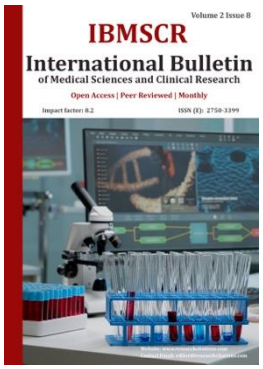

ETIOLOGY AND SPECIFIC FEATURES OF DIABETES INSIPIDUS

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Annotation : Diabetes insipidus (DI) is an endocrine condition involving the posterior pituitary peptide hormone, antidiuretic hormone (ADH). ADH exerts its effects on the distal convoluted tubule and collecting duct of the nephron by upregulating aquaporin-2 channels (AQP2) on the cellular apical membrane surface. DI is marked by expelling excessive quantities of highly dilute urine, extreme thirst, and craving for cold water. The two main classifications of DI are central diabetes insipidus (CDI), characterized by a deficiency of the posterior pituitary gland to release ADH, and nephrogenic diabetes insipidus (NDI), characterized by the terminal distal convoluted tubule and collecting duct resistance to ADH.

Keywords : diabetes insipidus, nephrogenic diabetes insipidus, antidiuretic hormone, central diabetes insipidus, gestational diabetes insipidus, dipsogenic diabetes insipidus, vasopressin

Diabetes insipidus (DI) is a disorder characterized by a high hypotonic urinary output of more than 50ml per kg body weight per 24 hours, with associated polydipsia of more than 3 liters a day. Central DI results from inadequate secretion and usually deficient synthesis of Arginine vasopressin (AVP) in the hypothalamus or pituitary gland. Besides central DI further underlying etiologies of DI can be due to other primary forms (renal origin) or secondary forms of polyuria (resulting from primary polydipsia). All these forms belong to the Polyuria Polydipsia Syndrom (PPS). In most cases central and nephrogenic DI are acquired, but there are also congenital forms caused by genetic mutations of the AVP gene (central DI) or by mutations in the gene for the AVP V2R or the AQP2 water channel (nephrogenic DI). Primary polydipsia (PP) as secondary form of polyuria includes an excessive intake of large amounts of fluid leading to polyuria in the presence of intact AVP secretion and appropriate antidiuretic renal response.

Etiology

DI can be divided into four main different groups of defects. Central diabetes is the most common type and is due to insufficient AVP production and secretion from the posterior pituitary in response to osmotic stimulation. In most cases this is caused by destruction of the neurohypophysis by pressure or infiltration through a variety of acquired or congenital lesions. A second form of DI is caused by reduced renal sensitivity to the antidiuretic effect of physiological levels of AVP. This nephrogenic variant of the syndrome can be caused by an acquired or genetic defect in renal mechanisms for urine concentration. A third etiology of the clinical syndrome is Primary polydipsia. It is caused by physiological suppression of AVP secretion by excessive, osmotically-independent fluid intake. It is referred to as Primary polydipsia to differentiate it from the other types of DI, where secondary polydipsia occurs in response to water loss. Besides to psychiatric patients and health enthusiasts presenting with Primary polydipsia, there is a small subgroup of patients with Primary polydipsia commonly

referred to as having dipsogenic DI, in which polydipsia appears to be due to an abnormally low thirst threshold. The fourth type is the gestational DI, that is caused by an increased degradation of AVP by the placenta enzyme vasopressinase, leading to a similar presentation as can be seen in central DI. In some cases, patients may have a predisposition to its occurrence by pre-existing, subclinical deficiency in AVP.

The most common type, central diabetes insipidus (CDI), is due to a deficiency in ADH production. This is primarily caused by acquired factors such as traumatic brain injuries (TBI), infections, loss of blood to the posterior pituitary or hypothalamus, neurosurgery, and tumors. 25% of CDI cases involve hypothalamo-neurohypophyseal axis lesions. The pituitary gland, the pituitary stalk, and the hypothalamus are quite vulnerable to injury from head trauma, which can result in 16% of CDI cases. 20% of CDI cases are iatrogenic post neurosurgery. Although rare, there are cases of genetic defects in ADH synthesis. These defects can be inherited as autosomal dominant, autosomal recessive, or X-linked recessive traits that can result in CDI. The inherited/familial causes account for 1% of CDI cases. The specific gene mutation most commonly seen is the loss of the AVP gene located on chromosome 20p13. In addition to the genetic mutation in the AVP gene, there is another rare autosomal recessive disorder that involves DI. This mutation is in the WFS1 gene, which encodes for wolframin. This protein has been shown to function as a transmembrane endoplasmic reticulum element that acts as a calcium channel as well as maintaining the endoplasmic reticulum in pancreatic beta cells. The exact mutation in WFS1 leads to Wolfram Syndrome, characterized by AVP-sensitive DI, insulin-dependent juvenile-onset diabetes mellitus, optic atrophy, and sensorineural deafness. DI occurs in ~70% of patients and all four disorders present together in ~50% of patients. Unfortunately, patients presenting with Wolfram Syndrome only survive until the 3rd or 4th decade of life.

Nephrogenic diabetes insipidus (NDI) is related to the terminal distal convoluted tubule and collecting duct's insensitivity to circulating ADH. Most adults with NDI have an acquired abnormality, with the most common causes being lithium therapy or other medications, hypercalcemia, hypokalemia, protein malnutrition, aging, and release of a ureteral obstruction. Lithium therapy is a common practice in treating bipolar disorders. Unfortunately, about 40%-55% of individuals treated with lithium develop the nephrogenic class of DI and can be observed as early as eight weeks after onset of treatment. Lithium is filtered and reabsorbed by the kidney similar to that of sodium and can enter into the collecting duct principal cells. Accumulation of cytotoxic concentrations of lithium within the cells ultimately leads to a decrease in AQP2 expression. In addition to lithium therapy resulting in DI, there are reports of other medications causing drug-induced NDI. Foscarnet and clozapine have also been shown to elicit NDI, however, these manifestations are rare and far less common than DI association with lithium. In rare circumstances, the cause of NDI is congenital involving the AQP2 gene. These congenital forms include an X-linked pattern of inheritance (the most common), an autosomal recessive, or an autosomal dominant pattern.

In addition to the two major forms of DI mentioned above, the two less common forms are dipsogenic DI and gestational DI. Dipsogenic DI, also known as primary polydipsia, is classified as having an abnormally low osmotic thirst threshold. This leads to increased fluid intake causing physiological suppression of ADH secretion, excretion of large amounts of dilute urine exceeding 40-50 ml/kg body weight, and risk of hyponatremia. In patients with dipsogenic DI, the desire for water decreases after drinking water, but quickly rebounds due

to a disrupted oropharyngeal regulation, which is responsible for the physiological suppression of water intake. Unlike nephrogenic and central DI, there is an increase in body water leading to a decrease in plasma osmolarity, but like nephrogenic and central DI there is a decrease in ADH secretion and urine concentration. This form of DI is most commonly seen in patients with psychotic or neurodevelopmental disorders. There are multiple underlying etiologies contributing to the development of dipsogenic DI. These include damage to the hypothalamus, brain injuries, infiltrative or vascular diseases, hippocampus deformations, lesions to certain brain regions such as the amygdala, and stress-reducing behaviors, which release dopamine leading to the secretion of ADH resulting in excessive thirst. Genetics may also play a role in primary polydipsia, where a polymorphism in the orexin 1 receptor has been linked to DI.

Gestational DI occurs due to the rise in placental vasopressinase during pregnancy. Vasopressinase is an enzyme that degrades ADH resulting in dilute polyuria. Placental trophoblasts produce vasopressinase, and the amount produced is proportional to placental size, with twins and multiple pregnancies having the highest levels. Vasopressinase can be detected at 10 weeks and increases approximately 300-fold throughout the pregnancy. Vasopressinase levels are at their highest at the end of the second trimester or beginning of the third, which is when gestational DI most commonly occurs. Women with asymptomatic DI prior to pregnancy may become symptomatic once pregnant because their bodies cannot produce ADH at a rate to replace the ADH being degraded. These patients experience symptoms earlier and with every pregnancy. During pregnancy, the anterior pituitary becomes enlarged, which compresses the posterior pituitary resulting in decreased release of ADH similar to CDI. The renal tubule also becomes resistant to ADH, as seen in NDI. Progesterone and corticosteroid levels in pregnant women increase causing ADH levels to decrease. Additionally, pregnant women may experience acute fatty liver and HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, which impairs liver function allowing vasopressinase activity to increase because it is not being properly degraded. Gestational DI can lead to complications in pregnancy, such as increasing the risk of pre-eclampsia.

Clinical manifestations of diabetes insipidus

The clinical manifestation of DI, i.e. excessive renal excretion of large volumes of diluted urine is caused by a decrease in the secretion or action of AVP, which is encoded by the AVP gene located on the short arm of chromosome 20 (20p13). The main clinical symptoms of DI are polyuria and polydipsia resulting from the underlying impairment of urinary concentrating mechanisms. They do not necessarily differ in their specific manifestation between DI and Primary polydipsia. Patients with central DI more frequently complain about nocturia and a sudden onset of symptoms, resulting from the fact that urinary concentration can often be maintained quite well until the residual neuronal capacity of the hypothalamus to synthesize AVP drops below the border of 10-15% of normal, after which urine output increases dramatically. Under normal circumstances the thirst mechanism in DI patients is intact, so that the patients are able to maintain normal serum osmolality and volume status with no other clinical symptoms besides polyuria and polydipsia. But especially those patients with DI with underlying osmoreceptor defect syndromes can develop varying degrees of dehydration and hyperosmolality, if renal water losses cannot be fully compensated by fluid intake. Resulting symptoms can be divided into two groups. Those symptoms produced by

dehydration, which are mainly cardiovascular and include hypotension, acute tubular necrosis secondary to renal hypoperfusion, and shock and those caused by hyperosmolality, which are mostly neurologic and demonstrate the degree of brain dehydration as a result of osmotic water shifts from the intracellular compartment. The clinical manifestations can vary from unspecific symptoms such as irritability and cognitive dysfunction to more severe manifestations such as disorientation, reduced consciousness, seizure, coma, focal neurologic deficits and cerebral infarction. Additionally, the incidence of subarachnoid haemorrhage and deep venous thrombosis are increased in patients with hyperosmolality. Another possible consequence of untreated chronic polyuria in hereditary central DI (or nephrogenic DI) is the dilation of the ureters and bladders. This predisposes to vesicoureteral reflux and ascending urinary tract infections, as well as secondary renal failure. Similar to adults, polyuria and polydipsia are the main clinical manifestations in children. Additionally, young children may have severe dehydration, vomiting, constipation, fever, irritability, sleep disturbance, failure to thrive and growth retardation.

Differential diagnosis

When symptoms of urinary frequency, enuresis, nocturia, and/or persistent thirst are present, the possibility of DI should be evaluated after excluding glucosuria by collecting a 24-hour urine on ad libitum fluid intake. If the volume exceeds 50 mL/kg per day (3500 mL in a 70-kg male) and the osmolarity is < 300 mosmol/L, DI is confirmed and the patient should be evaluated further to determine the type. In differentiating among the various types of DI, the history alone may be sufficient if it reveals a likely antecedent such as pituitary surgery. Usually, however, that type of indicator is absent, ambiguous, or misleading and other approaches are needed. Except in the rare patient with hypertonic dehydration under basal conditions, differentiation should begin with a fluid deprivation test. It can be performed on an outpatient basis if the necessary staff and facilities are available. To minimize patient discomfort, avoid excessive dehydration, and maximize the information obtained, the test should be started in the morning and continued with hourly monitoring of body weight, plasma osmolarity and/or sodium concentration, urine volume, and urine osmolarity until either of two endpoints is reached. If fluid deprivation does not result in urine concentration (osmolarity > 300 mosmol/L, specific gravity > 1.010) before body weight decreases by 5% or plasma osmolarity/sodium rise above the upper limit of normal, the patient has severe pituitary or severe nephrogenic DI. These disorders usually can be distinguished by administering desmopressin (0.03 μg/kg SC or IV) and repeating the measurement of urine osmolarity 1–2 hours later. An increase of > 50% indicates severe pituitary DI, whereas a smaller or absent response is strongly suggestive of nephrogenic DI.

Conversely, if fluid deprivation results in concentration of the urine, severe defects in AVP secretion and action are excluded and the question becomes whether the patient has partial pituitary DI, partial nephrogenic DI, or primary polydipsia. The maximum levels of urine osmolarity achieved before and after desmopressin injection are of no help in this regard because the values in the three groups vary widely and overlap owing to impairment of renal concentrating capacity caused by polyuria per se. Therefore, another approach is needed to differentiate among them. The easiest and least expensive method is to measure plasma AVP before and during the fluid deprivation test and analyze the results in relation to the concurrent plasma and urine osmolarity. This approach invariably differentiates partial nephrogenic DI from partial pituitary DI and primary polydipsia. It also differentiates partial

pituitary DI from primary polydipsia if plasma osmolarity and/or sodium are clearly above the normal range when the hormone is measured. However, the requisite level of hypertonic dehydration may be difficult to produce by fluid deprivation alone when urine concentration occurs. Therefore, it is usually necessary to continue the fluid deprivation and infuse hypertonic (3%) saline at a rate of 0.1 mL/kg per min until plasma osmolarity/sodium measured every 20 to 30 minutes reach or slightly exceed the upper limit of normal. At that point, the measurement of plasma AVP should be repeated and the result related to the plasma osmolarity/sodium.

An alternative method of differential diagnosis is MRI of the pituitary and hypothalamus. In most healthy adults and children, the posterior pituitary emits a hyperintense signal in T1-weighted midsagittal images. This “bright spot” is almost always present in patients with primary polydipsia but is invariably absent or abnormally small in patients with pituitary DI. It is usually also small or absent in nephrogenic DI presumably because of high secretion and turnover of AVP. Thus, a normal bright spot virtually excludes pituitary DI, argues against nephrogenic DI, and strongly suggests primary polydipsia. Lack of the bright spot is less helpful, however, because it is absent not only in pituitary and nephrogenic DI but also in some healthy adults and patients with empty sella who do not have DI or AVP deficiency. The other way to distinguish among the three basic types of DI is a closely monitored trial of desmopressin therapy.

Treatment

The signs and symptoms of uncomplicated pituitary DI can be eliminated completely by treatment with desmopressin (DDAVP), a synthetic analogue of AVP. DDAVP acts selectively at V2 receptors to increase urine concentration and decrease urine flow in a dose-dependent manner. It is also more resistant to degradation than is AVP and has a three- to fourfold longer duration of action. Desmopressin can be given by IV or SC injection, nasal inhalation, or oral tablet. The doses required to control pituitary DI completely vary widely, depending on the patient and the route of administration. However, they usually range from 1–2 μg qd or bid by injection, 10–20 μg bid or tid by nasal spray, or 100–400 μg bid or tid orally. The onset of action is rapid, ranging from as little as 15 minutes after injection to 60 minutes after oral administration. When given in doses sufficient to normalize urinary osmolarity and flow completely, desmopressin produces a slight (1–3%) increase in total body water and a commensurate decrease in plasma osmolarity and sodium concentration that rapidly eliminates thirst and polydipsia. Consequently, water balance is maintained and hyponatremia does not develop unless the osmoregulation of thirst is also impaired or fluid intake is excessive for another reason such as a misconception about of desmopressin. If resistance is partial, it may be overcome by tenfold higher doses, but this treatment is too expensive and inconvenient to be useful chronically. However, treatment with conventional doses of a thiazide diuretic and/or amiloride in conjunction with a low-sodium diet and a prostaglandin synthesis inhibitor (e.g., indomethacin) usually reduces the polyuria and polydipsia by 30–70% and may eliminate them completely in some patients. Side effects such as hypokalemia and gastric irritation can be minimized by the use of amiloride or potassium supplements and by taking medications with meals.

Conclusion

Decreased secretion or action of AVP usually manifests as diabetes insipidus, a syndrome characterized by the production of abnormally large volumes of dilute urine.

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