptor).[17,18] There are different types of receptor for vasopressin. The V1 receptor present in the endothelial cells leads to a pressor effect by the activation of Ca++ pathway whereas the V2R is the one responsible for water reabsorption by activating cyclic adenosine monophosphate (cAMP) in the kidneys and opening of the aquaporin channels.[19,20]

Although there are many factors responsible for the secretion of vasopressin like nausea, acute hypoglycemia, glucocorticoid deficiency, smoking, the most important stimulus is increased plasma osmolality.[21] The increase in plasma osmolality can be as small as 1%.[22] The baroregulatory system usually does not cause the secretion of vasopressin during the normal circumstances unless there is a large volume loss, in which case there is release of some amount of this hormone.[23] Vasopressin acts as an antidiuretic by reabsorbing water via the principle cells of collecting ducts and the thick ascending loop of Henle, thereby increasing the plasma blood volume and decreasing the plasma osmolality.[24,25] It can also cause contraction of the smooth muscles in the blood vessels and release of von Willebrand factor and is regulated at the para-

ventricular and supra-optic nuclei, which sense the changes in osmolality.[9]

NDI arises from a defect or absent receptor site at the cortical collecting duct segment of the nephron (X- linked, vasopressin V2 receptor deficiency of locus Xq28) or of a defective or absent aquaporin, the probe that transport water at the collecting duct (autosomal recessive, locus 12q13, with several mutations being associated with ND1. The X- linked variety of ND1 accounts for about 90% of such cases.[26-28]

Polyuria and polydipsia with dilute urine, hypernatremia and dehydration are the hallmark of DI in infants and children. There are three common conditions that give rise to polydipsia and polyuria in these patients. The commonest is CDI, related to a deficiency of vasopressin, and less common is NDI, including X-linked recessive, autosomal recessive, and autosomal dominant types due to renal resistance to vasopressin. Finally, these symptoms can also occur in some compulsive water-drinking (CWD) patients who demonstrate physiologic inhibition of vasopressin secretion.[2-4]

Table I
Main etiological causes of polyuria in children[2-4]

Increased solute-load like diabetes mellitus
Central (neurogenic)
Diabetes Insipidus (vasopressin deficiency)
Acquired (more common)
Primary tumours or metastasis: germinoma, craniopharyngioma, glioma
Infectious/infiltrative lesions e.g. histiocytosis
Meningitis (encephalitis)
Congenital (less common)
AVP-NPH gene defect
Familial, autosomal dominant, autosomal recessive
Congenital anatomic defects
Agenesis of corpus callosum
Septo-optic-dysplasia
Familial pituitary hypoplasia
Nephrogenic diabetes insipidus (vasopressin resistant)
Acquired - drugs e.g. lithium, amphotericin B, methicillin and rifampin
Congenital - renal failure, X-linked, autosomal recessive and dominant
Primary polydipsia
Psychogenic - compulsive water drinking
Dipsogenic - defect thirst mechanism

Clinical manifestations

The age of presentation is dependent on the etiology, it can present at any age, and the prevalence is equal among males and females although there is one study showing higher prevalence in the males.[27] In an alert and conscious patient, diabetes insipidus presents with intense thirst (polydipsia), craving for ice water together with polyuria. The volume of fluid ingested may range from 2L to even 20L a day.[29] Less severe cases may present with persistent enuresis. Most patients with an intact hypothalamic thirst centre maintain their fluid balance by drinking water. But patient who are unable to access free water as seen in neonates and elderly present with clinical features of hypernatremia and dehydration.[30] Lethargy, altered mental status, hyperreflexia, seizure, or, may be other presenting symptoms especially in the older age group, neonates and infants (Table-II).

Table II
Clinical characteristics of patient presenting with central and nephrogenic diabetes insipidus

	Central diabetes insipidus	Nephrogenic diabetes insipidus
Age at presentation	Child between 5-6 years, rarely adulthood	Antenatal hydramnios, neonatal age, early infancy
Incidence	Rare	Common
Aetiology	Often acquired	Mostly acquired
Mode of inheritance	AD, AR	X-linked, AD, AR
Gene	AVPNP11, WFSI	AVPR2, AQD2
Clinical presentation	Marked thirst, Growth failure	Severe thirst, Failure to thrive, Mental retardation

AD - Autosomal Dominant, AR - Autosomal Recessive

Dehydration may lead to contraction of intravascular volume which in severe cases causes traction of dural veins and sinuses leading to intracranial hemorrhage.

Diagnosis

Diagnosis of DI can be difficult, as the non- specific symptoms of excessive crying, poor feeding, failure to thrive and irritability, are common in infants. Therefore, high index of suspicion is necessary. In addition to a complete medical history and physical examination, including the child's daily fluid intake, dietary intake, medication and bowel and bladder (voiding) habits, the diagnostic procedure may include: assessing the urine specific gravity of the first morning sample can be helpful. In doubtful cases, an accurate 24-hour urine collection is important to confirm polyuria in the first place. Diluted urine with a relatively high serum sodium concentration and osmolality effectively establish the diagnosis. The serum sodium level may be high >150 mmol/L (150 mEq/L), with the serum osmolality greater than 300mosmol/kg. A serum osmolality >300 mosmol/kg with urinary osmolality <300 mosmol/kg in a case with pathologic polyuria and polydipsia is diagnostic for DI. Serum potassium, and calcium concentrations are important to exclude the possibility of polyuria secondary to hypokalemia or hypercalcemia; both can interfere with renal concentrating mechanisms.[2-4]

The definitive diagnostic study is water deprivation test (WDT), which can be used both to confirm the diagnosis and distinguish between CDI and NDI on the basis of response to vasopressin analogue. The test should be performed by an experienced individual and under close supervision.[2-4] The normal response to dehydration or desmopressin includes urine osmolality greater than 450 mosml/kg, urine to serum osmolality ratio of 1.5 or higher, and an increase in urine to serum osmolality of 1 or more from baseline. A normal response to dehydration would be observed in CWD and to vasopressin analogue in CDI, but not in NDI, which is due to renal tubular unresponsiveness to vasopressin.

However, patients with CWD may have limited ability to concentrate urine and both of CDI and NDI may be partial, therefore a diagnostic confusion may arise between these conditions may arise as all may be capable of producing a similar rise in urine osmolality during WDT.[31,32] The hypertonic saline test offers an alternative approach to WDT in diagnosing DI and differentiating it from other polyuric states such a challenging situation. It is based on defining the relation between serum osmolality and plasma AVP concentrations. The test is well established in adults, with some limitations of reporting experience of its use in children.[33,34] Mohn et al[35] from UK reported using this test in five children (11 months to 18 years) who had diagnostic problems.

MRI pituitary and hypothalamus is an important tool for the assessment of the cause of CDI, and should always be performed after gadolinium injection, to check for abnormal enhancement within the stalk.[36]

Renal Ultrasonography helps ruling out primary renal disorders like polycystic renal disease and ureteric obstruction. Massive hydronephrosis and mega ureter are seen in children with polyuria-polydipsia of long duration. Gene testing for familial forms of CDI and NDI are now available.[27]

Management

The first step in DI management starts with patient's education about the disease and its management. The therapeutic goals are primarily reducing polyuria and decreasing thirst, so that the patient is able to grow adequately and maintain a normal life-style. This can be achieved through several strategies; a free access to water; patients with DI can drink enough fluid to replace their urine losses. When oral intake is inadequate and hypernatremia is present, replace losses with dextrose in water or intravenous hypo-osmolar fluids with respect to patient's serum osmolality.[2-4] Only sterile water cannot be administered intravenously without dextrose, as it can cause hemolysis.[33] To avoid hyperglycemia, volume overload, and overtly rapid correction of hypernatremia, the fluid replacement should be provided slowly aiming to reduce serum sodium by 0.5 mmol/L (0.5 mEq/L) every hour. Careful monitoring in intensive care settings should be provided.[34]

Dietary management aims to optimize free water excretion. Modification in the diet is helpful in decreasing solute load to renal and has been shown to be useful especially in NDI. Diet with low sodium (1 mmol/kg/day), low protein intake of 2 g/kg/day with high calories food providing a high caloric value which is also essential for growth and development.[37]

Vasopressin and its analogues should also be used in treating CDI, and lifelong supplementation

remains the mainstay of management. In older children with CDI aqueous vasopressin, lysine vasopressin may be used to minimize water excretion. Desmopressin (1-deamino-8-*D*-arginine vasopressin, dDAVP) is the current drug of choice for long-term therapy of CDI.[38] This synthetic analogue has more specific antiduretic action, negligible pressor activity and a longer half-life than the native molecule. It can be given parenterally, orally, or intranasally. Oral tablets although 20 folds less potent than the intranasal form, are highly effective and safe in children, with more flexibility of dosing and have largely replaced the intranasal form. The recommended dose off dDAVP is 100-1200 µg/ day in three divided doses orally; 2-40µg once or twice a day intranasally; and, 0.1-1µg parenterally.[36] There is a large variability in action amongst individuals and hence the duration between doses needs to be determined in each patient.[39] It is a safe practice to allow a short period of diuresis between two doses. Dilutional hyponatremia, headache, hypertension and nasal congestion are some of the side effects occasionally seen. Vasopressin tannate in oil is also used in the dose of 2-5U intramuscular every 25-72 hours. Lysine vasopressin is used if shorter duration of action of 2-8 hours is needed.[40]

Certain precautions should be taken for known patients or suspected ones for hypopituitarism undergoing surgery, considering hormonal replacement therapy such as corticosteroid, vasopressin and adequate fluids. As a practical consideration, any patient with post-operative anterior pituitary insufficiency should receive corticosteroid replacement therapy. Decreased bone mineral density has been reported in children with CDI; and significant improvement in bone mineral density was observed after treatment with oral alendronate.[41]

NDI is difficult to treat and cannot be effectively treated with desmopressin. Underlying pathology should be treated first. In idiopathic cases, hydrochlorothiazide in a dose of 2-4 mg/kg/day in divided doses could be used to ameliorate the sodium and water loss in the urine in addition to other general measures.[42,43] Amiloride given additionally or alone; and it has similar effect but is useful in preventing hypocalcaemia. A similar reduction in urine flow may be achieved with the prostaglandin synthetase inhibitor indomethacin, given in doses of 1.5-3.0 mg/kg.[36] A relatively new and promising approach is the combination of a thiazide, indomethacin, and desmopressin, which may reduce urine output by up to 80%. It is essential that all these patients drink adequate fluid volumes to quench their thirst.[43]

Prognosis

Central DI occurring after pituitary surgery usually remits within days to weeks but if structural damage has occurred to the stalk, it may even be permanent. The clinical course of chronic central DI is more of inconvenience to daily life than a dire medical condition. Currently available treatments with Desmopressin do a good job to control symptoms but patients must be watched closely for side effects, water intoxication, and hypernatremia. Prognosis of NDI is satisfactory only where the underlying aetiology could be resolved adequately.

Conclusion

DI is not that uncommon pediatric disorder. The clinical presentation varies with age of onset and underlying cause. Water deprivation test is useful in establishing the diagnosis, when it is not typical, and help in differentiating between the various causes; however, it should be performed under close supervision by an experienced team familiar with the test. Management of DI is essentially planned to treat the underlying cause. Desmopressin is the drug of choice for CDI, and the oral formulation is more preferred. Thiazide diuretics with other oral drugs showed promising result in NDI management.

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