

Chapter 69

Algorithmic Approach for the Diagnosis of Polyuria

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INTRODUCTION

Polyuria is a very common clinical dilemma often not worked up systematically. Routinely, we tend to ascribe it to diabetes mellitus (DM), but there are many causes to be considered in the differential diagnosis and a thorough work-up will be needed in most cases. Polyuria is the passage of excessive quantity of urine. It implies water or solute diuresis. In polyuria, fluid of at least 2.5–3.0 L/day is excreted with the urine output going up to more than 40 mL/kg/day. Polyuria usually is associated with polydipsia, which results in an excessive water intake. A water intake of more than 100 mL/kg/day (6 L/day) is termed as polydipsia. Frequent passage of small amounts of urine has many causes such as urinary tract infection, benign prostatic hyperplasia, urinary tract stones and urinary incontinence. It is entirely different from polyuria.

WATER METABOLISM

Our total body water content is about 35 liters, of which 60% (21 L) is extracellular and 40% (14 L) is intracellular. The extracellular water is further distributed as plasma (about 2.5 L) and interstitial fluid (about 18.5 L). The intracellular water is mainly in the cytoplasm of the cells. The approximate input of water per day is 2.4 L. Of this, water intake as fluids is 1.5 L; water content of food consumed is 0.5 L and water from biological oxidation is 0.4 L. Solutes are substances dissolved in body water such as sodium chloride, glucose. Solvent is the liquid in which solutes are dissolved and mostly this solvent is water. We need to be familiar with the two expressions namely “Osmolality” and “Osmolarity”. When the solutes are expressed as milliosmoles/kilogram (mOsm/kg) of the solvent, it is referred to as “Osmolality” and when expressed as milliosmoles/liter (mOsm/L) of the solvent, we refer it as “Osmolarity”. Our plasma osmolality depends on the number of particles in solution. Normally it is maintained within a very narrow range of about 285 mOsm/kg H₂O. Sodium is the principle determinant of the osmolality of the plasma as can be seen by the formula given below.

Osmolality is calculated as follows: $2(\text{Na} + \text{K}) + (\text{Glucose}/18) + (\text{BUN}/2.8)$, which is $2(132 + 4) + (108/18) + (14/2.8)$ and that is equal to $(2 \times 136) + 6 + 5 = 272 + 11 = 283$.

HYPOTHALAMIC PITUITARY ENDOCRINE AXIS

Antidiuretic hormone (ADH), also known as vasopressin, is synthesized and secreted by the posterior pituitary gland or neurohypophysis. It is also known as arginine vasopressin (AVP). Plasma osmolality is always maintained in a very narrow physiological range of about 285 mOsm/kg H₂O by the plasma ADH concentration

of 4 pg/mL. Release of ADH is immediately stopped and water is excreted, if the plasma osmolality reaches 280 mOsm/kg H₂O (just five points less than normal). This is called the threshold for ADH release. Secretion of ADH is immediately doubled and thirst is stimulated if the plasma osmolality increases to 290 mOsm/kg H₂O (just five points more than normal). This is called the threshold for thirst.

Renal handling of water excretion is very fascinating. A primary urine of about 170 liters is filtered [glomerular filtration rate (GFR) of 120 mL/minute x 60 minutes x 24 hours = 170 L]. Such a large volume of water is needed to flush out all the solutes and waste molecules through the microfilters of the glomeruli. But we cannot afford to lose even a small fraction of that filtered primary urine (as our total water in the body is itself 65 liters and plasma volume is mere 2.5 liters). Hence, all the filtered 170 mL should almost be reabsorbed back into the system. The final urine volume is only about 1.5 liters, which means 99% of the filtered primary urine is reabsorbed and only 1% is finally excreted. This is made possible by both passive and active reabsorption in the renal tubules. About 70% of water is reabsorbed in the proximal convoluted tubule (PCT) by the aquaporin-1 (AQP-1) channels. Rest of the 29% is reabsorbed by AQP-2, 3 and 4 channels in the loop of Henle and distal convoluted tubule (DCT). (Prof. Peter Agre, the winner of Nobel prize in Chemistry for 2003, has characterized these AQP channels). Reabsorption of water in the collecting tubules (CT) is mediated by the ADH.

Decrease in plasma volume triggers secretion of renin, which initiates angiotensin formation. Angiotensin II is a powerful dipsinogen and stimulates thirst and also AVP release. Increase in plasma osmolality stimulates AVP release, which reduces the urine output and balances the increase in osmolality. If there is deficiency of AVP, we will have a water diuresis. The countercurrent multiplier and countercurrent exchange mechanisms in the renal tubules and renal parenchyma maintain this delicate and tricky balance of water and solutes. Complex interactions of plasma osmolality, plasma volume, thirst center, kidney, neurohypophysis and the bandmaster—the hypothalamus regulate the fine and delicate water and solute balance. Dysfunction in any of these areas results in polyuria and polydipsia.

The clinical disorders of water balance include cardiac failure, cirrhosis of liver, renal failure, hyper and hypothyroidism, Addison's disease, central diabetes insipidus (CDI), nephrogenic diabetes insipidus (NDI), psychogenic polydipsia (PPD) or compulsive water drinking (CWD) and pregnancy.

POLYURIA

Polyuria is the passage of excessive quantity of urine and it implies water or solute diuresis of at least 2.5–3 L/day or urine volume of more than 40 mL/kg/day. Polyuria is usually associated with polydipsia. Polydipsia is defined as water intake of more than 100 mL/kg/day (6 L/day).

There are four mechanisms, which can cause polyuria. One or more of these will be operating.

1. Increased intake of fluids as in psychogenic causes, stress and anxiety
2. Increased GFR as in hyperthyroidism, fever, hypermetabolic states
3. Increased output of solutes as occurs in DM, hyperthyroidism, hyperparathyroidism, use of diuretics (which present more solute at the DCT)
4. Inability of the kidney to reabsorb water in DCT as in CDI, NDI, drugs and chronic renal failure (CRF).

Clinical History in a Case of Polyuria

This must include the following:

- Is it increased volume of urine or just increased frequency of urination?
- Is there associated polydipsia?
- Is there weight loss as occurs in DM or underlying malignancy?
- Is there family history of DM or diabetes insipidus?
- History of neurosurgery, meningitis, head injury, psychiatric illness or CWD
- Drugs such as diuretics, lithium, analgesics, Vitamin D, hypercalcemia, nephrotoxic drugs
- Recurrent infections as in DM
- History of hypertension, chronic kidney disease (CKD), hypercalcemia, urinary tract obstruction, polycystic kidney disease.

Physical Examination in a Case of Polyuria

This must include the following:

- Ascertain wasting or cachexia as occurs in DM, DI and malignancy
- Look for skin manifestations as in cancers and DM
- Examination of nails for clubbing, CKD nails, carcinoma of bronchus
- Anemia as occurs in CKD and malignancy
- Look for lymphadenopathy as in infiltrative disorders and malignancy
- Fundus examination in DM and hypertension for papilledema.

Etiological Classification of Polyuria

- *Endocrine:* DM, CDI, Cushing's syndrome
- *Renal:* CRF, relief of urinary tract obstruction, chronic pyelonephritis, NDI, Fanconi syndrome
- *Iatrogenic:* Diuretic therapy, alcohol, lithium, tetracyclines
- *Metabolic:* Hypercalcemia, potassium depletion
- *Psychological:* PPD or CWD
- *Other causes:* Sickle cell anemia, pulmonary and systemic venous thromboembolism (PSVT).

Diabetes Insipidus

There are four types:

Central Diabetes Insipidus (Neurogenic)

It is due to abnormality of ADH or AVP. Causes may be acquired as in brain tumors, head trauma, granulomatous diseases and autoimmunity. Or, they may be inherited as in genetic mutation of vasopressin gene, which may be autosomal dominant or recessive or

X-linked recessive. Or, it may be idiopathic. Lack of AVP production and/or secretion may be partial or complete. Usually the urine volume is very high (> 8–10 L/day). Polydipsia is usually a feature and is very troublesome. Any disturbance or injury of the hypothalamus and/or pituitary is a potential cause. It may be due to idiopathic cause, or trauma, neoplasia, cysts and inflammation.

Nephrogenic Diabetes Insipidus

Nephrogenic diabetes insipidus occurs due to nonresponse of kidneys to ADH. It can be congenital or acquired; V_2 -vasopressin receptor mutations are known. About 180+ mutations are documented in chromosome region Xq28. Protein misfolding of V_2 receptor is noted. Ninety percent of NDI is genetic and only 10% is acquired. The acquired causes include hypokalemia and hypercalcemia, bilateral urinary tract obstruction, lithium therapy, acute renal failure and advanced CRF. The polyuria of acquired NDI is of a moderate degree (3–4 L/day). The genetic form of NDI commonly occurs at birth, presenting as increased urinary frequency, nocturia, enuresis, and frequent or constant thirst. In infants, thirst and polyuria cannot be verbalized. So, we need to look for features such as inconsolable crying, unusually wet diapers, frequent need to nurse, dry skin with cool extremities and failure to thrive.

Primary Polydipsic Diabetes Insipidus

It occurs due to suppression of ADH by excessive fluid intake like in dipsogenic, psychogenic or iatrogenic DI—excessive water drinking is prescribed as a treatment. Usually it is acquired and is mostly idiopathic. Sometimes it may be due to chronic meningitis, granulomatous diseases, multiple sclerosis or other diffuse pathology of the brain and psychiatric illness.

Gestagenic Diabetes Insipidus

It occurs in pregnancy due to destruction of ADH by placental vasopressinase.

24-Hour Urine Collection

We need to collect urine in a clean 5 liter plastic container with 10 mL of acetic acid during normal fluid and food intake. Polyuria is urine excretion of more than 40 mL/kg body weight per day. The urine osmolality is less than 300 mOsm/kg of water and the urine specific gravity is less than 1.010. Polydipsia is defined as water intake of more than 100 mL/kg/day. Measurement of plasma sodium on the day of urine collection is needed for further calculations.

Hare-Hickey Test (Water Deprivation Test)

It is indicated in the evaluation of DI. The technique includes complete fluid deprivation and injection of hypertonic sodium chloride solution. Exogenous injection of 1-desamino-8-D-arginine vasopressin (DDAVP) is given and ADH to serum osmolality ratio is measured. Decreased ADH to serum osmolality ratio indicates CDI and increased ratio means it is NDI.

Treatment with 1-desamino-8-D-arginine Vasopressin

Several formulations of DDAVP are available. These include intranasal solution of 100 µg/mL, intranasal spray 10 µg/spray and parenteral preparation of 4 µg/mL for IV/IM injections. These are used rarely. Oral 200 µg tablets (roughly 10 µg intranasal = 200 µg oral tablet) are also available.

Nocturnal Polyuria

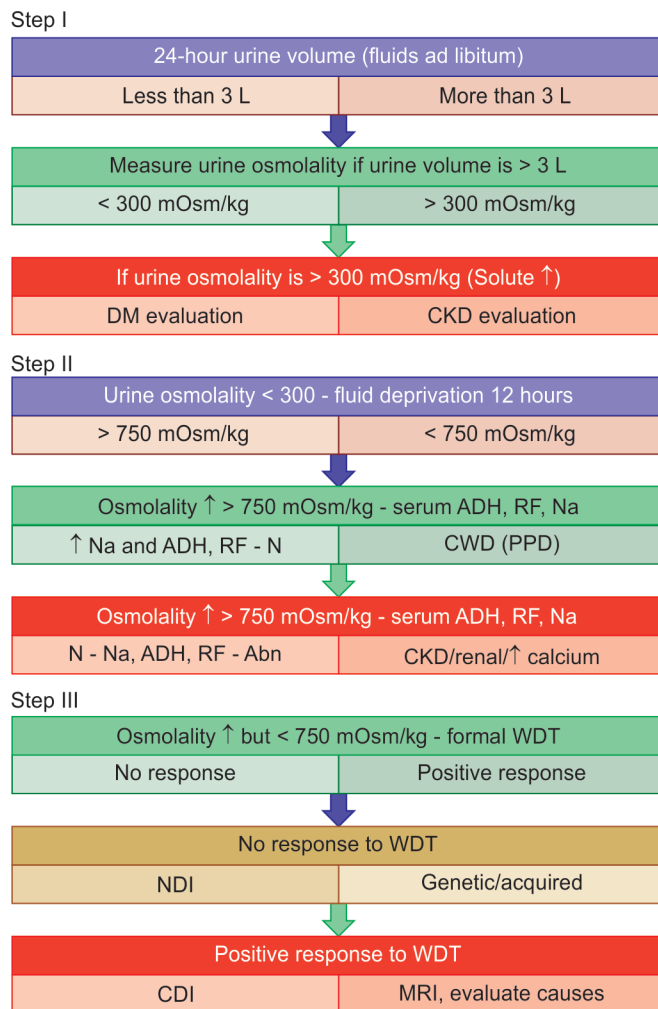
Nocturnal polyuria (NP) is a disorder of the circadian rhythm in AVP secretion. There will be an increase in natriuretic peptides

[atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP)]. Measurement of plasma AVP and urinary AVP will clinch the diagnosis. Urine AVP to urine creatinine ratio is a good laboratory test to pick up NP due to defective AVP secretion.

An Algorithmic Approach to the Diagnosis of Polyuria

A three-step algorithm for evaluation of a case of polyuria has been discussed in **Flow chart 1**. First, the 24-hour urine volume is measured. If it is less than 3 liters, it is not a case of polyuria. If the 24-hour urine volume is more than 3 liters, then we need to measure

Flow chart 1: Algorithm for the differential diagnosis of polyuria



Abbreviations: DM, Diabetes mellitus; CKD, Chronic kidney disease; ADH, Antidiuretic hormone; RF, Renal function; PPD, Psychogenic polydipsia; CWD, Compulsive water drinking; WDT, Water deprivation test; NDI, Nephrogenic diabetes insipidus; CDI, Central diabetes insipidus; MRI, Magnetic resonance imaging

the urine osmolality. If the urine osmolality is more than 300 mOsm/kg, it indicates solute diuresis and the underlying cause will be either DM or CKD. Evaluation must be directed at these conditions.

On the other hand, if the urine osmolality is less than 300 mOsm/kg, then we do a fluid deprivation test. During the next 12-hour period, all fluid intake is stopped. At the end of 12 hours of fluid deprivation, we need to measure urine osmolality, serum ADH, renal function and serum sodium. After fluid deprivation, normally the urine osmolality must increase to greater than 750 mOsm/kg. If this is so, and if the serum sodium and ADH are reduced and the renal function is normal, it confirms PPD or CWD.

On the other hand, if the serum sodium and ADH are normal and the renal function tests are abnormal, it indicates CKD or NDI or hypercalcemia.

The other scenario, after 12-hour fluid deprivation, will be that the urine osmolality has not increased to greater than 750 mOsm/kg. Then, we do a formal water deprivation test (WDT or Hare-Hickey Test). The result could be a nonresponse to WDT (no further increase in urine osmolality), which confirms NDI. Then, we need to evaluate for genetic or acquired causes of NDI. But, if the WDT shows a positive response (there is definite increase in urine osmolality), then the diagnosis of CDI is confirmed.

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