Polyuria: A Pathophysiologic Approach

By Kirstie Lithgow, BSc, MD and Bernard Corenblum MD, FRCPC

About the Authors

Kirstie Lithgow and Bernard Corenblum are with the Department of Medicine, Cumming School of Medicine, University of Calgary, Calgary, AB. Corresponding author: kclithgo@ucalgary.ca

A 22-year-old man presented with a 3-week history of increased thirst, polydipsia, and polyuria. He described consuming large volumes of water and waking up multiple times throughout the night to drink and urinate. He also endorsed symptoms of fatigue and frequent headaches. Prior to this, he had been well. There was no history of diuretic use, lithium use, or renal disease. There was no prior head trauma, cranial irradiation, or intracranial pathology. He denied consumption of nutritional or protein supplements. Clinical exam revealed a well appearing young man with normal heart rate and blood pressure. Visual fields and general neurologic exam were grossly normal.

Baselines investigations revealed serum sodium ranging from 141–142 mmol/L (reference range 133–145 mmol/L), creatinine 92 µmol/L (50–120 µmol/L), random glucose 5.4 mmol/L (3.3–11.0 mmol/L), potassium 4.0 (3.3–5.1 mmol/L) and ionized calcium 1.25 mmol/L (1.15–1.35 mmol/L).

A 24-hour urine collection was arranged, and returned a urine volume of 5.6L (normal less than 3 litres/24 hours). Further investigations revealed a serum sodium of 142 mmol/L, serum osmolality 306 mmol/kg (280–300 mmol/kg), and urine osmolality of 102 mmol/kg (50–1200 mmol/kg). AM cortisol was 372 nmol/L (200–690 nmol/L).

These results demonstrated inability to concentrate the urine, despite the physiologic stimulus of hyperosmolality. Based on this, a presumptive diagnosis of diabetes insipidus was made. The patient was instructed to drink as much as he needed to satiate his thirst, and to avoid fluid restriction. The patient was started on DDAVP intranasal spray, which provided immediate relief from his symptoms. Magnetic resonance imaging of the brain revealed an unremarkable pituitary gland with abnormal thickening of the pituitary stalk and loss of the posterior pituitary bright spot. This confirmed the diagnosis of central diabetes insipidus, presumed secondary to infiltrative disease affecting the pituitary stalk.

Introduction

Polyuria is defined as inappropriately high urine output relative to effective arterial blood volume and serum sodium. In adults, polyuria can be objectively quantified as urine output in excess of 3–3.5 L per day with a low urine osmolality (<300 mmol/kg).²

Daily urine output is dependent on 2 major factors. The first is the amount of daily solute excretion, and the second is the urine concentrating capability of the nephron.³ Disturbances in either of these factors can occur by many different mechanisms, and can lead to a diuresis. This diuresis can be driven either by solute (solute diuresis), water (water diuresis) or a combination of these processes.⁴ A diagnostic algorithm for polyuria is outlined in Figure 1.

Solute Diuresis

Daily solute intake varies between individuals, but typically averages about 10 mmol/kg or 500–800 mmol/day.^{2,3} Solute diuresis is the result of a higher solute load that exceeds the usual solute excretion.⁴ Higher solute loads can be a consequence of either increased solute intake or increased solute generation through metabolism. High solute intake can occur from intravenous fluids, enteral or parental nutrition, and any other sources of exogenous protein, glucose, bicarbonate, or sugar alcohols.^{2,4} Metabolic processes leading to increased solute generation include hyperglycemia and azotemia.^{2,4} Increased solute excretion drives urine output in a linear fashion.³ Furthermore, solute diuresis impairs the ability of the kidney to concentrate urine. Typically, in a pure solute diuresis, urine concentration is between 300 and 500 mmol/kg.^{2,4} The specific cause of solute diuresis can be further delineated with estimation of the urine electrolyte solute over 24 hours: $2(\text{urine [Na]} + \text{urine [K]}) \times 24 \text{ hours}$.⁴ Values greater than 600 mmol/day suggest electrolytes are the solutes driving the diuresis, while values less than 600 mmol/day imply that the diuresis is due to a non-electrolyte solute, typically glucose or urea.

Figure 1. Diagnostic approach to polyuria

Water Diuresis

Water diuresis can occur due to excessive amounts of free water consumption (primary polydipsia) or impaired secretion or response to ADH (diabetes insipidus). In both cases, urine osmolality should be less than 100 mmol/kg.² Primary polydipsia is characterized by excessive water consumption. This can be a result of compulsive water drinking (often observed in psychiatric disorders) or a defect in the thirst centre of the hypothalamus due to an infiltrative disease process.^{5,6}

The osmotic threshold for ADH release occurs at 280–290 mmol/kg. Failure to maximally concentrate the urine (1000–1200 mmol/kg in healthy kidneys) when serum osmolality rises above the osmotic threshold suggest diabetes insipidus.³ Diabetes insipidus (DI) can result from either insufficient ADH secretion from the posterior pituitary (central DI) or ADH resistance (nephrogenic DI).¹

Central DI can be caused by both congenital and acquired conditions known to affect the hypothalamic-neurohypophyseal system^{7,8} (Table 1). Polyuria occurs when 80% or more of the ADH secreting neurons are damaged.⁷ Metastatic disease has a predilection for the posterior pituitary, as its blood supply is derived from the systemic circulation, in contrast to the anterior pituitary which is supplied by the hypophyseal portal system.⁹ Rapid onset of polydipsia and polyuria in a patient older than

50 years of age should therefore raise immediate suspicion for metastatic disease.⁹ Treatment of adrenal insufficiency may “unmask” or exacerbate central DI, as normalization of blood pressure following glucocorticoid replacement inhibits ADH release.¹⁰

In the pregnant state, ADH degradation is increased due to placental production of vasopressinase. Any mechanism of hepatic dysfunction that occurs in pregnancy (pre-eclampsia, HELLP, acute fatty liver) will augment this normal physiology by reducing vasopressinase clearance, and can subsequently lead to transient DI.¹¹

In nephrogenic DI, ADH is present but the kidneys are unable to respond appropriately.⁸ In normal physiology, ADH acts to concentrate the urine via activation of the vasopressin V2 receptor, which leads to insertion of aquaporin-2 water channels in the collecting duct.^{3,12} Nephrogenic DI can be primary (genetic) or secondary (acquired). Primary nephrogenic DI occurs as a result of genetic mutations affecting either the vasopressin 2 receptor or aquaporin-2 water channels; typically, such conditions present in infancy.¹² Secondary nephrogenic DI can occur by a variety of mechanisms; the most common is chronic lithium administration. Lithium enters the principal cell in the collecting duct via epithelial sodium channels, and is thought to impair urinary concentrating ability via reduction in the number of principal cells and interference in signalling pathways involved

in aquaporin.^{12,13} Hypercalcemia, hypokalemia, obstructive uropathy, and pregnancy can lead to transient nephrogenic DI.^{12,13} Hypercalcemia can lead to nephrogenic DI by causing a renal concentrating defect when calcium levels are persistently above 2.75 mmol/L.¹⁴ Increased hydrostatic pressure from obstructive uropathy may lead to suppression of aquaporin-2 expression, resulting in transient nephrogenic DI.¹² Nephrogenic DI can be caused by various renal diseases due to impairment of renal concentrating mechanisms, even before glomerular filtration rate is impaired. Polycystic kidney disease causes anatomic disruption of the medullary architecture. Polyuria in sickle cell disease results from a similar mechanism, as sickling in the vasa recta interferes with the countercurrent exchange mechanisms.¹⁶ Infiltrative renal disease including amyloid and

Sjogren's syndrome impair renal tubular function due to amyloid deposition and lymphocytic infiltration.^{17,18}

Mixed Water-Solute Diuresis

In some cases, polyuria can be caused by a combination of both mechanisms. The linear relationship between solute excretion and urine output described above is strongly influenced by ADH. In the setting of a solute diuresis, absence or deficiency of ADH can augment the degree of polyuria quite dramatically.^{14,19} Clinical examples of mixed diuresis include concurrent loading of both water and solute, chronic renal failure or infiltrative renal disease, relief of prolonged urinary obstruction, and partial DI.^{2,4} Typically in such scenarios, urine osmolality ranges from 100–300 mmol/kg.²

Table 1. Etiologies of Central Diabetes Insipidus

Tumours	Pituitary adenoma (with suprasellar extension) Craniopharyngioma Germinoma Metastatic disease
Trauma	Closed head injury Pituitary apoplexy Post-surgical
Infiltrative/autoimmune	Langerhan's cell histiocytosis Lymphocytic hypophysitis IGG4 related disease Sarcoidosis Immune checkpoint inhibitors
Congenital	Familial Central Diabetes Insipidus Wolfram syndrome Septo-optic dysplasia Congenital hypopituitarism

Conclusion

Polyuria has a broad range of causes and can be a diagnostic challenge for clinicians. Understanding the pathophysiology that underpins the different mechanisms of polyuria is essential to appropriate workup, diagnosis, and treatment of this condition. If this is a complaint, the first step is to quantitate the 24-hour urine volume. **We recommend referral to endocrinology when there is evidence of hypothalamic or pituitary disease, when a water deprivation test is required, or in cases where the diagnosis is unclear.**

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