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Review Article

Presentation and Management of Diabetes Insipidus

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Abstract

Diabetes insipidus (DI) is a disorder of disruption in water equilibrium, characterized by the excretion of large volumes of dilute urine, identified through polyuria, a urine volume of more than 3 liters/24 hours in adults (> 4 ml/kg/hr), polydipsia (water consumption > 2 L/m2/d). DI is an ailment that causes either lowered serum level of antidiuretic hormone (ADH), additionally referred to as arginine vasopressin (AVP) or decreased kidneys sensitivity to AVP, which can trigger water and electrolyte imbalance. Central DI (CDI) is more commoner than nephrogenic DI. The symptoms and signs differ along with pathogenicity, the age where the disease developed. Diagnosis is based upon demonstration of plasma osmolality disturbances as well as reduced urine osmolality along with considerable water diuresis. Water deprivation along with vasopressin challenge tests, though possesses constraints, is performed to differentiate NDI from CDI. Analysis of urinary aquaporin 2 and plasma copeptin concentration presents an encouraging ability to shape improved treatment. Hypothalamus-neurohypophyseal region Magnetic Resonance Imaging (MRI) aids in the etiological diagnosis of CDI. Untreated DI can cause hypovolemia, dehydration, and electrolyte imbalances. The goal of treatment in both forms of DI is to decrease urine output, maintain appropriate fluid and sodium balance and improve quality of life. The oral desmopressin which is safe and helpful, adds additional versatility to treatment and has mainly replaced the intranasal variant. Nephrogenic DI does not respond to desmopressin (ADH). It is treated by discontinuing any drugs that may be causing it and correcting hypokalemia and hypercalcemia along salt restriction along medicines to increase water diuresis (thiazide, amiloride, indomethacin) if still persistent.

Keywords: *Diabetes Insipidus (DI); Arginine Vasopressin (AVP); Antidiuretic Hormonal (ADH)*

Introduction

DI belongs to a genetic or acquired polyuria as well as polydipsia conditions. It is linked with insufficient secretion of arginine vasopressin (AVP), also called antidiuretic hormonal (ADH), or kidney insensitivity to AVP action. DI leads to hypotonic polyuria as well as polydipsia. Polyuria (urine volume of more than 3 liters/24 hours or > 50 mL/kg), urine osmolality < 300 mOsm/L, and thirst that's increased to water intake of up to 20 L/day are classical signs of DI. The goal of treatment in both forms of DI is to decrease urine output, maintain appropriate fluid and sodium balance and improve quality of life. Untreated DI can cause hypovolemia, dehydration, and electrolyte imbalances. This paper will review the physiology, causes, as well as the treatment of DI.

Pathophysiology

DI could be triggered by 2 major defects: Inadequate or impaired secretion of AVP secreted from the posterior pituitary gland and decreased kidney(s) sensitivity to AVP (ADH).

AVP, a neurohypophyseal nonapeptide, moderates physical body water as well as osmotic homeostasis. AVP is delivered to the posterior pituitary via the nerve axons in hypothalamus (neurohypophysis), right into the systemic flow, and plays an essential function in water equilibrium by reabsorbing water through the V2 receptor in the kidney Secretion of AVP from neurohypophysis is regulated by a complex signaling pathways that involves volume sensors, osmoreceptors and baroreceptors. The osmoregulation of the AVP system is so specific that just an increase of 1 - 2% in serum sodium (Na) concentration will trigger the transcription of the AVP in the Supraoptic nuclei (SON) and paraventricular nuclei (PVN) of hypothalamus. The aquaporin-2 water channel (AQP2) is expressed in the renal principal cells. AVP facilitate AQP2-mediated water reabsorption via activation of the vasopressin V2 receptors (AVPR2) in the collecting tubules thus enabling concentration of urine [1].

Etiology

Central diabetes insipidus (CDI)

CDI, the most common type of DI, is characterized by deficient secretion of AVP. CDI It occurs in both sexes equally with incidence is around 1: 25,000. It is a result of many acquired conditions that affect hypothalamus-neurohypophyseal region. Common causes include neurosurgical treatment, craniopharyngioma or germinoma, Langerhans cell histiocytosis, trauma resulting from road traffic accidents and vascular diseases.

Neurosurgical intervention in the suprasellar region creates CDI acutely with the characteristic "triple stage" feedback. The first phase of short-term DI, lasting 0.5 to 2 days, is associated with axonal shock and/or edema disrupting vasopressin secretion followed by an antidiuretic phase, lasting 10 - 14 days, due to uncontrolled release of vasopressin. Ultimately, the phase of irreversible DI sets in if greater than 90% of vasopressin producing neurons have been destroyed. The marked antidiuretic stage hints at a long-term CDI. Within this scenario, polyuria shows up after surgical procedure but then after that, it resolves spontaneously in majority of cases, although it could continue entirely if AVP nerve cells are destroyed significantly [2]. Children may also have malfunctioning thirst sensation. Injury to the base of the brain, minor, can create transient or irreversible CDI and 50% of kids with fracture of sella turcica would create CDI but may be delayed as late as 1-month post-injury. Tumors triggering CDI may show up with neurological manifestation such as visual disruption, as well as other pituitary hormone deficiencies. CDI is likewise triggered by inflammatory conditions like lymphocytic infundibuloneurohypophysitis (LINH) as well as IgG4-related diseases. Idiopathic CDI represent 15 - 40% of DI cases [3,4]. The rate of idiopathic DI, thereby differ amongst different studies DI. Tuberculosis, sarcoidosis, Langerhans cell histiocytosis, lymphocytic hypophysitis, autoimmune variants accounted for some cases of idiopathic CDI. Meningitis or encephalitis as a result of meningococci, cryptococcus, listeria, cytomegalovirus involving the brain might present as transient CDI.

Gestational DI, a rare disorder that manifests in the third trimester and early postpartum period due to accelerated degradation of vasopressin due to increased activity of placental vasopressinase causing ADH deficiency. This type of often disappears 6 weeks after delivery, but often recurs with subsequent pregnancies [5].

Hereditary forms of CDI are a rare causes of CDI accounted for < 2% of all cases. It caused by mutations in the vasopressin gene (*AVP*). This subdivision of DI includes familial neurohypophyseal diabetes insipidus (FNDI), which usually inherited in an autosomal dominant pattern. Much more than 80 anomalies that induce FNDI have been mentioned thus far, and they are generally positioned in the coding area of neurophysin II gene located in chromosome 20p135 [6]. The age where it presents differs. The autosomal dominant type of hereditary CDI shows up by 5 - 6 years old, however, it might show up as late as the 3rd decade. The autosomal recessive form manifest in early-stage and also around the same age as Wolfram syndrome or DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and also Deafness). Midline brain defects like septo-optic-dysplasia, holoprosencephaly, pituitary hypoplasia and stalk flaws, corpus callosum agenesis might even show up earlier.

Nephrogenic DI (NDI)

NDI is characterized by insensitivity of the distal nephron to the antidiuretic effects of AVP.

Acquired forms of NDI are more common than congenital forms. A wide range of drugs can cause acquired NDI. lithium, demeclocycline, clozapine, amphotericin B, Colchicine, foscarnet, methicillin and also rifampin are implicated in the development of NDI. Chronic hypercalcemia and hypokalemia additionally trigger excess complimentary water discharging, with the cause still being unidentified. Sickle cell anemia and chronic renal diseases are well recognized causes of NDI.

In children, a rare congenital types of NDI need to be considered. Mutations in the gene encoding the ADH type 2 receptor (V2 receptor) causes congenital X linked NDI is essentially a disease of males. X linked NDI represent 90% of cases of congenital NDI and occurs with frequency of 4 - 6 cases per one million of male born. Different mutations have been described. Hereditary NDI (autosomal dominant, autosomal recessive) due to mutations in the gene encoding the ADH-dependent water channel aquaporin-2 can manifests as early as the first week of life. Serious types can present in utero as polyhydramnios and early birth. Children might present with recurrent episodes of high temperature, vomiting, dehydration. Marked developmental failure is seen in some cases [7].

Manifestations

Common symptoms in patients with diabetes insipidus are polyuria, nocturia, and also polydipsia. Polyuria is specified as urine outcome more than 3 L/day in grownups or even 2 L/m^2 in kids. In youngsters, signs may be broad, as well as they might show with extreme dehydration, bowel irregularity, nausea, depression and also developmental complications. In people with the central nervous system (CNS) cysts, aggravations and aesthetic problems might arise. Auxiliary symptoms and signs in patients with diabetic insipidus might consist of weakness, sleepiness, tiredness, and myalgias. The difference for polyuria needs to consist of key polydipsia and unrestrained diabetic issues [8].

Diagnosis of DI

DI is defined through hypotonic polyuria along with polydipsia. Daily urine quantities surpass 3 liters on average. The preliminary action in the diagnosis of DI is to establish the presence of polyuria which may be identified with a precise 24 hrs urine collection. Urine volume of more than 3 liters/24 hours in adults or more than 4 ml/kg/hr in kids as well as more than 6 ml/kg/hr in the newborn confirm polyuria. The patients are extremely unlikely to have CDI if regular water consumption seems to be less than 2 liters. It is additionally significant to inquire about the patients about how frequently they drink water as well as urinate in the evening, since simply daytime polydipsia, as well as polyuria, may suggest psychologic polydipsia as opposed to CDI. It is required to conclude out solute diuresis i.e. glu-

cosuria, hypercalciuria or uremia through urine testing as well as biochemistry the moment polyuria is noticed. Serum potassium, as well as calcium, is likewise essential to exclude polyuria caused by hypokalemia or hypercalcemia. Presence of polyuria in the absence of solute diuresis should raise the possibility of DI. CDI and NDI can show up as either partial or complete forms. The first-morning urine collection is a useful test to check the urine osmolality or specific gravity. Urine osmolality is less than 300 mOsmol/kg in the presence of polyuria is highly suggestive of DI. In young infants, finding a disparity between pathological failure to concentrate urine might be challenging since children usually exhibit a constitutional hyposthenuria. Early morning measurement of synchronized serum osmolality, urine osmolality, as well as electrolytes is crucial in the pediatric age group while examining a situation of presumed DI. Osmolality of more than 800 mOsm/ kg in urine with an osmolality of much less than 270 mOsm/kg in serum dismiss the medical diagnosis of DI, whereas urine with an osmolality less than 300 mOsm/kg, as well as a serum osmolality of more than 300 mOsm/kg is highly suggestive of the diagnosis of DI.

If the initial urine osmolality is less than 300 mOsm/kg in the presence of polyuria, a water deprivation test (WDT is done to validate the diagnosis. The water deprivation test is the gold standard for diagnosis of DI. The subjects are inhibited to intake water and food items for 4 to 18 hours or till their BW is deducted 3 - 5%. In ordinary patients, urine osmolality raises greater than 300 mOsm/kg. On the other hand, urine osmolality decreases to below 300 mOsm/kg during the exam in DI individuals. At this point, the serum ADH level is measured, followed by 1 µg of desmopressin parentally (DDAVP, a synthetic analogue of ADH) to differentiate CDI from NDI. urine osmolality raises to response to desmopressin in patients with CDI (urine osmolality increases by more than 50%), however in NDI, urine osmolality remains less than plasma osmolality; after giving desmopressin, urine osmolality increases by less than 50%. In patients with psychogenic polydipsia the urine osmolality is greater than the plasma osmolality following fluid restriction, and the urine osmolality increases less than 10% after desmopressin injection. WDT is a possibly dangerous test and ought to be carried out only in centers with the proper experience to do so. 1-deamino-8D-arginine vasopressin (dDAVP) plasma level (available in specialized centers) can be done to differentiate between CDI and NDI. Plasma AVP level is reduced or perhaps absent in patients where it is high in NDI. Osmolality measurement after water deprivation is an "indirect test" of vasopressin adequacy, whereas the measurement of vasopressin (AVP) post water deprivation is a "direct test" of vasopressin action [9,10].

Occasionally hypertonic saline loading test is done. In the hypertonic saline evaluation, 5% NaCl 0.05 ml/kg body weight (BW)/minutes is infused intravenously for 2 hours, the blood Na and blood AVP are assessed just before and after every 30 minutes after beginning the treatment. The serum Na concentration typically raise around 10 mEq/L, and also plasma AVP amounts are enhanced symmetrically to serum Na changes in normal people.

WDT is technically difficult and the results can be inaccurate. Hypertonic saline or arginine stimulated copeptin (a 39-amino acid glycopeptide) measurement is considered to be a good surrogate marker for secretion of AVP with high diagnostic accuracy [11].

Once the diagnosis of CDI is biochemically proven, investigations to determine the cause is needed. Pituitary MRI is additionally valuable for the diagnosis of CDI. The typical MRI finding in CDI is loss of the posterior pituitary bright spot. Other MRI abnormality could be thickening of the pituitary. However, it is non-specific finding and could be related to many infiltrative lesions [12]. Further testing is dependent on history and physical findings. Genetic testing for DI can be very useful to verify diagnosis in congenital cases and should be considered in all patients with afamily history of DI.

Treatment

Chronic central diabetes insipidus (CDI)

The drug of choice for long-term treatment of CDI is desmopressin (DDAVP), analog of the endogenous hormone AVP but with much lower vasopressor effect. Desmopressin comes in different forms such as intranasal spray, oral pill, an orally disintegrating tablet or parenteral forms. DDAVP dose depends on severity of symptoms. Oral preparation of desmopressin may be more convenient for some

patients. Usual starting dose is 100 - 200 µg orally at night Therefore, desmopressin dosage and scheduling should be adjusted individually according to the degree of polyuria. The dose may be titrated up to 200 µg two to three times daily until symptom control is achieved. The mean urine osmolality at 4h was just partially higher for the intranasal compared to the oral formulation. There was no significant distinction in the mean urine volume for up to 8 hours. Dosages of the oral solution were roughly 20 times higher than those for the nasal formulation. Variation in the absorption of orally carried out desmopressin have been reported in children and adults. Occasional minor side effects of intranasal form include nasal irritation, epistaxis, eye irritation, headache and flushing. Discrepancies in the activity of desmopressin based on gender have been reported in a study of ODT desmopressin for nocturia and among healthy volunteers. Female are more sensitive to the antidiuretic effect of desmopressin compared to males. Hyponatremia is a potential side effect of desmopressin administration; which require carful adjustment of the dose and monitoring [13,14].

Chlorpropamide, an oral hypoglycemic agent lowers the excretion of solute-free water if the neurohypophysis possesses residual secretory ability and stabilizes plasma osmolality [15]. Carbamazepine stimulates the release of vasopressin directly from the pituitary gland as well as functions, particularly on kidney tubules. Carbamazepine increases water absorption in the lack of AVP where the effect was depend on cyclic adenosine monophosphate (cAMP) [16]. Thiazide diuretics can be also used for treating partial CDI. Indapamide at 2.5 mg/day for DI showed a reduction in the 24-h urinary quantity (from 5 - 16L to 2.3 - 9.2L) in patients with CD [17]. Carbamazepine, thiazide or thiazide related diuretics and chlorpropamide employed when all other measures prove unsatisfactory.

Nephrogenic diabetes insipidus (NDI)

NDI is treated by discontinuing any drugs that may be causing it and correcting hypokalemia and hypercalcemia. It does not respond to desmopressin (ADH). Salt restriction along with thiazide diuretics to reduce sodium and chloride absorption in the distal renal tubules, allowing more sodium absorption and water absorption in the proximal renal tubules.

Thiazide diuretics can be utilized to treat both NDI as well as CDI. They act at the distal tubules and also hinder cotransport of salt as well as chloride. Long term administration decreases the extracellular volume, permitting water and sodium reabsorption at the proximal tubules. Inevitably, there is a decrease in urine production. Lithium-induced NDI demonstrated that chronic hydrochlorothiazide therapy up-regulates NCC as well as ENa C, which improves salt reabsorption among the distal sections of the nephron. Treatment with chlorothiazide (5 - 10 mg/kg/day) or hydrochlorothiazide (1 - 2 mg/kg/day) was safe and effective, with a hospital stay for hypernatremia required in only 1 out of 13 patients. Therapy with chlorothiazide or hydrochlorothiazide lowered water intake by 23 - 40% in patients with NDI. The administration of a combination of amiloride and hydrochlorothiazide gave better results than hydrochlorothiazide alone and also prevented urinary potassium alkalosis and hypokalemia. Though hydrochlorothiazide reduces urine quantity by approximately 50%, the side effects of hypokalemia and hypovolemia should make them moderately used in gestational DI [18]. Amiloride is a diuretic that might be beneficial in the therapy of some cases of lithium-induced NDI [19].

Indomethacin is a nonsteroidal anti-inflammatory drug which has antidiuretic activity.

NDI managed with indomethacin that persisted after lithium therapy was discontinued. When used along with desmopressin, there was a significant reduction in polyuria. A person that did not react to desmopressin, thiazides, as well as amiloride for the treatment of lithium-induced NDI, reacted quickly to indomethacin with a decrease in urine output from 24 L/day to 12 L/day, and eventually to 2 L/day. Indomethacin efficiently treated streptozocin-induced NDI, with a rapid modification in polyuria that was independent of the glomerular filtration rate. Indomethacin may impair renal feature as well as have severe negative results such as intestinal blood loss, hyperkalemia, hypernatremia, and elevated creatinine [20].

Prognosis

The prognosis of CDI due to neoplasm or inflammatory condition depends on that of the primary diseases. On the other hand, the prognosis of idiopathic CDI patients is taken into consideration to be similar to that of volunteers without CDI, as long as the individuals can drink water as required. However, the adipic CDI patients are connected with significant morbidity, and also the incidence of serious infections needing a hospital stay and the mortality rate is higher in adipsic compared to non-adipsic CDI patients [21].

Conclusion

DI is a disorder that can be incapacitating. It is essential to determine the etiology of DI to be able to treat it properly. Desmopressin has been shown as a safe and also efficient medication for the control of CDI in the long term. Newer formulations including oral and ODT solutions are beneficial over nasal preparations as they are useful in people that are senior, mentally, or physically handicapped or have chronic rhinitis.

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