

Diabetes insipidus: Overview

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Abstract

Diabetes insipidus is mainly characterized by polyuria, urinary volume over 3 L/day or 40mL/kg/day in adults, leading to subsequent polydipsia; these features are also present in most cases of diabetes mellitus. But today we can use natural treatment to remedy our problems concerning diabetes. This review is about diabetes insipidus which is entirely different from diabetes mellitus. We have read much about diabetes mellitus but now we must know about the diabetes insipidus. Diabetes insipidus is a uncommon condition, in which the kidneys are unable to conserve water. The amount of water which is conserved by the kidney is controlled by anti diuretic hormone (ADH) also called as vasopressin. In this disease there is lack of vasopressin in the body. In this overview there is a full disease profile of diabetes insipidus, so we came to know about the causes, sign & symptoms, treatment and medication for this disease.

Keywords: Diabetes insipidus, Diabetes mellitus, Overview.

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Introduction

When most people hear "diabetes," they think of diabetes mellitus. That's a condition in which blood sugars are chronically elevated. In fact, diabetes is a general term for conditions that cause increased urine production. And when it comes to increased urine production, diabetes insipidus takes the cake[1]. Diabetes insipidus results in excessive thirst and urination. The reason is problems with a particular hormone or its receptor. Diabetes insipidus increases the risk for dehydration. Diabetes insipidus is a condition in which the body cannot retain enough water. The patient is excessively thirsty and excretes large amounts of extremely diluted urine - a reduction in fluid intake does not reduce amounts and consistency of urine excretion. Diabetes insipidus is not related to diabetes mellitus (sugar diabetes). Inappropriate secretion or action of serum antidiuretic hormone (ADH) is termed Diabetes Insipidus (DI), characterized by polyuria (defined as 24 hour urine output in excess of 40 ml/kg) and polydipsia [2]. As

opposed to Diabetes Mellitus, where the urine is hypertonic and sweet (mellitus means honey in Greek), DI is defined as having urine that is hypotonic and bland, in the setting of polyuria. There are various mechanisms of pathogenesis of DI, all leading to the same clinical manifestation. In cases where the disorder is due to inadequate secretion of ADH, the disorder is termed Central DI, whereas when the disease is a result of renal insensitivity to ADH, the disease is termed Nephrogenic DI [3]. In cases where polyuria is due to vast amounts of ingested fluids driven primarily by behavioral or thirst disorders, it is called Primary Polydipsia (PP). Pregnant women can metabolize ADH in an accelerated manner leading to Gestational DI [2]. Overall, there are 3 cases of DI per 100,000 in the general population [4]. With regard to some familial forms of nephrogenic DI, incidence varies and some regions with common ancestry have higher incidence than other in the general population [5].

Cause

DI is an uncommon condition that occurs when the kidneys are unable to conserve water as they perform their function of filtering blood. The amount of water conserved is controlled by ADH, also called vasopressin.

ADH is a hormone produced in a region of the brain called the hypothalamus. It is then stored and released from the pituitary gland, a small gland at the base of the brain.

DI caused by a lack of ADH is called central diabetes insipidus. When DI is caused by a failure of the kidneys to respond to ADH, the condition is called nephrogenic diabetes insipidus.

Central diabetes insipidus can be caused by damage to the hypothalamus or pituitary gland as a result of:

- Head injury
- Infection
- Loss of blood supply to the gland
- Surgery
- Tumor

Sign and symptoms

Diabetes Insipidus leads to frequent urination, and this is the most common and clear symptom.

Frequent urination, unusual thirst, and dehydration are all symptoms of DI.

Children suffering from the condition may become irritable or listless, with fever and vomiting also possible.

Different types of diabetes insipidus

Central Diabetes insipidus: occurs when the pituitary gland is damaged resulting in ADH deficiency. It is treated with desmopressin, a synthetic hormone.

Gestational Diabetes insipidus : is associated with pregnancy, and occurs when an enzyme created by the placenta destroys ADH in the mother.

Nephrogenic Diabetes insipidus : is a form of diabetes insipidus due primarily to pathology of the kidney. This is in contrast to central/neurogenic diabetes insipidus, which is caused by insufficient of ADH/AVP. Nephrogenic diabetes insipidus is caused by an improper response of the kidney to ADH, leading to a decrease in the ability of the kidney to concentrate the urine by removing free water.

Etymology

- Diabetes - from L. diabetes, from Gk. diabetes "excessive discharge of urine," lit. "a passer-through, siphon," from diabainein "to pass through," from dia- "through" + bainein "to go"

- Insipidus - "without taste or perceptible flavor," from Fr. insipide, from L.L. insipidus "tasteless," from L. in- "not" + sapidus "tasty," from sapere "have a taste"

This is because patients experience polyuria (an excretion of over 2.5 liters of urine per day), and that the urine content does not have an elevated glucose concentration, as opposed to diabetes mellitus.[6]

Causes

Acquired : NDI is most common in its acquired forms, meaning that the defect was not present at birth. These acquired forms have numerous potential causes. The most obvious cause is a kidney or systemic disorder, including **amyloidosis**, **polycystic kidney disease**, electrolyte imbalance, or some other kidney defect.

The major causes of acquired NDI that produce clinical symptoms (e.g. polyuria) in the adult are lithium toxicity and hypercalcemia. Chronic lithium ingestion - appears to affect the tubules by entering the collecting tubule cells through sodium channels, accumulating and interfering with the normal response to ADH (ADH Resistance) in a mechanism that is not yet fully understood. Hypercalcemia causes natriuresis (increased sodium loss in the urine) and water diuresis, in part by its effect through the calcium sensing receptor (CaR). [7]

Osmotic : Other causes of acquired NDI include: hypokalemia, post-obstructive polyuria, sickle cell disease/trait, amyloidosis, Sjogren syndrome, renal cystic disease, Barter syndrome and various drugs (Amphotericin B, Orlistat, Ifosfomide, Ofloxacin, Cidofovir, Vaptanes).

In addition to kidney and systemic disorders, nephrogenic DI can present itself as a side-effect to some medications. The most common and well known of these drugs is lithium, although there are numerous other medications that cause this effect with lesser frequency. [8]

Hereditary : This form of DI can also be hereditary: means if a father is having this type of diabetes insipidus so a son or a daughter can also suffer from the same disease because it is hereditary disease.

Diagnosis

Differential diagnosis includes nephrogenic diabetes insipidus, neurogenic central diabetes insipidus and psychogenic polydipsia. They may be differentiated by using the water deprivation test. Recently, lab assays for ADH are available and can aid in diagnosis.

If able to rehydrate properly, sodium concentration should be nearer to the maximum of the normal range. This, however, is not a diagnostic finding, as it depends on patient hydration.

DDAVP can also be used; if the patient is able to concentrate urine following administration of DDAVP, then the cause of the diabetes insipidus is neurogenic; if no response occurs to DDAVP administration, then the cause is likely to be nephrogenic. [6]

Treatment

Treat any underlying cause, allow the patient to drink as much as required. Correct metabolic abnormalities. The first line of treatment is hydrochlorothiazide and amiloride. Consider a low-salt and low-protein diet.

In nephrogenic diabetes insipidus caused by lithium (seen in bipolar patients for example), K-sparing diuretics such as amiloride would be used. The goal in this case is to excrete lithium. Using Hydrochlorothiazide in this case would increase aldosterone, which would lead to increased sodium retention (and lithium as well). [9, 10]

Neurogenic diabetes insipidus

More commonly known as central diabetes insipidus, is due to a lack of vasopressin production in the brain. Vasopressin acts to increase the volume of blood (intravascularly), and decrease the volume of urine produced. Therefore, a lack of it causes increased urine production and dehydration.[11]

It is also known as "neurohypophyseal diabetes insipidus".

Causes

Idiopathic : In at least twenty-five percent of cases (the most commonly occurring classification), neurogenic diabetes insipidus is **idiopathic**, meaning that the lack of vasopressin production arose from an unknown cause. It is also due to damage of the hypothalamus, pituitary stalk, posterior pituitary, and can arise from head trauma.[12]

Acquired: The lack of vasopressin production usually results from some sort of damage to the pituitary gland. The damage to the brain could have been caused by a benign tumor (20 percent of cases), trauma (17 percent of cases), neurosurgery (9 percent of cases) or some rather rare causes which include hemochromatosis, sarcoidosis, and histiocytosis.[13]

Vasopressin is released by the posterior pituitary, but unlike most other pituitary hormones, vasopressin is produced in the hypothalamus. Neurogenic diabetes insipidus can be a failure of production at the hypothalamus, or a failure of release at the pituitary. [14]

Genetic : The most rare form of central DI is familial neurogenic diabetes insipidus. This form of DI is due to an inherited mutation of the arginine vasopressin-neurophysin II (AVP-NPII) gene, inherited in an autosomal dominant manner. At one point, only 45 families worldwide were known to possess this genetic

trait. It is now more widely recognized, although the precise number of people affected with this form of DI is unknown at the present time.[15]

Treatment

The disorder is treated with vasopressin analogs such as Desmopressin.[16]

Fluid Replacement and Pharmacotherapy

In an emergency, most patients with diabetes insipidus (DI) can drink enough fluid to replace their urine losses. Replace losses with dextrose and water or an intravenous (IV) fluid that is hypo-osmolar with respect to the patient's serum. Avoid hyperglycemia, volume overload, and overly rapid correction of hypernatremia. A good rule of thumb is to reduce serum sodium by 0.5 mmol/L every hour. The water deficit may be calculated on the basis of the assumption that body water is approximately 60% of body weight.[17]

In case of inadequate thirst, desmopressin is the drug of choice. A synthetic analogue of antidiuretic hormone (ADH), desmopressin is available in subcutaneous, intranasal, and oral preparations. Generally, it can be administered 2-3 times per day. Patients may require hospitalization to establish fluid needs. Frequent electrolyte monitoring is recommended.[18]

Alternatives to desmopressin as pharmacologic therapy for DI include synthetic vasopressin and the nonhormonal agents chlorpropamide, carbamazepine, clofibrate (no longer on the US market), thiazides, and indomethacin (limited efficacy).

In central DI, the primary problem is a hormone deficiency; therefore, physiologic replacement with desmopressin is usually effective. Use a nonhormonal drug for central DI if response is incomplete or desmopressin is too expensive. Nonhormonal drugs usually are more effective in treating nephrogenic DI.[19]

Monitor for fluid retention and hyponatremia during initial therapy. Follow the volume of water intake and the frequency and volume of urination, and inquire about thirst. Monitor serum sodium, 24-hour urine volumes, and specific gravity. Request posthospitalization follow-up visits with the patient every 6-12 months. Patients with normal thirst mechanisms can usually self-regulate. [20]

Postoperative setting

In patients with DI who have undergone surgery, administer the usual dose of desmopressin and give (hypotonic) IV fluids to match urine output.

After pituitary surgery, patients should undergo continuous monitoring of fluid intake, urine output, and specific gravities, along with daily measurements of serum electrolytes. In patients who develop DI, administer parenteral desmopressin every 12-24 hours,

along with adequate fluid to match losses. Follow the specific gravity of the urine, and administer the next dose of desmopressin when the specific gravity has fallen to less than 1.008-1.005 with an increase in urine output. When the patient can tolerate oral intake, thirst can become an adequate guide. [21]

Dietary Measures

No specific dietary considerations exist in chronic DI, but the patient should understand the importance of adequate and balanced salt and water intake. Patients with DI also must take special precautions, such as when traveling, to be prepared to treat vomiting or diarrhea and to avoid dehydration with exertion or hot weather. [22]

Consultations

In the setting of neurosurgery or head trauma, the diagnosis of DI may be obvious and even expected. The intensivists and the nurses who manage the patient acutely are in the best position to treat him or her acutely. In the more subtle forms of DI, and certainly in all chronic forms of DI for which therapy is expected to be indefinite, the clinical endocrinologist is an invaluable aid in establishing the diagnosis and designing therapy. [23]

Medication

Treat diabetes insipidus (DI) with desmopressin, nonhormonal drugs, or both. In central DI, the primary problem is a hormone deficiency; therefore, physiologic replacement with desmopressin is usually effective. Use a nonhormonal drug if response is incomplete or desmopressin is too expensive. Nonhormonal drugs usually are more effective in treating nephrogenic DI.

Hormones

Class Summary: Hormones prevent complications of DI and reduce morbidity.

Desmopressin (DDAVP)

Desmopressin is a synthetic analogue of antidiuretic hormone (ADH)—also known as arginine vasopressin (AVP)—with potent antidiuretic activity but no vasopressor activity.

Vasopressin (Pitressin)

Vasopressin has vasopressor and ADH activity. It increases water resorption at collecting ducts (ADH effect) and promotes smooth muscle contraction throughout the vascular bed of renal tubular epithelium (vasopressor effects). However, vasoconstriction is also increased in splanchnic, portal, coronary, cerebral, peripheral, pulmonary, and intrahepatic vessels. Vasopressin decreases portal pressure in portal hypertension. A notable undesirable effect is coronary artery constriction, which may dispose patients with

coronary artery disease to cardiac ischemia. This can be prevented with concurrent use of nitrates.[24]

Sulfonylurea Compounds

Class Summary: Hypoglycemic agents help relieve diuresis.

Chlorpropamide

Chlorpropamide promotes renal response to ADH.[25]

Anticonvulsants

Class Summary: Certain antiepileptic drugs, such as carbamazepine, have proven helpful in DI.

Carbamazepine (Tegretol, Carbatrol, Equetro)

Carbamazepine ameliorates DI by releasing ADH. It is not useful in total DI and generally is not a first-line drug. [26]

Diuretics

Class Summary: Diuretics may reduce flow to the ADH-sensitive distal nephron.

Hydrochlorothiazide (Microzide)

Hydrochlorothiazide is a thiazide diuretic that decreases urinary volume in the absence of ADH. It may induce mild volume depletion and cause proximal salt and water retention, thereby reducing flow to the ADH-sensitive distal nephron. Its effects are additive to those of other agents.

Amiloride (Midamor)

Amiloride is a potassium-sparing diuretic. It has a potassium-sparing effect, so the risk of hypokalemia is decreased in combination with hydrochlorothiazide. In addition, the 2 agents are synergistic with respect to antidiuresis.[24]

Nonsteroidal Anti-inflammatory Agents (NSAIDs)

Class Summary: The mechanism of action of nonsteroidal anti-inflammatory drugs (NSAIDs) is not known, but these agents may act by inhibiting prostaglandin synthesis.

Ibuprofen (Caldolor, Advil, Motrin)

Inhibition of prostaglandin synthesis reduces the delivery of solute to distal tubules, reducing urine volume and increasing urine osmolality. Ibuprofen is usually used in nephrogenic DI.

Indomethacin (Indocin)

Inhibition of prostaglandin synthesis reduces the delivery of solute to distal tubules, reducing urine volume and increasing urine osmolality. Indomethacin is usually used in nephrogenic DI. [27]

How does diabetes insipidus compare with diabetes mellitus?

Diabetes insipidus and diabetes mellitus should not be confused. Mellitus occurs due to insulin deficiency or insulin resistance and subsequent high blood glucose levels.

The two forms of diabetes are unrelated, and diabetes mellitus is far more common. Diabetes insipidus is a completely different type of illness. Diabetes Mellitus

is mainly caused by deficiency of insulin due to either destruction of Islet of Langerhans present in the pancreas or any autoimmune cause. Here there is increased blood sugar level and sugar starts to appear to come with urine. It even becomes fatal when sugar level increases very much. While Diabetes insipidus is caused by defect in secretion of vasopressin (Antidiuretic Hormone) which is secreted from pituitary gland present in hypothalamus. Its function is to reabsorb water from distal tubules in the kidney and due to this it control the concentration of urine. But its deficiency causes increased water excretion through urine even in low intake of water.[28-30]

Conclusion

DI is a disease of polydipsia and hypotonic polyuria caused by one of 4 etiologies: 1) Inadequate ADH secretion such as in CDI 2) Lack of response to ADH, as seen in NDI 3) Increased metabolism of ADH as occurs in GDI 4) Massive fluid ingestion as in psychogenic or dipsogenic polydipsia. Both CDI and NDI can be inherited or acquired. CDI is usually acquired as a result of an idiopathic/autoimmune process, and inherited mostly as an autosomal dominant disease. NDI is usually acquired as a result of lithium toxicity and occasionally inherited as an X-linked recessive trait. GDI is thought to be related to decreased hepatic clearance of vasopressinase, with increased metabolism of ADH. PP is usually caused as a result of psychiatric illness but can also be caused by a damaged thirst center, leading to the polydipsia. Treatment of DI consists of correcting deficits and preventing further polyuria. CDI is treated effectively with DDAVP; milder cases benefit from therapy with chlorpropamide. Caution should be used with DDAVP so as not to induce hyponatremia, while titrating the initial dosage. NDI is treated with less satisfactory results through volume contraction via sodium restriction and thiazide diuretics. Prostaglandin synthase inhibitors are effective as well, but should be used with caution, as they may cause renal disease on a long-term basis. PP is treated with fluid restriction, which is rarely successful although patients do not suffer from serious complications as they are able to maintain homeostasis at the expense of increased urine output and fluid intake This is an article about disease Diabetes insipidus, it is a rare condition affecting approximately 1 in every 25,000 people.. So, we concluded that diabetes insipidus is totally different from diabetes mellitus, because diabetes mellitus is related with increase blood sugar level & diabetes insipidus is related to thirst & frequent urination.

References

1. Jhuma Deb, Anoop Singh, Gouri Kumar Dash, Nilip Kanti Deb. Studies on antidiabetic activity of *Acacia ferruginea* DC. stem bark. *Indian J. Pharm. Biol. Res.* 2015; 3(4):11-15.
2. Karet FE (2011) Disorders of water and acid-base homeostasis. *Nephron Physiol* 118: p28-34.
3. Aleksandrov N, Audibert F, Bedard MJ, Mahone M, Goffinet F, et al. Gestational diabetes insipidus: a review of an underdiagnosed condition. *J Obstet Gynaecol Can* 2010;32: 225-231.
4. Saborio P, Tipton GA, Chan JC, Diabetes Insipidus. *Pediatr Rev* 2000;21: 122-129.
5. Arthus MF, Lonergan M, Crumley MJ, Naumova AK, Morin D, et al., Report of 33 novel AVPR2 mutations and analysis of 117 families with X-linked nephrogenic diabetes insipidus. *J Am Soc Nephrol* 2000;11: 1044-1054.
6. Madhavulu, Pathapati Rama Mohan, Devaraju Sreebhusan Raju, Acute effect of excess water intake on blood pressure in healthy Individuals Buchineni, *Asian Pac. J. Health Sci.*, 2014; 1(4): 496-499.
7. Marples D, Frokiaer J, Dorup J, Knepper MA, Nielsen S. Hypokalemia-induced downregulation of aquaporin-2 water channel expression in rat kidney medulla & cortex. *Clin. Invest*, 1996, 97(8), 1960-1968
8. Kavanagh S. Nephrogenic diabetes insipidus. Patient uk. Retrieved, 2009
9. Christensen S, Kusano E, Yusufi AN, Murayama N, Dousa TP. Pathogenesis of nephrogenic diabetes insipidus due to chronic administration of lithium in rats. *J.clin.invest.* 1985, 75(6), 1869-1879
10. Kirchlechner V, Koller DY, Seidl R, Waldhauser F. Treatment of nephrogenic diabetes insipidus with hydrochlorothiazide & amiloride. *Arch Dis.child.* 1999,80(6), 548-552.
11. Chitturis, Harris M, Thomsett MJ, et al. Utility of AVP gene testing in familial neurohypophyseal diabetes insipidus. *Clin Endocrinol.* 2008,69(6),926-930
12. Lee YW, Lee KW, Ryu JW, et al. Mutation of glu 78 of the AUP-NP11 gene impairs neurophysin as a carrier protein for arginine vasopressin in a family with neurohypophyseal diabetes insipidus. *Ann.clin.lab.sci.* 2008.38(1): 12-14
13. http://www.medical.library.org/journals4a/diabetes_insipidus.htm

14. Central diabetes insipidus: Pituitary gland disorders. Merck manual home health handbook. Retrieved 2009
15. http://www.the-doctors-doctor.com/diseases/diabetes_insidus.htm
16. http://diabetesinsipidus.org/4di_familial.htm
17. Los EL, Deen PM, Robben JH. Potential of non peptide (ant)agonists to rescue vasopressin V2 receptor mutants for the treatment of X-linked nephrogenic diabetes insipidus. *J neuroendocrinol.* 2010, 22(5), 393-399
18. Rochdi MD, Vargas GA, Carpentier E, et al. Functional characterization of V2-vasopressin receptor substitutions (R137H/C/L) Leading to nephrogenic diabetes insipidus & nephrogenic syndrome of inappropriate Antidiuresis; implications for treatment. *Mol pharmacol.* 2010
19. Kristof RA, Rother M, Neuloh G, et al. Incidence, clinical manifestations & cause of water & electrolyte disturbances following transphenoidal pituitary adenoma surgery: a prospective observational study. *J neurosurg.* 2009.
20. Hedrich CM, Zauhurzok- Buczynska A, Gawlik A, et al. Autosomal dominant neurohypophyseal diabetes insipidus in two families. Molecular analysis of the vasopressin-neurophysin 2 gene & functional studies of three missense mutation. *Horm Res.* 2009, 71(2), 111-119
21. Krahulik D, Zapletalova J, Frysak Z, et al. Dysfunction of hypothalamic- hypophysial axis after traumatic brain injury in adults. *J neurosurg.* 2009
22. Li G, Shao P, Sun X, et al. Magnetic resonance imaging & pituitary function in children with panhypopituitarism. *Horm Res Paediatr.* 2010,73(3), 205-209
23. Schier RW. Systemic arterial vasodilation, vasopressin & vasopressinase in pregnancy. *J Am son nephrol.* 2010. 21(4), 570-572
24. Hadjizacharia P, Beale EO, Inaba K, et al. Acute diabetes insipidus in severe head injury: A prospective study. *J Am coll surg.* 2008, 207(4), 477-484
25. Spanakis E, Milard E, Gragnolic C. AVPR2 variants & mutations in nephrogenic diabetes insipidus: review & missense mutation significance. *J cell physiol* 2008, 217(3), 605-617
26. Vande Walle J, Stockner M, Raes A, et al. Desmopressin 30 yrs in clinical use: a safety review. *Curr drug saf.* 2007, 2(3), 232-238
27. Ausiello JC, Bruce JN, Freda PU. Postoperative assessment of the patients after transphenoidal pituitary surgerg. 2008,11(4), 391-401
28. Dhar HL. Meditation therapy in cardiovascular & metabolic disorders special reference to coronary artery disease & diabetes. *Bombay hospital journal.* 2009;51(4):1.
29. Arima H, Kondo K, Kakiya S, Nagasaki H, Yokoi H, Yambe Y, et al. Rapid and sensitive vasopressin heteronuclear RNA responses to changes in plasma osmolality. *J Neuroendocrinol,* 1999; 11:337–341.
30. Di Iorgi N, Napoli F, Allegri AE, Olivieri I, Bertelli E, Gallizia A, et al. Diabetes insipidus--diagnosis and management. *Horm Res Paediatr,* 2012; 77: 69–84.

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