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 umol/L (50–120 umol/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 hyperosmolarity. 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 confirms the diagnosis of central diabetes insipidus, presumed secondary to infiltrative disease affecting the pituitary stalk.
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. Primary polydipsia is characterized by excessive water consumption. This can be the 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. 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 suggests diabetes insipidus. Diabetes insipidus (DI) can result from either insufficient ADH secretion from the posterior pituitary (central DI) or ADH resistance (nephrogenic DI).

Central DI can be caused by both congenital and acquired conditions known to affect the hypothalamic-neurohypophyseal system (Table 1). Polyuria occurs when 80% or more of the ADH secreting neurons are damaged. 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. Rapid onset of polydipsia and polyuria in a patient older than 50 years of age should therefore raise immediate suspicion for metastatic disease. Treatment of adrenal insufficiency may “unmask” or exacerbate central DI, as normalization of blood pressure following glucocorticoid replacement inhibits ADH release.

In the pregnant state, ADH degradation is increased due to placentonal 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.

In nephrogenic DI, ADH is present but the kidneys are unable to respond appropriately. 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. 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. 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 water reabsorption.
Hypercalcemia, hypokalemia, obstructive uropathy, and pregnancy can lead to transient nephrogenic DI. Hypercalcemia can lead to nephrogenic DI by causing a renal concentrating defect when calcium levels are persistently above 2.75 mmol/L. Increased hydrostatic pressure from obstructive uropathy may lead to suppression of aquaporin-2 expression, resulting in transient nephrogenic DI. 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. Infiltrative renal disease including amyloid and Sjogren’s syndrome impair renal tubular function due to amyloid deposition and lymphocytic infiltration.

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. 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. Typically in such scenarios, urine osmolality ranges from 100–300 mmol/kg.

Table 1. Etiologies of Central Diabetes Insipidus

<table>
<thead>
<tr>
<th>Tumours</th>
<th>Pituitary adenoma (with suprasellar extension)</th>
<th>Craniorhynangia</th>
<th>Germinoma</th>
<th>Metastatic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma</td>
<td>Closed head injury</td>
<td>Pituitary apoplexy</td>
<td>Post-surgical</td>
<td></td>
</tr>
<tr>
<td>Infiltrative/autoimmune</td>
<td>Langerhan’s cell histiocytosis</td>
<td>Lymphocytic hypophysitis</td>
<td>IGG4 related disease</td>
<td>Sarcoiosis</td>
</tr>
<tr>
<td>Congenital</td>
<td>Familial Central Diabetes Insipidus</td>
<td>Wolfram syndrome</td>
<td>Septo-optic dysplasia</td>
<td>Congenital hypopituitarism</td>
</tr>
</tbody>
</table>

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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References


