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LITHIUM CAUSING NEPHROGENIC DIABETES INSIPIDUS

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ABSTRACT
Diabetes insipidus brought on by drugs is usually nephrogenic, meaning the kidneys are not responding to the effects of antidiuretic hormone. This syndrome can be easily identified by administering a modified antidiuretic hormone, desmopressin, to establish renal unresponsiveness, or by measuring urine concentrating capacity during a thirst test (e.g., 12 hours of water restriction). Except for people undergoing lithium salt medication for affective disorders, where it may affect roughly 10% of patients treated for a lengthy period of time (15 years), drug-induced nephrogenic diabetes insipidus is not a frequent condition. Critically sick patients in intensive care units who are taking a variety of medications, mostly cytostatics and antimicrobials, are typically the ones that develop drug-induced nephrogenic diabetes insipidus. Lithium is the most important cause of drug induced nephrogenic diabetic insipidus. Most studies showed people respond well to treatment, and the offending substance should be discontinued. Treatment with thiazides and amiloride has been recommended if urine volumes above 4 L per day.

KEYWORDS: Lithium, Nephrogenic, Diabetic insipidus, Anti-diuretic, Osmolarity.

INTRODUCTION

A rare endocrine disorder, diabetes insipidus (DI) affects approximately 1 in 25,000 people, or 0.004% of the world's population.[1] Because of its low prevalence, the different types of DI may be overlooked in medical education and research aimed at improving clinical management.[1] Despite being an uncommon endocrine disorder, the outcome of untreated DI can have a negative impact on the patient's quality of life. Epidemiologically, DI does not show a predilection for males or females, and it can develop at any age, with hereditary forms developing earlier in life.[1]

DI can be divided into four main categories

- Central
- Nephrogenic
- Dipsogenic or
- Gestational.

Diabetic insipidus

The most prevalent definition of DI is when an adult has a urine osmolality of less than 300 mOsmol/kg and a urine volume of more than 3-3.5 liters in a 24-hour period. Urine volume far exceeds 3-3.5 liters in a 24-hour period in the majority of DI cases.[2]

One of the primary factors influencing the body's water homeostasis is the posterior pituitary hormone, or ADH, which is the primary hormone causing diabetes insipidus. The kidney is the target organ of antidiuretic hormone (ADH), which raises urine osmolality.[3]

Arginine vasopressin disorder

An unusually high volume of urine (diabetes) that is diluted (hypotonic) and devoid of dissolved solutes (i.e., insipid) is a clinical illness known as arginine vasopressin disorder. They are part of a category of polyuria and polydipsia illnesses that can be acquired or inherited. Hypotonic polyuria and compensatory/underlying polydipsia are linked to inadequate arginine vasopressin (AVP), antidiuretic hormone (ADH) secretion, or renal response to AVP.[5] Polyuria (>50 mL/kg), diluted urine (osmolality <300 mOsm/L), and increased thirst with a daily fluid consumption of up to 20 L are the hallmarks of diabetes insipidus (DI).[6] Dehydration, electrolyte abnormalities, and hypovolemia can result with untreated DI.[7]

The two main negative feedback systems that regulate ADH secretion are osmoregulation and baro-regulation.[4]

The hypothalamic osmoreceptors pick up on even the smallest shifts in plasma osmolality, such as those of less than 1%. The posterior pituitary gland releases ADH as a result of detecting an increase in osmolality. When baroreceptors are triggered by a drop in blood volume, a comparable reaction can be investigated. About a 5%–10% change in volume is needed to account for the blood volume deviation.[2] After leaving the hypothalamus with its transport protein carrier, neurohypophysin II (NPII), ADH moves to the posterior pituitary, where it is held until it is released.

ADH is a water-soluble peptide hormone that is released into the bloodstream in response to stimulation of baroreceptors or a change in plasma osmolality. It binds to the aquaporin-2 receptors (AQP2) in the collecting duct's basolateral membrane to act on its target. After binding to the receptor, it triggers the Gs-adenylyl cyclase system pathway, which raises cAMP levels inside cells. Protein kinase A is activated by this rise in cAMP levels, which ultimately causes preformed AQP2 channels to become phosphorylated. The phosphorylation causes AQP2 to be inserted onto the cell's apical membrane surface. It is known that the renal collecting duct would continue to be practically impervious to water in the absence of this AQP2 insertion.

Concentrating the urine and eliminating water from the renal filtrate are the goals of AQP2. When DI occurs, water cannot flow freely along an osmotic gradient from the nephron lumen into the collecting duct cells, resulting in the emission of diluted urine. ADH can lower urine output to 0.5 ml/min, or roughly 700–800 ml/day, and raise urine osmolality to around 1,200 mOsmol/kg. Levels of circulating ADH decrease and the quantity of inserted AQP2 channel proteins in the apical plasma membrane is down-regulated once the body's water balance is established.[2,3]

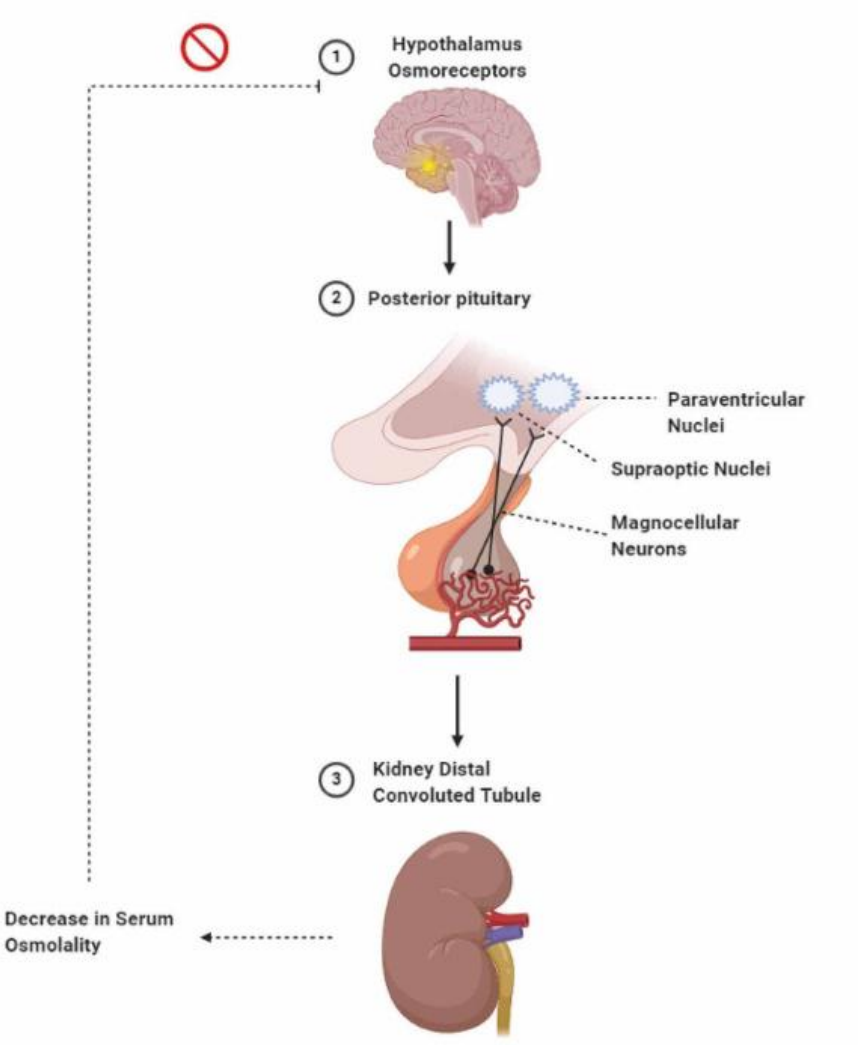

Figure 1: Osmoreceptors in the hypothalamus detect increased serum osmolality.

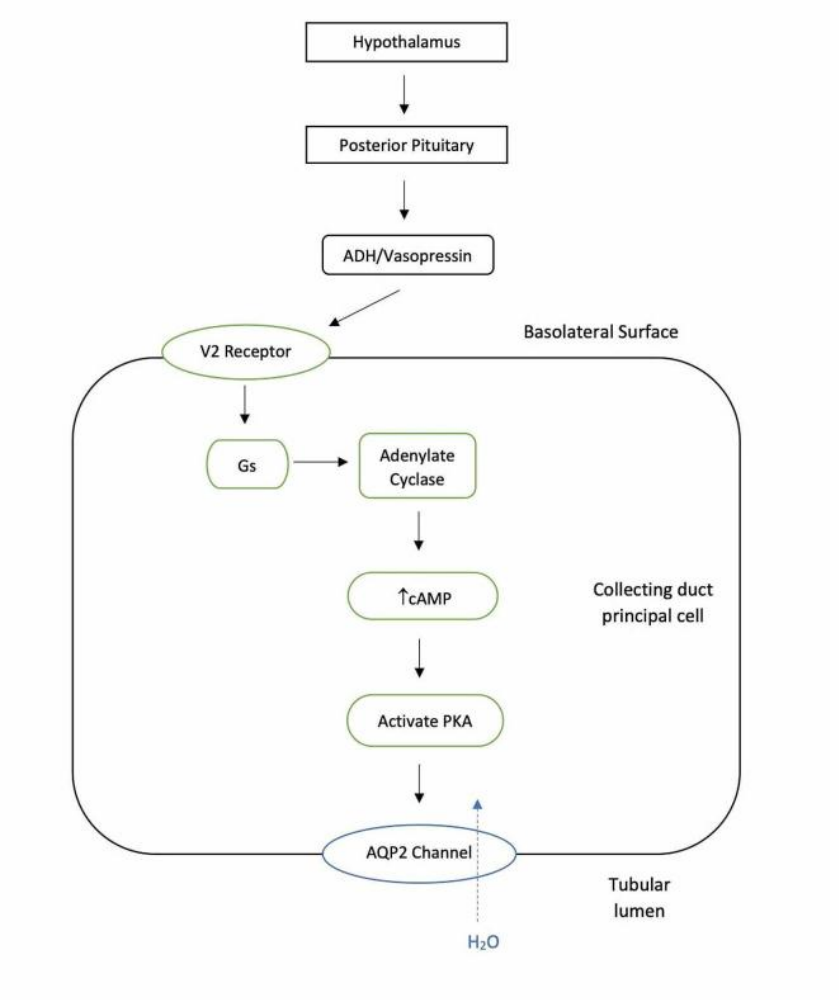

Figure 2: ADH function on cells of the collecting duct.

Etiology

There are two main types of DI: central (neurogenic) and nephrogenic. The most common type, called central diabetes insipidus (CDI), is caused by a lack of ADH production. It is mainly brought on by acquired factors like traumatic brain injury (TBI), infections, loss of blood to the posterior pituitary or hypothalamus, neurosurgery, and tumors.[3] Lesions in the hypothalamo-neurohypophyseal axis are responsible for 25% of CDI cases.[8] The pituitary gland, pituitary stalk, and hypothalamus are particularly susceptible to damage from head trauma, which can cause 16% of CDI cases.

CDI may arise from these abnormalities, which can be inherited as X-linked recessive traits, autosomal dominant characteristics, or autosomal recessive traits. One percent of CDI cases had hereditary or family origins.[8] The deletion of the AVP gene on chromosome 20p13 is the particular gene mutation that is most frequently observed.[9] DI is involved in another uncommon autosomal recessive illness in addition to the genetic mutation in the AVP gene. The WFS1 gene, which codes for 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 element that functions as a calcium channel.[10,11]

AVP-sensitive DI, insulin-dependent juvenile-onset diabetes mellitus, optic atrophy, and sensorineural deafness are the hallmarks of Wolfram Syndrome, which is caused by a specific mutation in WFS1. About 70% of patients have DI, and about 50% of patients have all four illnesses at the same time.[12] Sadly, individuals with Wolfram Syndrome only live beyond their third or fourth decade of life.[12]

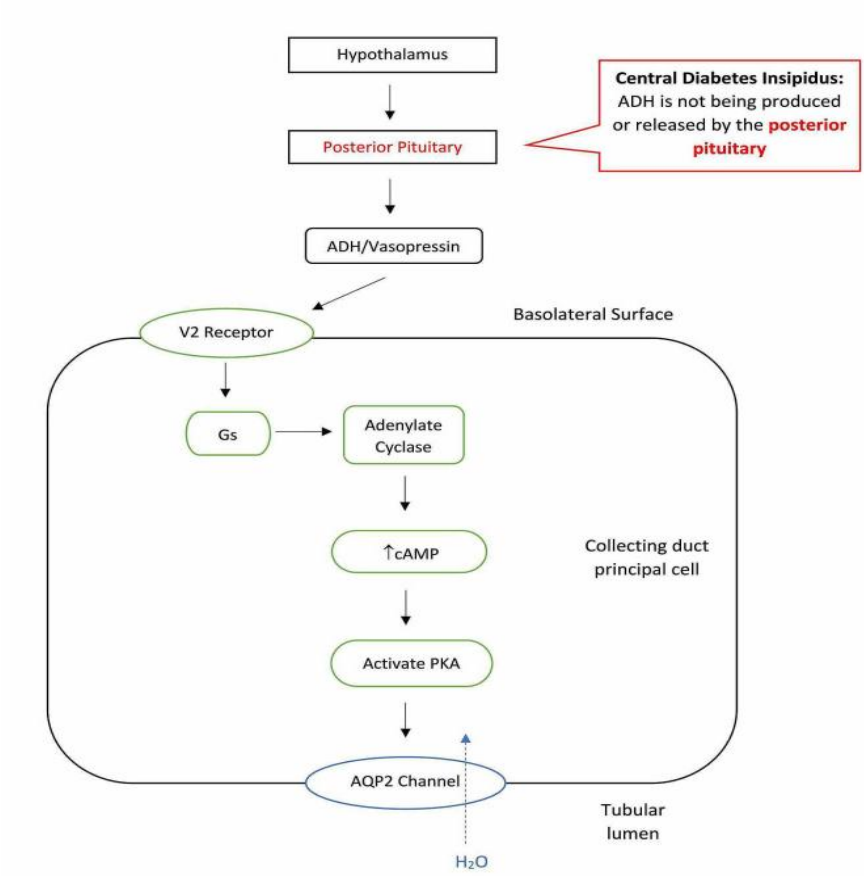

Figure 3: ADH production is inadequate in central diabetes insipidus, which is frequently brought on by pituitary gland injury. Urine becomes diluted as a result.

The terminal distal convoluted tubule and collecting duct's insensitivity to circulating ADH is linked to nephrogenic diabetic insipidus (NDI) (see Figure 4). The majority of individuals with NDI have an acquired anomaly, and the most common causes include aging, protein deficiency, hypercalcemia, hypokalemia, lithium therapy or other drugs, and the release of a ureteral blockage.[13] Bipolar disorders are frequently treated with lithium treatment. Regretfully, the nephrogenic class of DI develops in approximately 40% to 55% of patients on lithium treatment, and symptoms may appear as early as eight weeks after treatment begins. Like sodium, lithium is filtered and reabsorbed by the kidney and can enter the main cells of the collecting duct.

AQP2 expression eventually declines as cytotoxic lithium concentrations build up inside the cells.[13,14] There have been instances of additional drugs causing drug-induced NDI in addition to lithium therapy inducing DI. Although it has been demonstrated that foscarnet and clozapine can also cause NDI, these symptoms are uncommon and much less frequent than the DI linked to lithium.[14] Rarely, congenital abnormalities involving the AQP2 gene are the cause of NDI. These congenital variants include autosomal recessive, autosomal dominant, and the most prevalent, X-linked pattern of inheritance.[13]

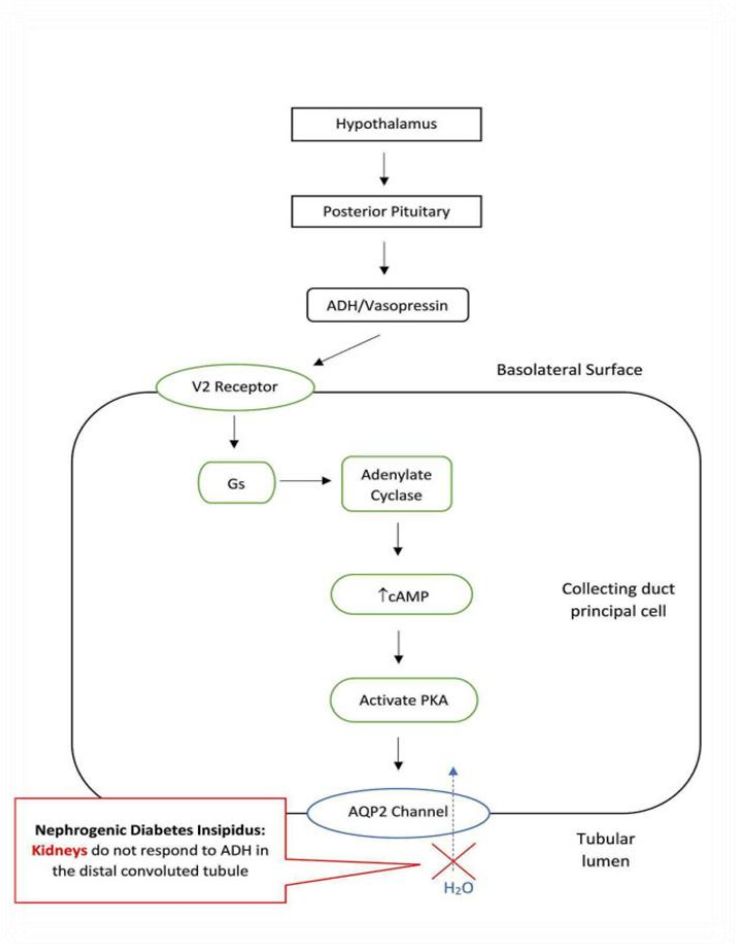

Figure 4: A malfunction in the renal tubules is the etiology of nephrogenic diabetes insipidus. Urine becomes diluted as a result of this defect's reduced reaction to ADH.

Pathogenesis

Each disease has a different beginning etiology, but they all result in severe dehydration, excessive thirst, and the outflow of huge volumes of diluted urine. Three interconnected determinants have a major role in the physiology of water balance in humans. These include the production and secretion of ADH, thirst, and healthy kidney function. The terminal distal convoluted tubule and collecting duct's sensitivity to ADH and its release are both directly impacted by DI.[14] The body undergoes a variety of modifications if the ADH systems are interfered with. Changes in serum and urine osmolality, water loss, and electrolyte imbalances all occur.

A low sodium level indicates primary polydipsia, while hypernatremia with serum sodium levels >145 mEq/L (the accepted normal range is 135-145 mEq/L) indicates central or nephrogenic DI at the outset of the condition.[16,17] Furthermore, DI is indicated by a serum osmolality greater than 295 mOsm/kg, whereas primary polydipsia may be indicated by a normal or low serum osmolality (less than 285 mOsm/kg).[18] Additional symptoms include decreased blood volume (hypovolemia), urine osmolality <200 mOsm/kg, decreased sodium level in the urine, urine specific gravity of 1.003 to 1.030, decreased volume of extracellular fluid (ECF), decreased body weight (3%–5%), and mild hypertension that starts out mildly and progresses to hypotension.[19] Confusion, irritation, low skin turgor, and dry mucous membranes are other assessment findings.[19]

The effects of DI and the two main negative feedback loops related to bodily water balance are very severe. Changes in serum osmolality trigger the osmoregulation negative feedback loop; a normal serum osmolality ranges from 285 to 295 mOsm/kg. Blood is more concentrated and there has been a loss of bodily water when the osmolality is more than 295 mOsm/kg. Variations in blood pressure and volume trigger the baroregulation negative feedback loop. In response to the baroreceptor alterations, the hypothalamus either increases or decreases the posterior pituitary gland's production and release of ADH. ADH release can be triggered by even small changes, like a 5–10% drop in blood volume or a 5% drop in mean arterial pressure. Generally speaking, the body responds to osmoregulation by first controlling ADH secretion. Osmoregulation is subordinated to baroreceptor activation of ADH in cases of severe volume deprivation.[20]

Arginine Vasopressin Resistance (AVP-R, formerly known as Nephrogenic Diabetes Insipidus or NDI)

The term AVP-R describes a reduction in the kidney's capacity to concentrate urine as a result of resistance to the antidiuretic hormone's (AVP/ADH) effect. Resistance in the collecting tubules at the ADH site of activity or interference with the countercurrent mechanism, such as medullary damage or reduced sodium chloride reabsorption in the medullary aspect of the thick ascending limb of the loop of Henle, may be the cause of the pathology.

In children, inherited nephrogenic DI is the most common cause of AVP-R; in adults, chronic lithium consumption and hypercalcemia are the main reasons. Acquired causes can frequently be partially reversed by stopping the offending medication or treating hypercalcemia.

Lithium toxicity: About 20% of patients receiving long-term lithium therapy get polyuria, which results in NDI. The epithelial sodium channel (ENaC) allows lithium to enter the main cells of the collecting tubule, which mediates its harmful effects.[41] At cytotoxic quantities, lithium inhibits the signaling pathway, which results in malfunction of the aquaporin-2 water channel.[21]

Hypercalcemia: Renal concentrating ability may be hampered by a plasma calcium concentration that is consistently higher than 11 mg/dl (2.75 mmol/L).[22] We don't fully understand the mechanisms underlying these. Reduced sodium chloride reabsorption in the thick ascending loop of Henle may be linked to this problem, which would disrupt the countercurrent process and ADH's capacity to raise collecting tubule water permeability.[22]

When the serum calcium concentration returns to normal, the concentrating deficiency caused by hypercalcemia is usually reversible. However, in patients who have irreversible medullary injury, the defect could not go away.

Hypokalemia: Severe hypokalemia that persists over time can affect the ability to concentrate when urinating. We don't fully understand the mechanisms underlying this. The reduction of urine concentrating ability brought on by potassium deficiency may also be attributed to downregulation of urea transporters.[23]

Drugs: In addition to lithium, NDI has been demonstrated to be caused by a number of drugs, including cidofovir, foscarnet, amphotericin B, ofloxacin, ifosfamide, and orlistat. AVP-R brought on by drugs is usually reversible, at least partially.

For the maintenance treatment of bipolar disorder, lithium is a helpful mood stabilizer (Belmaker 2004; Gershon et al. 2009).[33,34] According to Belmaker (2004) and Gershon et al. (2009),[33,34] it has a proven antimanic effect and is effective in preventing the recurrence of emotional episodes. Lithium's demonstrated capacity to lower suicide attempts and suicidal deaths among bipolar individuals is another benefit. Concern has grown in recent years regarding the possibility that lithium therapy could, in certain rare circumstances, result in chronic renal failure and perhaps the need for kidney dialysis.

Lithium induced NDI

Since the 1970s, lithium salts have been utilized in medicinal settings. Lithium is frequently used to treat and prevent bipolar disorder, although it has a very limited therapeutic index, and individuals who use it frequently experience toxicity. Lithium's effects on the kidney, thyroid, and parathyroid lead to congenital abnormalities as well as alterations in skin and body weight. Although lithium is frequently used to treat a variety of mood disorders, it has also been linked to many types of renal damage, the most common of which is reduced urine concentrating ability, which is thought to affect at least 50% of patients on long-term lithium therapy. Nearly all cases of drug-induced diabetes insipidus are nephrogenic. The most often implicated medicine is lithium.

Pathophysiology of Lithium-Induced Nephrogenic Diabetes Insipidus

A guanyl-nucleotide regulatory protein (G protein) is triggered when antidiuretic hormone (ADH) attaches to its receptor on the basolateral membrane of the main cell in the cortical and medullary collecting tubules. This process raises intracellular cyclic adenosine monophosphate (cAMP) and activates adenylate cyclase. Following the opening of water channels, water permeability and absorption rise. Lithium inhibits the ADH-stimulatory impact on adenylate cyclase, which lowers cAMP and, consequently, the diffusion of water through the collecting tubules' cell membrane pores. The inability to maximally concentrate urine is the end result.[30,31]

The acute action of lithium on the renal tubules can be explained by its influence on cAMP, but it is unable to account for the concentrating deficiency that is occasionally seen even after stopping lithium. Lithium's irreversible effect on concentration after stopping the medicine may have a different mechanism, according to some writers. The current perspective on the permanent irreversible concentrating defect caused by lithium is summarized in Walker8's most recent literature review. Individuals on lithium, particularly those receiving long-term treatment, may experience an irreversible concentrating impairment that may continue to vary in severity even after stopping lithium.

A persistent tubulointerstitial pathologic alteration linked to this impairment is also present in animal models of lithium. However, other research has shown that psychiatric patients who had never used lithium experienced comparable pathologic alterations. Persistent

concentration difficulties are linked to lithium and these pathologic alterations.[29] According to Neithercut et al., patients with a glomerular filtration rate of less than 60 mL/min may be at risk for the permanent concentrating defect of lithium.[28] However, neither a reduction in the glomerular filtration rate nor chronic renal failure are brought on by lithium.[29]

At dangerous serum concentrations, lithium is linked to degenerative changes and tubular cell necrosis. It also builds up in the kidneys' distal tubular cells at concentrations 10–20 times greater than those in serum. Chronic lithium treatment frequently results in a defect in the kidney's ability to concentrate because antidiuretic hormone inhibits the production of cyclic adenosine monophosphate at the distal tubule. Lithium most likely acts through adenylate cyclase and may also act at a point distal to the production of cyclic adenosine monophosphate. Lower maximal urine osmolality is seen in between 30% and 90% of individuals.[32]

Lithium induced nephrogenic diabetes insipidus

Despite normal or high levels of the antidiuretic hormone vasopressin, the most frequent renal adverse effect of lithium is the concentration of urine. Reduced urine osmolality and increased urine volume (polyuria) are the results of the concentrating problem. Urine osmolality tests are rarely performed when the urine volume is near-normal, therefore a urinary concentrating deficiency without overt polyuria is usually clinically unimportant.

According to various studies, the prevalence of nephrogenic diabetes insipidus (NDI) in patients receiving lithium varies widely, ranging from 20% to 87%.

(Baylis and Heath 1978; Vestergaard et al. 1979; Vestergaard and Amdisen 1981; Schou and Vestergaard 1988; Okusa and Crystal 1994).[33-38]

For example, in a thorough meta-analysis of research including 1172 patients receiving lithium, Boton et al. (1987).[39] found that over 54% of patients showed a decrease in their ability to concentrate when they urinated, but only 19% had overt polyuria.

According to numerous research, the following are the main variables influencing the prevalence and seriousness of urine concentrating problems in patients receiving lithium treatment: frequency of acute lithium intoxications, blood lithium level, and length of treatment (longer duration increases the risk of NDI). (Vestergaard et al. 1979; Vestergaard and Amdisen 1981; Schou and Vestergaard 1988; Markowitz et al. 2000; Bucht and Wahlin 1980; Boton et al. 1987; Walker 1993; Turan et al. 2002; Timmer and Sands 1999; Bendz et al. 2001).[29,36,40,46]

However, Lepkifker et al. (2004) found that episodes of lithium intoxication were more predictive and positively correlated with the likelihood of urinary concentrating defect, but plasma concentrations and the length of lithium medication were not linked to an elevated risk of this condition. A urinary concentrating deficiency could appear as soon as two to four months after starting lithium.[43,47]

Even after stopping lithium treatment, NDI can still occur (Paw et al. 2007). Furthermore, while some studies showed that stopping long-term lithium therapy may lessen the concentrating defect, others showed that it does not always restore the kidney's ability to concentrate urine (Markowitz et al. 2000; Bendz et al. 2001; Khairallah et al. 2007). The level of tubulointerstitial damage at which lithium was stopped may be connected to these differences. It may be completely reversible at an early stage when just functional tubulointerstitial damage has occurred.[42,48-51]

On the other hand, stopping lithium won't fix fibrosis, which is a late stage of permanent morphological tubulointerstitial alterations. Crucially, those with polyuria who do not drink enough water run the danger of volume depletion, which raises the possibility of lithium toxicity even more (Vestergaard et al. 1979; Vestergaard and Amdisen 1981; Smigan et al. 1984).[36,47] Additionally, compared to patients receiving only lithium treatment, those receiving both lithium and neuroleptic medications concurrently experienced noticeably greater rates of urine concentrating abnormalities. Urinary concentrating abnormalities were consistently more common in patients treated with antipsychotics (alone) than in comparable healthy volunteers (Bucht and Wahlin 1980).[42] These findings raise the possibility that antipsychotic medications play a role in the emergence of urine concentrating abnormalities.

Vasopressin's antidiuretic action is diminished by acute lithium administration (Singer et al. 1972).[52] Similarly, it has been demonstrated that long-term lithium medication decreases vasopressin's antidiuretic action through a number of potential pathways. The potassium-sparing diuretic amiloride is the most well-established pharmaceutical treatment for lithium-induced NDI (Boton et al. 1987; Timmer and Sands 1999; Feuerstein et al. 1981; Bedford et al. 2008).[43,45,53,54] Amiloride, however, is probably only going to work in cases where there is a mild to severe urinary concentrating deficiency that may be curable. The following are some hypothesized ways that amiloride reduces lithium-induced urinary concentrating defect: i) blocking the epithelial sodium channel ENaC, which lowers the amount of lithium absorbed by collecting duct cells (Walker et al. 1982); and ii) bringing AQP2 and AQP3 expression levels back to normal (Bedford et al. 2008).[29,54]

Mukhopadhyay et al[55] reported two patients. The first is a 68-year-old woman who had been vomiting for two

days. Despite receiving enough fluid replacement, her hypernatraemic condition and increased serum salt content did not initially improve. Later on, she experienced polyuria and polydipsia. After receiving treatment for a chest infection one week prior, the second patient, a 77-year-old lady, arrived with acute hypernatraemia and confusion. Both individuals were receiving long-term treatment for lithium. After the blood biochemistry returned to normal, a supervised water-deprivation test revealed partial nephrogenic diabetic insipidus in both patients.

Fotso soh et al.[56] carried out atorvastatin for lithium-induced NDI in a 12-week, double-blind, placebo-controlled RCT at McGill University in Montreal, Canada. Sixty current lithium users, ages 18 to 85, were recruited. They defined NDI as urine osmolality (UOsm) < 600 mOsm/kg following a 10-hour fluid restriction.For 12 weeks, they randomly assigned patients to receive atorvastatin (20 mg/day) or a placebo. After adjusting for baseline, they investigated whether this enhances NDI measurements, including UOsm and aquaporin (AQP2) excretion at 12-week follow-up.

CONCLUSION

One crucial component of treating affective disorders is preventing lithium-induced nephrogenic diabetic insipidus. It seems to be only partially reversible in patients receiving long-term lithium treatment. It is advised to closely monitor the course of treatment with a 12-hour trough value of 0.4 to 0.6 mmol/L. Both the patient and the doctor can be effectively informed about the onset of drug-induced nephrogenic diabetes insipidus by measuring the urine volume each day on an annual basis. Because of the potential for dehydration and worsening of drug intoxications, the condition is a major side effect.

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