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A Comprhensive Review on Diabetes Insipidus

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ABSTRACT

Antidiuretic hormone and posterior pituitary peptide hormone are both involved in the endocrine disorder known as diabetes insipidus (DI) (ADH). By activating aquaporin-2 channels (AQP2) on the cellular apical membrane surface, ADH has an impact on the distal convoluted tubule and collecting duct of the nephron. Extreme thirst and a need for cold water are characteristics of DI. Excessively large amounts of extremely diluted urine are also discharged. Central DI caused by reduced arginine vasopressin (AVP) secretion can be caused by traumatic brain damage, surgery, or tumours, but nephrogenic DI caused by inability of the kidney to respond to AVP is typically hereditary.The two less typical categories are gestational DI, which is characterised by an increase in placental vasopressinase levels during pregnancy, and dipsogenic DI, which is characterised by excessive thirst brought on by a low osmotic threshold. DI treatment is based on the illness categorization, but if treated improperly, significant consequences may develop. Maintaining fluid intake in advance of fluid loss is the most crucial stage in symptom management, with a focus on maintaining quality of life. The prescription of synthetic ADH, desmopressin, is the most frequent treatment for CDI and gestational DI (DDAVP).Although more difficult, nephrogenic treatment necessitates stopping drugs and adhering to a renal-friendly diet in order to avoid hypernatremia. The mainstays of treatment for dipsogenic DI include behavioural therapy aiming at controlling water intake and/or the use of pharmacological antipsychotic medication. Thiazide diuretics have a paradoxical treatment for the central and nephrogenic subtypes of DI.

KEY WORDS: DIABETES INSIPIDUS, ANTIDIURETIC HORMONE, ARGININE VASOPRESSIN, POLYURIA, POLYDIPSIA

I. INTRODUCTION

Diabetes insipidus (DI) belongs to a class of acquired or hereditary polyuria and polydipsia illnesses. The most frequent definition of DI is a urine volume of more than 3-3.5 litres in a 24-hour period in adults with a urine osmolality of less than 300 mOsmol/kg. It is related with inadequate arginine vasopressin (AVP) or antidiuretic hormone (ADH) secretion or renal response to AVP. Urine volume far exceeds 3-3.5 litres in a 24-hour period in the majority of DI cases.[1] The major hormone of diabetes insipidus is the posterior pituitary hormone ADH, which is one of the main determinants of water homeostasis inside the body. The kidney, the antidiuretic hormone's target organ, responds by raising the osmolality of urine. The two main negative feedback mechanisms that regulate ADH secretion are osmoregulation and baroregulation.[2]The osmoreceptors of the hypothalamus can detect extremely minute changes, even those of less than 1% in plasma osmolality. The posterior pituitary gland releases ADH as a result of the detection of an increase in osmolality. Regarding baroreceptors that are activated by a drop in blood volume, a comparable response can be investigated. ADH is released from the hypothalamus with the help of its transport protein carrier, neurohypophysin II (NPII), and moves to the posterior pituitary where it is stored until released. The deviation in blood volume necessitates a volume difference of roughly 5%–10%.ADH is a water-soluble peptide hormone that is released into the bloodstream after being triggered by a change in plasma osmolality or the

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stimulation of baroreceptors. It then acts on its target by binding to the aquaporin-2 receptors (AQP2) in the basolateral membrane of the collecting duct.[3]When it binds to the receptor, it starts the Gs-adenylyl cyclase system, which raises the levels of cAMP inside the cell. Following the activation of protein kinase A by this rise in cAMP levels, produced AQP2 channels are phosphorylated. The phosphorylation causes AQP2 to be inserted onto the cell's apical membrane surface. It has been determined that the renal collecting duct would continue to be substantially water-impermeable without this insertion of AQP2.The kidney filtrate's water content is reduced by AQP2 in order to concentrate the urine. In the case of DI, water is unable to freely flow along an osmotic gradient from the nephron lumen into the cells of the collecting duct, resulting in the outflow of diluted urine. ADH has the ability to lower urine output to 0.5 ml/min, or roughly 700–800 ml/day, and raise urine osmolality to around 1,200 mOsmol/kg. ADH levels in the blood decrease as the body achieves water balance, and the number of AQP2 channel proteins introduced into the apical plasma membrane is down-regulated. [3,4].

EPIDEMIOLOGY

DI is a condition that affects only 1 in 25,000. DI can manifest at any age, and both men and women are equally likely to develop it. The etiology determines the age of presentation. Only 10% of DI is inherited. 90% of cases of congenital NDI are caused by X-linked nephrogenic DI (NDI), which happens 4–8 times per million live male births. 10% of the remaining cases had autosomal NDI as their cause.[1]

TYPES OF DIABETES INSIPIDUS

The two major forms of DI are central (neurogenic) and nephrogenic. In addition to the two major forms of DI, the two less common forms are dipsogenic DI and gestational DI.

A. Central diabetes insipidus

The most prevalent kind, central diabetes insipidus (CDI), is brought on by a shortage in ADH synthesis. Acquired factors such traumatic brain injuries (TBI), infections, blood loss to the posterior pituitary or hypothalamus, neurosurgery, and tumours are the main causes of this. The pituitary gland, the pituitary stalk, and the hypothalamus are highly prone to injury from head trauma, which might result in 16% of CDI cases. Hypothalamo-neurohypophyseal axis injuries account for 25% of CDI cases. After neurosurgery, 20% of CDI infections are iatrogenic. There are instances of hereditary abnormalities in ADH synthesis, however these are uncommon.[4] The deletion of the AVP gene, which is located on chromosome 20p13, is the specific gene mutation that is most frequently observed. There is another uncommon autosomal recessive condition including DI in addition to the genetic mutation in the AVP gene. The WFS1 gene, which produces wolframin, has this mutation. It has been demonstrated that this protein maintains the endoplasmic reticulum in pancreatic beta cells and functions as a transmembrane endoplasmic reticulum component that functions as a calcium channel. Wolfram Syndrome, which is caused by a specific mutation in WFS1, is characterised by AVP-sensitive DI, juvenile-onset diabetes mellitus with insulin dependence, optic atrophy, and sensorineural deafness..[5,6]

B. Nephrogenic diabetes insipidus (NDI)

Because of the elevated plasma osmolality in nephrogenic diabetes insipidus, the posterior pituitary is hyperstimulated and produces an adequate amount of ADH, but the kidneys are unable to respond by producing maximally concentrated urine.[7] The majority of people with NDI have an acquired anomaly, and the most frequent reasons are ureteral blockage release, ageing, protein deficiency, hypercalcemia, hypokalemia, lithium therapy, and other drugs. Bipolar disorder is frequently treated with lithium treatment. Unfortunately, the nephrogenic subtype of DI can appear as early as eight weeks following the start of treatment in roughly 40%–55% of people on lithium. Similar to how sodium is filtered and reabsorbed by the kidney, lithium can enter the main cells of the collecting duct. AQP2 expression eventually decreases as lithium concentrations become cytotoxic inside of the cells.[8,9]

Nephrogenic diabetes insipidus can be characterized by three main disturbances in kidney function:

- Disruption of the corticomedullary osmotic gradient, which is what propels the osmotic water flow from collecting ducts into the interstitial tissue. This can affect the gradient's formation, maintenance, or both.
- An imbalance in the osmotic pressure between the contents of the tubules and the medullary interstitium caused by a problem with either the distal or proximal parts of the ADH-cyclic adenosine monophosphate system.
- Osmotic diuresis, which causes the fluid in the tubules to flow quickly and osmotically

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equilibrate with the medullary interstitium only partially.[7]

C. Dipsogenic diabetes insipidus

It is categorised as having an abnormally low osmotic thirst threshold and is also referred to as primary polydipsia. This causes physiological suppression of ADH secretion, the excretion of significant amounts of dilute urine surpassing 40–50 ml/kg body weight, and a risk of hyponatremia. It also causes an increase in fluid intake. In patients with dipsogenic DI, the physiological suppression of water intake is caused by a disturbed oropharyngeal control, which causes the urge for water to drop after drinking water but quickly return. While there is a drop in plasma osmolarity due to an increase in body water, unlike nephrogenic and central DI, there is also a decrease in ADH secretion and urine concentration. Patients with neurodevelopmental or psychotic illnesses are most likely to experience this type of DI.[10]

D. Gestational diabetes insipidus

The increase in placental vasopressinase during pregnancy causes DI. Vasopressinase is an enzyme that breaks down ADH, causing diluted polyuria as a result. Vasopressinase is generated by placental trophoblasts, and the amount is inversely correlated with placental size, with twin and multiple pregnancies having the highest levels. At 10 weeks, vasopressinase can be found, and it grows by about 300 times throughout the pregnancy. When gestational DI most frequently occurs, around the end of the second trimester or the start of the third, vasopressinase levels are at their peak. Because their systems are unable to manufacture ADH quickly enough to replace the ADH that is being degraded, women with asymptomatic DI before to becoming pregnant may develop symptoms once they become pregnant. [11,12].As demonstrated in NDI, the renal tubule also develops ADH resistance. ADH levels fall as progesterone and corticosteroid levels rise in pregnant women. Additionally, HELLP syndrome (hemolysis, high liver enzymes, and low platelet count), which inhibits liver function and causes vasopressinase activity to rise because it is not being effectively destroyed, may be experienced by pregnant women. Pregnancy consequences from gestational DI can include an elevated risk of pre-eclampsia.[2]

ETIOLOGY

1. The causes of central diabetes insipiduscan be divided into three major categories.

- Trauma to the head, operations, or primary or metastatic cancers that cause damage to the hypothalamo-neurohypophyseal area. More neurons of the hypothalamo-neurohypophyseal tract are killed by injury to the proximal part of this sensitive region than by distal lesions. Meningitis, encephalitis, radiation to the brain, neoplastic or autoimmune disease, cerebral edoema, intracranial haemorrhage, hypothalamic or pituitary surgery.[7]
- Idiopathic conditions may actually have a known cause. There have been reports of atrophic neurohypophyses, as well as supraoptic and paraventricular nuclei, in the limited autopsy series done on patients with this kind of central diabetes insipidus. ADH-secreting hypothalamic neurons have been targeted by circulating antibodies in other cases, raising the possibility that this condition has an autoimmune component.[13]
- Genetic. Recently, a mutation in the neurophysin II coding area of the ADH gene has been linked to some idiopathic forms of central diabetes insipidus.5,6 Exons 1 and 3 are normal, but at nucleotide 1884 in exon 2, thymine is exchanged for guanine. The ADH molecule then experiences a valine for glycine substitution as a result of this. The presence of both normal and mutant alleles in affected individuals shows that this mutation is heterozygous.The clinical condition of diabetes insipidus and cell death are caused by an accumulation of aberrant ADH in the posterior pituitary cells. The signal peptide gene for ADH-neurophysin II/copeptide precursor may contain a valine-to-alanine substitution, which could result in another type of familial central diabetes insipidus.[13]

2. The many causes of nephrogenic diabetes insipidus can be divided into two categories: acquired and familial Acquired forms of nephrogenic diabetes insipidus

- More often than familial forms, acquired forms. Because of illness (the most common cause), medications, or other factors, the kidney is physically or functionally altered, either permanently or briefly, making it less responsive to ADH. Hypokalemia, hypercalcemia, various forms of renal illness, and sickle cell anaemia are just a few of the systemic factors that can cause acquired nephrogenic diabetes insipidus. Hypokalemia. Polyuria, polydipsia, and a renal concentrating defect that is resistant to ADH are frequently brought on by potassium depletion as a result of inadequate dietary intake or losses (such as those caused by gastroenteritis.[14]Two processes, including a change in the production and

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maintenance of the medullary osmotic gradient and resistance of the collecting ducts to the hydro-osmotic impact of ADH, have been postulated to explain the diuresis seen with potassium deprivation. Chronic hypercalcemia may cause renal interstitial calcification and fibrosis along with subsequent anatomic renal concentrating mechanism disturbance, resulting in excessively diluted urine production. Sickle cell anaemia and advanced chronic renal failure both have defects in the renal concentrating capacity.2-4 Pregnancy is another cause because vasopressinase, which the placenta produces during pregnancy, can degrade ADH too quickly. Usually going away 4 to 6 weeks after delivery, this type of ADH deficiency frequently recurs with subsequent pregnancies.[7,14]

✓ Acquired nephrogenic diabetic insipidus can be brought on by a number of commonly used medications. Because lithium salts cause polydipsia and polyuria in addition to the underlying chronic nephrogenic diabetes insipidus, chronic lithium medication can also cause transitory central diabetes insipidus. For the chronic syndrome of incorrect ADH secretion, lithium salts have been suggested as a treatment; however, demeclocycline has been found to be more efficient.[13]Dermatologists frequently use demeclocycline, a tetracycline antibiotic, to treat acne. Demeclocycline causes polyuria and polydipsia at high doses (900–1,200 mg/day). The full recovery of renal function typically takes several weeks after the medicine is stopped using, and these adverse effects may not appear in the first days or weeks of use. Amphotericin B, a strong antifungal medication, is nephrotoxic. Both lithium salts and demeclocycline are thought to impact renal function by disrupting some portion of the proximal component of the ADH-cyclic adenosine monophosphate second-messenger pathway. It interferes with the kidney's medullary osmotic gradient's formation and maintenance. The cellular response to ADH appears to be compromised by gentamicin.By impairing microtubule activity, colchicine prevents the second messenger from acting. Foscarnet, a drug used to treat cytomegalovirus infection, has recently been shown to cause nephrogenic diabetes insipidus in some patients. Loop diuretics have also been shown to worsen renal function in some cases.[14]

✓ Familial nephrogenic diabetes insipidus is an uncommon condition that can be brought on by one of two genetic flaws. mutations in the V2 receptor. ADH type 2 receptor (V2 receptor) gene mutations lead to an X-linked variant of the illness. The V2 receptor gene has more than 60 distinct disease-causing mutations found in it13. Aquaporin-2 mutations. An autosomal-recessive version of the condition, and occasionally an autosomal-dominant form, are brought on by mutations in the gene encoding the ADH-dependent water channel aquaporin-2. Incorrect fluid exchange in the distal collecting system and polyuria are caused by the conformational shift in the aquaporin-2 channel.[15]

3.The emergence of dipsogenic DI is caused by a variety of underlying etiologies. These include lesions to specific brain areas, such as the amygdala, damage to the hypothalamus, brain injuries, infiltrative or vascular disorders, hippocampal malformations, and stress-relieving behaviours, which release dopamine and cause the release of ADH, which results in excessive thirst. In primary polydipsia, where a polymorphism in the orexin 1 receptor has been associated to DI, genetics may possibly be at play.[2]

CLINICAL MANIFESTATIONS

A clinical examination may offer crucial hints about potential underlying disorders. The age at which symptoms appear and the pattern of fluid intake may affect future diabetes insipidus research. Young children may also experience severe dehydration, vomiting, constipation, fever, irritability, disturbed sleep, failure to thrive, and growth retardation in addition to the main symptoms of persistent polyuria and polydipsia. In children, nocturia frequently manifests as enuresis.[16]Patients with early onset of mild polyuria and polydipsia, particularly those under the age of 10, typically experience symptoms that increase with age, while it is also possible that complete CDI manifests from the neonatal stage. Individual differences among these patients, such as the rate of production of the mutant precursor, the intensity of neurohypophyseal stimulation, individual susceptibility to the toxic effect of the mutant precursor, the capacity to degrade mutant precursors, and variations in the secretory reserve capacity or in the development of the gla, may account for the wide variation in the age of onset and the severity of the AVP deficiency among patients with the same mutation.The potential diabetes insipidus complications include:

- ❖ Chronic dehydration
- ❖ Tachycardia
- ❖ Decreased temperature
- ❖ Hypotension
- ❖ Weight loss
- ❖ Fatigue

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- ❖ Headaches
- ❖ Kidney damage
- ❖ Brain damage[17]

DIAGNOSIS

In order to diagnose diabetes insipidus, it is crucial to distinguish between polyuria and pollakiuria as well as to rule out other conditions like uncontrolled diabetes mellitus, hypercalcaemia, or hypokalaemia. Blood tests A blood test can measure your sodium levels as well as the quantity of various substances in your blood, which can aid in the diagnosis. Water withdrawal test. The water deprivation test (Hare-Hickey test) and desmopressin challenge test assess the capacity of the CNS to create AVP and the kidney's response to it. Confirmation of polyuria requires a 24-hour urine volume. Hourly measurements of body weight and urine osmolality are taken during water restriction until 2-3 samples differ by less than 30 mOsm/kg (or less than 10%), or until the patient loses 5% of body weight.Following the measurement of serum ADH and injection of ADH/desmopressin (5 units), urine osmolality is evaluated 30 to 60 minutes later. The test is discontinued if the patient loses >5% of his/her body weight and/or plasma Na+ surpasses 143 mEq/L and/or urine osmolality increases to normal. Desmopressin-induced responses allow for the separation of CDI and NDI. tests that stimulate. During these tests, your body is stimulated to make vasopressin using an intravenous solution, and the blood level of copeptin, a chemical that rises when vasopressin does, is then measured. Results may show the existence of primary polydipsia, a disease that can lead to excessive hydration, or diabetes insipidus.[18,19] To create images of the brain tissues, an MRI uses magnets and radio waves. Only a small percentage of magnocellular neurons degenerate, and intact cell bodies are able, over the course of weeks to months, to regenerate new axonal terminals at the level of the portal vessels of the median eminence. Proximal lesions account for 30% to 40% of all cases of posttraumatic and postoperative diabetes insipidus. When determining the functional importance of the lesion, it is frequently beneficial and required to pinpoint the anatomical location of the area of neuronal damage in the brain. Pituitary and hypothalamus magnetic resonance imaging is used for this.[7].Differential diagnosis include Hypercalcemia, Hypokalemia, Sickle cell anemia, Histiocytosis, Diabetes mellitus

TREATMENT

The patient's quality of life must be improved by DI treatment. Whether or whether symptoms can be completely relieved or treated depends on what caused the disease in the first place. There are a few first-line therapies that support maintaining fluid balance for both central and nephrogenic DI. It is crucial to always have access to water in order to avoid being severely dehydrated too rapidly. Thiazide diuretics, which inhibit the NaCl cotransporter in the renal distal convoluted tubule, are a paradoxical medication used to manage CDI and NDI.This area of the nephron is thought to be a part of the diluting segment since it is impervious to water. Therefore, it is unlikely that thiazide diuretics' ability to preserve water is due to a direct impact on the distal convoluted tubule.[20,21]

Treatment of central diabetes insipidus include Water in sufficient quantity, it will correct any metabolic abnormality due to excessive dilute urine, ADH replacement.

- For long-term treatment of central diabetes insipidus, desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP) has recently become the preferred medication. It can be administered intravenously, orally, or parenterally. The recommended beginning dose for all dosage forms is 10 mg at bedtime to treat nocturia. If symptoms last throughout the day, an additional morning dose may be administered. The duration of effect of this synthetic peptide is well reproducible in an individual. As a result, depending on the level of polyuria, desmopressin dosage and scheduling should be altered separately.
- The anti-diabetic medication chlorpropamide (Diabinese) reduces the clearance of solute-free water, but only if the neurohypophysis still has some secretory capability. Its antidiuretic effect is probably the result of increasing the sensitivity of the collecting duct epithelium to low levels of circulating ADH.Carbamazepine (Tegretol), an anticonvulsant, reduces the sensitivity of the osmoregulatory system of ADH secretion and simultaneously raises the sensitivity of the collecting duct to the hydro-osmotic action of the hormone.
- The current treatment of choice for central diabetes insipidus is clofibrate (Atromid-S), a lipid-lowering Desmopressin. When used on individuals with incomplete central diabetic insipidus, the agent promotes residual ADH

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production. In cases of partial central diabetes insipidus, clofibrate, carbamazepine, and chlorpropamide can all be used.

- Contrary to popular belief, thiazide diuretics can be used to treat central diabetic insipidus. They work by causing the distal tubule to absorb less sodium and chloride, allowing the proximal tubule to absorb more sodium and, consequently, more water. It's crucial to keep an eye on the treatment's effectiveness after beginning one of the aforementioned medications. Monitoring electrolyte readings makes this simple to do.[2,7]

A different regimen is required for the treatment of nephrogenic diabetes insipidus compared to the treatment of central diabetes insipidus. ADH is ineffective in treating nephrogenic diabetes insipidus; instead, hypokalemia and hypercalcemia must be corrected, and any medications that may be contributing to them must be stopped. To lessen the supply of filtrate to the nephron segments that dilute the filtrate, thiazide diuretics are used with minor salt restriction. They work by reducing the distal tubule's capacity to absorb sodium and chloride, allowing the proximal tubule to absorb more sodium and, in turn, more water.[7]

II. CONCLUSION

CDI is brought on by a deficit in the posterior pituitary gland's ability to secrete ADH. The collecting duct's tubular cells no longer respond to the effects of ADH in NDI. ADH deficit can be used to identify CDI, dipsogenic DI, and GDI. An abnormally low osmotic thirst threshold, which causes excessive fluid consumption, is the cause of dipsogenic DI. An increase in placental vasopressinase, which causes the mother's ADH to degrade, is a hallmark of GDI. The primary methods for diagnosing the various forms of DI are the measurement of urine osmolality after water deprivation, vasopressin response, and copeptin measurement after osmotic stimulation. With the help of copeptin and urine osmolality after water deprivation and DDAVP administration, CDI and NDI can be diagnosed.The diagnosis of CDI may potentially benefit from a brain MRI. When there is an excretion of diluted urine with an aberrant osmotic thirst threshold, dipsogenic DI can be diagnosed. By evaluating the osmolarity of the urine and serum, GDI can be diagnosed. Improving patient quality of life and reducing severe fluid loss are the cornerstones of DI management. In order to prevent dehydration, patients should be advised about travelling and prepared to handle diarrhoea and vomiting. The patient has to have easy access to water, and they should stay away from hot places where they might not always have access to medical assistance. DDAVP is given as part of the treatment for CDI, along with getting enough fluids. Ironically, thiazide diuretics can be used to treat both CDI and NDI.The first step in treating NDI is to stop using the problematic substance, like lithium. It should be emphasised that NDI does not respond to DDAVP administration, nor does dipsogenic DI. The main treatment for dipsogenic DI is on behavioural counselling to decrease water intake and, if necessary, the use of an antipsychotic drug. The main GDI therapeutic option is DDAVP. Each type's prognosis is often very good because patients' quality of life is significantly enhanced with effective treatment.

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