An Overview of Diabetes Insipidus in Childhood: Perspectives of Aetiology, Diagnosis and Management

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Abstract: Pediatric diabetes insipidus is a rare, but serious disease, as it can result in a life-threatening electrolyte and fluid imbalance. An overview of diabetes insipidus in children and infants to highlight the etiology, diagnosis and management, is presented here to familiarize general pediatricians and endocrine trainees who deal with this rare but potentially fatal disorder with its aetiology, diagnosis and management.

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

INTRODUCTION

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 [1]. 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 [2].

DI is characterized by polydipsia, polyuria, hypernatremia and dehydration [1-5]. 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 anti-diuretic 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 [1-16].

PATHOPHYSIOLOGY

Secretion of Arginine vasopressin (ADH) occurs in the posterior pituitary gland and is regulated at the para-ventricular and supra-optic nuclei, which sense the changes in osmolality (Figure 1) [17]. 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 [18-23].

Arginine vasopressin (ADH) 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 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) [24-26].
ND1 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 [28-30]. The X-linked variety of ND1 accounts for about 90% of such cases [27-29].

Polyuria and polyuria with dilute urine, hypernatremia and dehydrated 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 [1-3].

The incidence of DI in general population is 3 in 100,000, with a higher incidence among males (60%) [2]. X-linked NDI is very rare, with AVPR2 gene mutations among males estimated to be 4 in 1,000,000 [2]. The incidence of compulsive water drinker is unknown, but it seems to be that there is a female predisposition (80%) [2]. Although, the CWD commonly presents in the third decade of life, cases have been described in patients from 8-18 years of age [2].

### Table 1 - Main etiological causes of polyuria in children

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

### Table 2 - Clinical characteristics of patient presenting with central and nephrogenic diabetes insipidus

<table>
<thead>
<tr>
<th>Age at presentation</th>
<th>Central diabetes insipidus</th>
<th>Nephrogenic diabetes insipidus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>Infancy between 5-6 years rarely adulthood</td>
<td>Antenatal hydramnios, neonatal age, early infancy</td>
</tr>
<tr>
<td>Etiology</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Mode of inheritance</td>
<td>Often acquired</td>
<td>Mostly acquired</td>
</tr>
<tr>
<td>Gene</td>
<td>AD/AR</td>
<td>X-linked/AD/AR</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Marked thirst, Growth failure</td>
<td>Severe thirst, Failure to thrive, Growth failure, Mental retardation</td>
</tr>
</tbody>
</table>

AD – Autosomal Dominant
AR – Autosomal Recessive
### Table 3 - Vasopressin and vasopressin analogues

<table>
<thead>
<tr>
<th>Drug</th>
<th>Duration of action</th>
<th>Anti-diuretics</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aqueous Arginine-vasopressin</td>
<td>5-10 min</td>
<td>Most potent</td>
<td>Intravenous infusion</td>
</tr>
<tr>
<td>Lysine vasopressin</td>
<td>2-8 hours</td>
<td>20 times less than Pitressin</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Aquous vasopressin)</td>
<td></td>
</tr>
<tr>
<td>Desmopressin nasal solution</td>
<td>8-12 hours</td>
<td>20 times less than Pitressin</td>
<td>Intranasal</td>
</tr>
<tr>
<td>Desmopressin nasal spray</td>
<td>8-12 hours</td>
<td>20 times less than Pitressin</td>
<td>Nasal insufflation</td>
</tr>
<tr>
<td>Desmopressin oral tablets</td>
<td>8-12 hours</td>
<td>20 times less than Pitressin</td>
<td>Oral</td>
</tr>
<tr>
<td>Desmopressin parenteral</td>
<td>8-12 hours</td>
<td>20 times less than Pitressin</td>
<td>Intravenous, subcutaneous</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>intramuscular</td>
</tr>
<tr>
<td>Vasopressin tannate in oil</td>
<td>24-72 hours</td>
<td>20 times less than Pitressin</td>
<td>Intramuscular</td>
</tr>
</tbody>
</table>

**Fig-1 - Magnetic resonance images of two children showing** (A) **normal bright spot of the posterior pituitary** (arrow) (B) **DI patient demonstrating the abnormal bright spot of the posterior pituitary** (arrow).

**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. Diluted urine with a relatively high serum sodium concentration and osmolality effectively establish the diagnosis. The serum sodium level may be as high as 170 mmol/L (170 mEq/L), with the serum osmolality greater than 760 mosmol/kg. In doubtful cases, an accurate 24-hour urine collection is important to confirm polyuria in the first place. Serum potassium, and calcium concentrations are important to exclude the possibility of polyuria secondary to hypokalemia or hypercalcaemia; both can interfere with renal concentrating mechanisms [1-3].

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 [1-3]. The normal response to dehydration or desmopressin includes urine osmolality greater than 450 mosmol/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 [31-33]. 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 [34,35]. Mohn A et al. from UK reported using this test in five children (11 months to 18 years) who had diagnostic problems [36]. The WDT was equivocal or impractical; and inappropriately low ADH concentration was demonstrated in the presence of an adequate plasma osmolality in 2 patients in their report [36]. The hypertonic saline test was easy to perform, well tolerated by the patients, and was diagnostic in all cases [36]. In this test, continuous Intravenous saline (0.85 mmol/l) are administered at a rate of (0.05 ml/kg/min) through an indwelling catheter for up to a maximum of 3 hours, or until a plasma osmolality of 300 mosmol/kg is achieved and blood samples are taken 30 minutes before and at 30 minute intervals from the start of the test measuring plasma sodium, ADH concentrations, and osmolality as well as urine samples before the start of the test and at 60 minute intervals, where possible, for measurement of urinary sodium and osmolality [36]. Thirst behaviour and blood pressure should also be recorded at 30-minute intervals throughout [36].

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 (Table 2).

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 (Figure 1). The patient should also be well hydrated as the intensity of the posterior pituitary bright signal is inversely related to the degree of hydration. MRI findings have been heterogeneous and the most common feature is the absence of posterior pituitary bright signal in T1 weighted (contrast-enhancement) images (Figure 1). However, in familial CDI, when evaluated during infancy or early childhood, and chronic hyponatraemia the bright signal may remain visible [30, 37,38]. The diagnostic value of the size of the adeno-hypophysis and pituitary stalk thickness (PST) are of paramount importance. PST is observed in almost one third of children with CDI and may be the first sign of germinoma (15%) or of stalk infiltration, as in Langerhans-cell histiocytosis (15%). Spontaneous regression of PST has been observed. Changes in the size of PST and in the size of the adenohypophyses are observed during the first 2-3 years and remain unchanged thereafter [39,40].

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 standing duration. Gene testing for familial forms of CDI and NDI are now available [35].

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 hyponatraemia is present, replace losses with dextrose and water or intravenous hypo-osmolar fluids with respect to patient’s serum osmolality [1,2,4]. You should not administer sterile water without dextrose IV, as it can cause hemolysis [36-38]. To avoid hyperglycemia, volume overload, and overly rapid correction of hyponatraemia, 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.

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. Long-standing excess fluid intake may cause hydrenephrosis and hydro ureter and may also lead to fluorosis if the fluoride content of the water is high [39]. Renal ultrasound should be performed from periodically; as such complications are associated also with vasopressin resistance.

Vasopressin and its analogues (Table 3) should also be used in treating CDI, and remains the main stay of management. There is a large variability in action among the individuals and hence the duration between doses needs to be determined in each patient [40-43].
Certain precautions should be taken for known patients or suspected ones for hypopituitarism going 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 [44].

NDI is difficult to treat and cannot be effectively treated with desmopressin. 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 [35]. Amelioride given additionally or alone; and it has similar effect but is useful in preventing hypocalcaemia.

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, and the oral formulation is more preferred.

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REFERENCES
18. Al Agha AE, Thomset J, Ratcliffe JE, Cotterill AM, Batch JA; Acquired central diabetes insipidus...