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Review On Diabetes Insipidus

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1.Abstract:

Many disorders affecting the hypothalamic-neurohypophyseal system can lead to central diabetes insipidus (CDI). Germininoma/craniopharyngioma, Langerhans cell histiocytosis (LCH), vascular, autoimmune, or local inflammatory diseases; trauma from surgery or an accident; sarcoidosis; metastases; and midline cerebral and cranial malformations are among the known causes. Rarely, X-linked recessive, autosomal dominant, or autosomal recessive genetic abnormalities in vasopressin synthesis may be the underlying cause. Given that the underlying condition requires long-term follow-up, the diagnosis is difficult and causes anxiety in both patients and parents. The process of achieving an accurate etiological diagnosis involves a number of steps, beginning with clinical observations and moving on to more advanced instruments. The most notable findings that have contributed to the diagnosis and understanding of neurohypophyseal functional integrity have been obtained specifically from the MRI identification of pituitary hyperintensity in the posterior part of the sella, which is now recognized as a clear marker of neurohypophyseal functional integrity, and the meticulous examination of pituitary stalk shape and size. If left untreated, diabetes insipidus, which is characterized by large amounts of diluted urine excretion, can be fatal. It can be brought on by one of two essentially distinct defects: either impaired or insufficient renal response to ADH (nephrogenic diabetes insipidus) or inadequate or impaired secretion of antidiuretic hormone (ADH) from the posterior pituitary gland (neurogenic or central diabetes insipidus). Making the distinction is necessary for treatment to be effective. Antidiuretic hormone (ADH), a posterior pituitary peptide hormone, is involved in diabetes insipidus.

Key Words: Central diabetes insipidus _ Langerhans cell histiocytosis _Pituitary stalk _ Vasopressin central diabetes insipidus.

2.Introduction : Polyuria and polydipsia are the hallmarks of diabetes insipidus (DI), a water balance disorder. It has been reported that the prevalence is roughly 1:25,000, and it can happen at any age. Antidiuretic hormone (ADH) and arginine vasopressin (AVP) secretion or action can be affected by acquired (90%) or genetic (10%) factors. In the endocrine and neurosurgical units, DI is not as uncommon as it is in general practice. Significantly increased thirst and urination are not only uncomfortable, but in extreme cases they raise the risk of volume depletion and hypernatremia. Using the terms "diabetes insipidus," "central diabetes insipidus," "nephrogenic diabetes insipidus," "psychogenic polydipsia," "vasopressin," and "desmopressin."

3.CENTRAL DIABETES INSIPIDUS: Any illness that affects the synthesis, transport, or release of ADH leads to central diabetes insipidus. It impacts all age groups and affects both sexes equally, with the most common age of

onset falling between 10 and 20 years old.Aside from the symptoms of the underlying disease that initially damaged the neurohypophyseal system, polyuria and polydipsia are the primary indicators of poor health. Even a brief period of time without water causes rapid dehydration and obsessive thirst. The patient is even awakened in the middle of the night by the intense thirst**.** A more moderate partial form of the disease with only moderately excessive diuresis is more common than the disease's complete form. The normal value of 280–295 mOsm/kg for the osmotic concentration of plasma is usually not much higher than 290 mOsm/kg, as long as the patient can still seek water and their thirst center is intact.(1)

Etiology: Nephrogenic and central (neurogenic) DI are the two main types. ADH production is inadequate in the most prevalent type, central diabetes insipidus (CDI). Traumatic brain injuries (TBI), infections, blood loss to the posterior pituitary or hypothalamus, neurosurgery, and tumors are the main acquired factors responsible for this. Lesions in the hypothalamo neurohypophyseal axis are present in 25% of CDI cases. Head trauma can cause injury to the pituitary gland, pituitary stalk, and hypothalamus, accounting for 16% of cases of CDI. After neurosurgery, 20% of CDI cases are iatrogenic.Rarely, genetic defects in the synthesis of ADH can occur. The loss of the AVP gene, which is found on chromosome 20p13, is the particular gene mutation that is most frequently observed. Apart from the AVP gene mutation, DI is also associated with another uncommon autosomal recessive disorder. The WFS1 gene, which codes for wolframin, is the site of this mutation. It has been demonstrated that this protein functions as a transmembrane element of the endoplasmic reticulum in pancreatic beta cells, serving as a calcium channel and preserving the endoplasmic reticulum.(2)

These flaws can be inherited as X-linked recessive traits, autosomal dominant traits, or autosomal recessive traits.The MRI identification of pituitary hyperintensity in the posterior part of the sella now recognized as a clear marker of neurohypophyseal functional integrity—and the careful examination of pituitary stalk shape and size have yielded the most notable findings that have contributed to the diagnosis and understanding of neurohypophyseal functional integrity.(3)

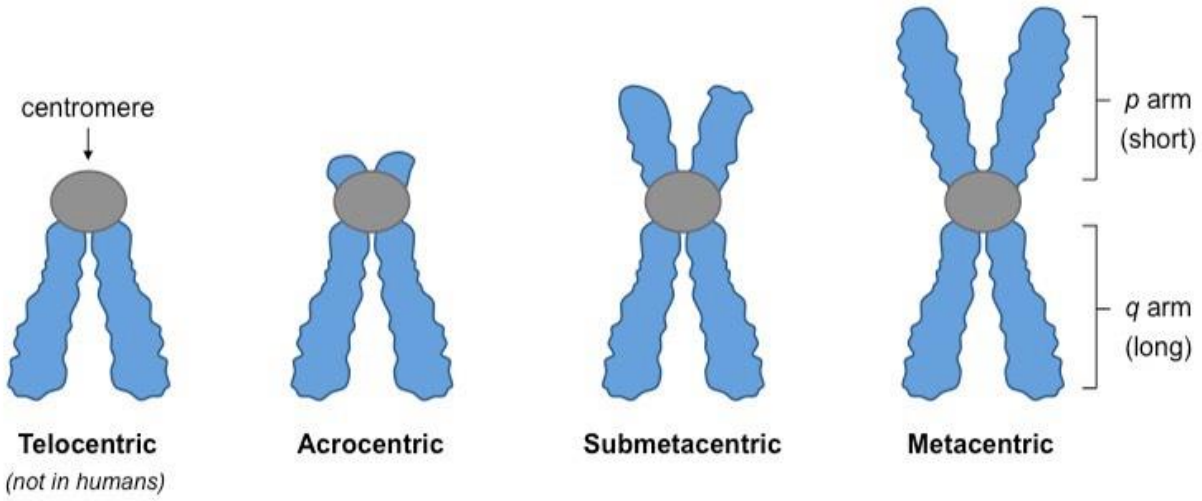

Fig no1: Types of Chromosomes

3.1 Pathogenesis and Pathology:

Anatomy*:* AVP and/or oxytocin are produced by magnocellular neurons found in the posterior pituitary. The paraventricular and supraoptic nuclei contain the cell bodies of magnocellular neurons, and their axons extend to the neurohypophysis, which secretes hormones into the bloodstream. AVP is stored in these axons in sufficient amounts to support basal release for 30–50 days or to permit maximal antidiuresis for 5–10 days.The posterior pituitary receives its vascularization directly from the inferior hypophyseal arteries, whereas the anterior pituitary receives its blood supply from the suprahypophyseal arteries through the hypothalamic-pituitary portal system.(4)

All diseases result in excessive thirst, severe dehydration, and the excretion of large volumes of diluted urine, despite the fact that each disease's initial etiology is unique. Three interconnected factors primarily govern the physiology of water balance in humans. These include the production and secretion of ADH, thirst, and healthy kidney function. ADH release and ADH sensitivity in the terminal distal convoluted tubule and collecting duct are directly impacted by DI. The body goes through a lot of changes if the ADH mechanisms are interfered with. Elevations in serum and urine osmolality, electrolyte imbalances, and water loss all transpire. When the disorder first manifests, low sodium levels indicate primary polydipsia, while hypernatremia with serum sodium levels >145 mEq/L (accepted normal range: 135-145 mEq/L) indicates central or nephrogenic DI.(5)

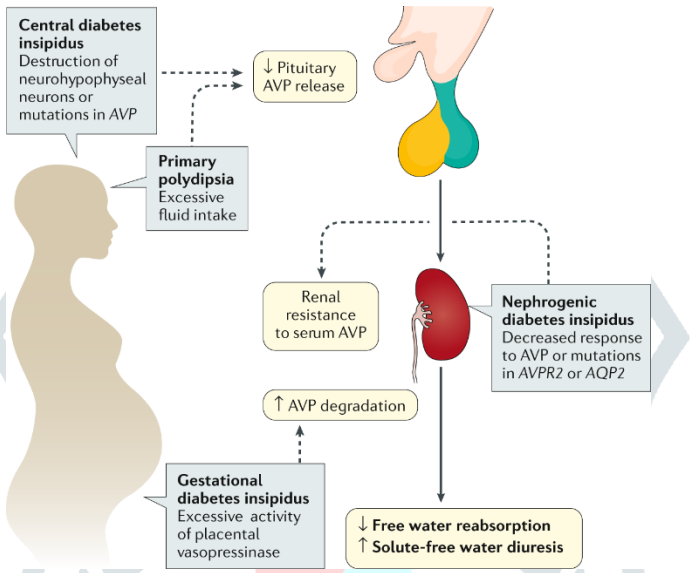

Fig no 2. Pathogenesis of Diabetes insipidus

Fig 2. A type of polyuria–polydipsia syndrome called diabetes insipidus (DI) can be brought on by a number of inherited or acquired lesions or illnesses. Insufficient arginine vasopressin (AVP) generation and/or release in the hypothalamic-neurohypophyseal system in response to osmotic stimulation causes central DI. Hereditary central DI results from mutations in AVP, whereas acquired central DI is brought on by disruption of the neurohypophysis. Nephrogenic DI is caused by the kidneys' inability to respond to AVP. This response can be hereditary (caused by mutations in the genes encoding the water channel aquaporin 2 (AQP2) or the arginine vasopressin receptor 2 (AVPR2)), or acquired (as a side effect of certain medications or due to electrolyte imbalances).

3.2 AVP Biosynthesis*:* The AVP-neurophysin II gene *(AVP-NPII)* is located distally at the short arm of chromosome 20 (20p13). The AVP preprehormone, which is the product of the AVP-NPII gene, is cotranslationally targeted to the endoplasmic reticulum (ER), where signal peptidase cleaves off the signal and core glycosylates the copeptide. Following cleavage, AVP and NPII bind together to form a tetramer, which strengthens AVP's binding affinity for NPII. The propriacursor is packed into neurosecretory granules after the formation of seven disulphide bonds within NPII and one bond within AVP, as well as after glycosylation of the copeptide. During axonal transport to the posterior pituitary, the propriacursor is then cleaved into the product peptides.(6)
The hormone is stabilized by neurophysin during storage and transportation, but copeptin may be crucial for the proper structural formation of the AVP precursor, which is necessary for the hormone's effective proteolytic maturation, according to recent research. The posterior pituitary releases AVP and its protein carrier NPII through calcium-dependent exocytosis in response to axon depolarization brought on by osmoreceptor or baroreceptor stimuli.(7)

3.3 Physiology of Water Homeostasis*:* Thirst, AVP, and kidney function are the three main interrelated determinants that maintain the water balance in healthy humans. Apelipin, a bioactive peptide that is related to ghrelin, another stomach-hypothalamus association, was recently isolated from bovine stomach extracts. It acts on particular receptors found on vasopressinergic neurons and is expressed in the paraventricular and supraoptic nuclei. Apelin inhibits AVP neuron activity and AVP release, acting as a strong diuretic neuropeptide to offset the

effects of AVP. Maintaining body fluids is probably largely dependent on apelin and AVP coexisting in magnocellular neurons as well as their opposing biological effects and regulation.(8)

Urine osmolality is raised when AVP acts on the kidney, which is one of its primary target organs. Through its binding to the V2-receptors in the renal collecting tubular basolateral membrane, it activates the Gs-adenyl cyclase system, leading to an increase in intracellular cyclic 3, 5-adenosine monophosphate (cAMP). The latter causes intracellular vesicles to contain preformed AQP2 water channels, which are then phosphorylated by protein kinase A.(9)

Urine is concentrated because the insertion of AQP2 makes the collecting duct water-permeable, enabling water to freely flow from the nephron lumen into the collecting duct cells along an osmotic gradient. AVP stimulation controls both the synthesis and movement of AQP2 channels.The basolateral membrane contains constitutively aquaporins 3 and 4, which are responsible for the subsequent passage of water from within the cell into the renal interstitium.(10)

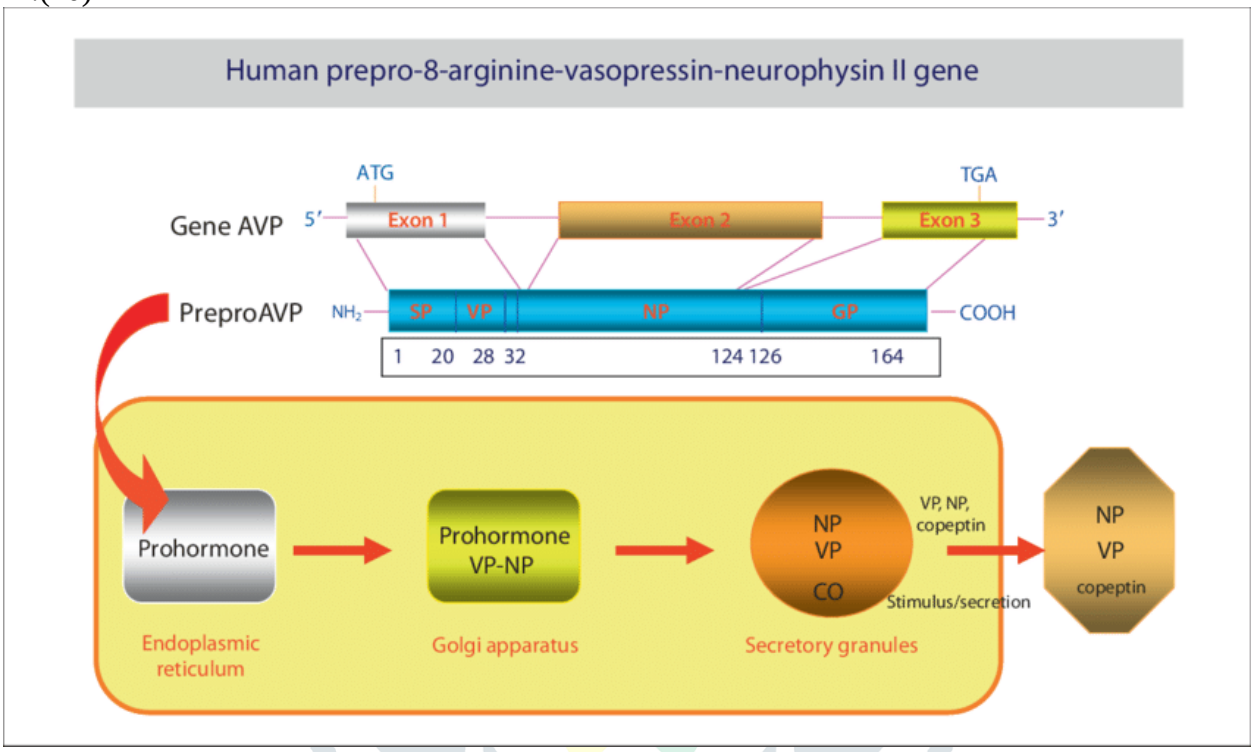

Fig. 3. Schematic representation of AVP biosynthesis. CO = Copeptin; NP = neurophysin

4. Pathogenesis*:* When more than 80% of the neurons that secrete AVP are damaged, polyuria increases. Numerous pathological processes, including genetic causes, can result in extensive destruction. The loss of large neurosecretory cells in the hypothalamic nuclei has been revealed by autopsy studies conducted following traumatic section of the pituitary stalk (PS). This happens in 4-6 weeks, and lesions that occur at or above the infundibulum will cause more damage.(11)

The condition may be brought on by the degeneration of these hypothalamic neurons, as evidenced by autopsy studies of patients with a familial form of diabetes insipidus. These studies reveal a selective loss of magnocellular neurons in the paraventricular nuclei associated with moderate gliosis and a relative preservation of small neurosecretory cells.(12)

5. Genetic Forms of CDI: Currently, familial neurohypophyseal CDI is associated with over 55 distinct mutations that cause a defective prohormone and an AVP deficiency; all but a few exhibit an autosomal dominant pattern of inheritance. Six patients exhibit an autosomal recessive pattern of inheritance due to homozygous missense mutations in the region encoding the AVP domain. The symptoms in these cases seem to be secondary to the reduced biological activity of the mutant AVP peptide, despite certain clinical similarities with the dominant form.

The high concentration of mutant hormone in the blood, the absence of normal AVP hormone in the homozygous state, and the lack of clinical or subclinical abnormalities in heterozygous carriers all lend support to this theory.(13)

Numerous mechanisms, including dominant negative activity through interactions between mutant and wildtype (WT) precursor, accumulation of mutant precursor in the ER leading to stress protein response and autophagy, and cellular toxicity through pathways that are still unclear, can cause the autosomal dominant inheritance of this disease. Research on the trafficking and processing of the mutant AVP prohormone in vitro has shown that the mutation prevents the ER from exiting the cell and from processing the AVP prohormone, which leads to an abnormal endoplasmic morphology and may even cause cell death or dysfunction. Although nonapoptotic cell death is suggested by the presence of cytosolic autophagy, programmed cell death cannot be ruled out.(14)

The ability of the signal peptide to initiate appropriate processing of the prepro-AVPNPII is reduced by mutations involving it. Additionally, mutant precursors hinder intracellular trafficking of the WT precursor by forming heterodimers, which lowers the bioavailability of active AVP through a "nontoxic mechanism," or dominant negative effect. The discovery of two pathways of degradation (via the ER lumen and directly from the cytosol) involving both the WT and the mutant prohormone raises the possibility that the processes causing the cytotoxic effect differ from those in cells expressing the WT protein in terms of quantity but not in terms of fundamentals.(15)

6. Drug-induced diabetes insipidus:

Numerous commonly used medications may result in acquired nephrogenic diabetes insipidus. Up to 60% of patients experience polydipsia and polyuria when taking lithium salts at first; in 20% to 25% of cases, these side effects last even when plasma lithium levels are within the therapeutic range. One documented instance involved a patient receiving long-term lithium therapy who also had underlying chronic nephrogenic diabetes insipidus and transient central diabetes insipidus.(16)

The chronic syndrome of inappropriate ADH secretion has been treated with lithium salts, but demeclocycline has shown to be a more successful medication.Dermatologists frequently use demeclocycline, an antibiotic belonging to the tetracycline group, to treat acne. Demeclocycline causes polyuria and polydipsia at high doses (900–1,200 mg/day). Within the first few days or weeks of treatment, these side effects may not materialize, and it typically takes several weeks for renal function to fully recover after stopping the medicationDemeclocycline and lithium salts are believed to impact renal function by disrupting a specific part of the ADH-cyclic adenosine monophosphate second-messenger system's proximal component.

Strong antifungal drug amphotericin B is nephrotoxic. It interferes with the kidney's ability to produce and maintain the medullary osmotic gradient.(17)

The cellular response to ADH appears to be hampered by gentamicin. Colchicine interferes with microtubule function to prevent the second messenger from doing its job. In some instances, loop diuretics have been demonstrated to deteriorate renal function.It has recently been demonstrated that some patients taking foscarnet for cytomegalovirus infection may develop nephrogenic diabetes insipidus.(18)

7. Diagnosis of Diabetes Insipidus:

Clinical examinations can offer crucial hints about potential underlying diagnoses. The age at which symptoms appear and the fluid consumption pattern may have an impact on the results of further research on diabetes insipidus.

Children may experience severe dehydration, vomiting, constipation, fever, irritability, sleep disturbance, failure to thrive, and growth retardation in addition to the main symptoms of persistent polyuria and polydipsia.

In children, nocturia frequently manifests as enuresis. Severe early-onset dehydration in males is highly suggestive of non-dementia infantile; reports of mild mental retardation are likely the result of repeated, undiagnosed dehydration before the condition has been fully diagnosed.

40% of patients in a sizable cohort with CDI of various etiologies presented with symptoms other than polyuria and polydipsia; headache was not a discriminatory factor, but visual impairment was linked to intracranial tumors. Contrary to earlier reports suggesting that such delays strongly suggest an intracranial tumor as the cause of CDI, growth retardation was not significantly more common in patients with CNS tumors. Furthermore, none of the patients with intracranial tumors was younger than five years old, and the patients without intracranial tumors were noticeably younger than the ones who did.(2)

Clinical illness onset in autosomal dominant CDI usually occurs between the first and sixth year of life, however early or delayed onset cases have also been documented. Patients who have mild polyuria and polydipsia that started early, especially before the age of 10, typically experience worsening symptoms as they age. However, it is also possible that complete CDI manifests from the neonatal period.

Individual differences among patients with the same mutation may account for the wide range in the age of onset and severity of AVP deficiency. These differences may include the rate at which the mutant precursor is produced, the degree of neurohypophyseal stimulation, the susceptibility of each patient to the toxic effects of the mutant precursor, and the ability to degrade mutant.(19)

Water is vital because, when consumed in sufficient amounts, it can rectify any metabolic abnormality brought on by overly diluted urine replacement of ADH. The first known form of ADH was a dried, crude acetone extract administered by nasal inhalation from the posterior pituitaries of cows or pigs. Variable activity duration and localized nasal mucosal irritation were issues with this preparation. Later on, ADH was refined further and given the name Pitressin (vasopressin tannate in oil). Every two to four days, this is injected intramuscularly, and it offers relief for a full day or two. Its adverse effects include angina, hypertension, and cramping in the abdomen.The development of oral medications to support antidiuresis was spurred by the drawbacks of these preparations.Currently, the preferred medication for long-term treatment of central diabetes insipidus is desmopressin (1-deamino-8-D-arginine vasopressin, or DDAVP).(20)

In the indirect water deprivation test, the patient is deprived of fluids while their urine osmolality, plasma sodium, and plasma osmolality are continuously measured. The patient is kept on fluid deprivation for a maximum of 17 hours, or until their plasma concentration reaches 150 mmol/L or they lose 3–5% of their body weight. The patient's urine osmolality is measured following the exogenous administration of desmopressin (DDAVP), or synthetic ADH, and compared to the osmolality prior to DDAVP administration.(21)

The patient's urine osmolality is measured following the exogenous administration of desmopressin (DDAVP), or synthetic ADH, and compared to the osmolality prior to DDAVP administration. For healthy people, the urine osmolality at the conclusion of the test should be greater than 800 mOsm/kg and should not rise after DDAVP. Urine osmolality in both nephrogenic and central DI cases will be less than 300 mOsm/kg. DDAVP response distinguishes between central and nephrogenic DI. Urine osmolality will rise >50% for CDI and <50% for NDI following DDAVP.(22).

In pregnancy, the indirect water deprivation test is not frequently employed.It must be used with careful observation if the patient is pregnant. Extended water restriction may raise the risk of uteroplacental insufficiency, cause hypernatremia, and dehydrate both the mother and the fetus.If serum osmolality is more than 285 mOsm/kg and persistent urine osmolality is less than 300 mOsm/L, gestational DI is verified.(23)

8. Treatment:

Improving the patient's quality of life requires treating DI. Whether or not symptoms can be completely relieved or treated depends on what caused the disorder in the first place. There are a few first-line therapies for both central and nephrogenic DI that support fluid balance. It is crucial to always have access to water in order to avoid becoming excessively dehydrated too soon. Thiazide diuretics, which block the NaCl cotransporter in the renal distal convoluted tubule, are a counterintuitive treatment for CDI and NDI.(24)

This section of the nephron is thought to belong to the diluting segment since it is impermeable to water. Consequently, it is unlikely that thiazide diuretics' ability to preserve water is due to a direct impact on the distal convoluted tubule. The most widely recognized theory contends that elevated renal sodium excretion is the primary cause of the antidiuretic effect. Renal sodium loss results in extracellular volume contraction, which raises sodium and water reabsorption in the proximal tubule and decreases the glomerular filtration rate (GFR). Other approaches to treatment vary according to principal type.(25)

Synthetic ADH (also referred to as desmopressin or DDAVP) is the preferred treatment for CDI. A synthetic substitute for the endogenous hormone ADH, DDAVP has an antidiuretic effect that is two to three times less potent. DDAVP can be given parenterally, intravenously, or orally. Given that plasma concentrations are attained in 40–55 minutes, intranasal or oral administration appears to be the most efficient method. Urine output usually starts to decrease one to two hours after administration, and the medication takes six to eighteen hours to take effect. Eye

irritation, headaches, dizziness, rhinitis or epistaxis, coughing, flushing, nausea, vomiting, abdominal pain, chest pain, palpitations, and tachycardia are uncommon side effects of intranasal DDAVP delivery.(26)

For mild cases of DI, treatment may not even be necessary if enough water is consumed. Polyuria is improved when aggravating factors (such as decreases in glucocorticoids that directly cause free water clearance) are removed.Central Division. Acetone-dried extract from the posterior pituitaries of cows and pigs was one of the earlier preparations used to treat central DI. Due to its inconsistent duration of action and potential for local irritation, an even more refined version of the ADH preparation was created that was suitable for intramuscular administration. However, angina, hypertension, and cramping in the abdomen are side effects that lead to the development of other medications.Desmopressin. DDAVP, or 1-deamino-8-arginine vasopressin, has become the go-to medication for the long-term treatment of central DI.(27)

1. Carbamazepine:

An anticonvulsant and psychotropic medication called carbamazepine is used to treat epilepsy and intellectual disabilities. It might directly affect renal tubules and cause the pituitary gland to release more vasopressin. In vitro, carbamazepine enhanced water absorption without AVP. Cyclic adenosine monophosphate (cAMP) was required for the effect to occur. In rats, carbamazepine directly affected the V2R-protein G complex, enhanced AQP2 expression, and increased water permeability and absorption in the inner medullary collecting duct.(28)

Extended administration of carbamazepine has been associated with a decrease in its antidiuretic effect, possibly as a result of the drug's auto-induction.(29)

2.Chlorpropamide:

If there is residual secretory capacity in the neurohypophysis, the antidiuretic medication chlorpropamide reduces the clearance of solute-free water and returns plasma osmolality to normal.(30). When children and adults were given chlorpropamide (125–1000 mg daily), their urine output decreased from 5.4–10.7 L/day to less than 2 L/day. It took three to four days to reach maximal diuresis, and the effect was dose-dependent.(31)

3.Clofibrate:

In six DI cases, the mean urine clearance decreased significantly from 280 mL/h to 141 mL/h and the mean free water clearance decreased from 158 mL/h to 10 mL/h with clofibrate treatment (500 mg every 6 h). In four out of six patients, there was a concurrent decrease in urinary ADH excretion as urine osmolality increased from 152 mOsm/kg to 317 mOsm/kg. Significant antidiuretic activity was observed even in patients with high water overload.(32)

4.Thiazide diuretics:

They block the cotransport of sodium and chloride at the distal convoluted tubule. Long-term administration lowers the volume of extracellular fluid, which permits the proximal tubules to reabsorb sodium and water. In the end, there is a decrease in urine production.(33)

Chronic hydrochlorothiazide therapy up-regulates NCC and ENa C, which improves sodium reabsorption along the distal segments of the nephron, according to an animal model of lithium-induced NDI.(34)

9. Prognosis and prevention:

The quality of life after DI onset and treatment can vary greatly, depending on the underlying cause of the condition. There is currently no treatment plan that completely relieves symptoms in every patient, despite advances in the identification of the primary type and causes of DI. This is due to the disorder's extreme variability, severity, and genetic foundation. When a severe trauma or head injury causes CDI, DI not only results in a reduced quality of life for the patient and their family, but the initial cause of the disorder may also cause a host of other complications. Compared to benign causes, the prognosis is cautious for patients whose cause is malignancy.(35)

If there is minimal nephron damage, as is the case with long-term lithium treatment, NDI can be completely relieved. The degree of nephron damage may be significantly less and manageable if the medication is stopped before the disease manifests. If there is minimal hypothalamic or pituitary damage, DDI can also be completely cured. Tumors, head injuries, infections, inflammations, and surgeries can all result in damage. It can also be resolved if the underlying mental health condition that is causing the excessive thirst is appropriately managed.(36)

Finally, gestational DI can only happen when the placenta secretes vasopressinase during pregnancy. The majority of women won't require treatment after giving birth, but they run the risk of getting type 2 diabetes mellitus and developing gestational DI if they become pregnant again. As previously mentioned, there is no treatment for permanent damage that results in an irreversible form if the damage is severe. A fairly bearable life can be created, depending on the severity of the disorder, by monitoring weight loss, adhering to a renal diet, ensuring adequate fluid intake meets excretion, maintaining adequate therapy through DDAVP, and using thiazide diuretics. Negligent DI management can be fatal.(37)

11.Abbreviation

Sr.no	Abbreviation	Meaning
1	CDI	Central diabetic insipidus
2	ADH	Anti diabetic hormone
3	TBI	Traumatic brain injuries
4	AVP	Vasopressin
5	ER	Endoplasmic reticulum
6	AQP2	Aquaporin 2
7	DDAVP	Desmopressin acetate
8	NDI	Nephrogenic diabetic insipidus
9	GDI	Gastrointenstinal diabetic insipidus
10	WFS1	wolframin ER transmembrane glycoprotein [(human)]

11. Conclusions:

Even though it is rare, the effects of untreated DI can be very taxing on the patient and have a detrimental effect on their quality of life. A better quality of life for the patient depends on an appropriate diagnosis and therapeutic intervention. CDI is caused by a shortage in the posterior pituitary gland's ability to release ADH. The tubular cells in the collecting duct stop responding to ADH in NDI. ADH deficiency is a characteristic shared by dipsogenic DI, GDI, and CDI. An unusually low osmotic thirst threshold, which results in increased fluid intake, is the cause of dipsogenic DI. Placental vasopressinase levels rise during gestational diabetes mellitus (GDI), which causes the mother's ADH to be degraded. Recognizing the different kinds of DI. When there is diluted urine excretion combined with an abnormal osmotic thirst threshold, dipsogenic DI can be diagnosed. Osmolarity measurements of the serum and urine can be used to diagnose GDI. Enhancing the quality of life for patients and preventing excessive fluid floss are the cornerstones of DI management. In order to treat CDI, DDAVP must be administered in addition to getting enough fluids. Ironically, thiazide diuretics can be used to treat both CDI and NDI. The first step in treating NDI is stopping the offending medication, like lithium. It should be mentioned that DDAVP administration has no effect on NDI or dipsogenic DI.

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