Sodium, Osmolality, and Antidiuretic Hormone

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Introduction

Endocrinopathies that disrupt water homeostasis are complex and differential diagnosis can be challenging, as an abnormal water balance can result from a variety of disorders. Appropriate diagnosis relies on clinical observation and proper laboratory evaluation. This section reviews relevant labs and their interpretations as well as the next steps in addressing abnormal values.

Polyuria and Polydipsia

When concerned for an endocrinopathy like diabetes insipidus, it is necessary to initially confirm that the patient truly has polyuria. Polyuria is defined as one of the following: urine output greater than 2 L/m^2/day, 150 ml/kg/ day in neonates, 100–110 ml/kg/day in children up to age 2, and 40–50 ml/kg/day in older children. It is also important to quantify liquid intake and assess for polydipsia resulting from thirst. Children with excessive thirst often exhibit a preference for water, whereas children with excessive consumption of juice or other sugary beverages may be driven by taste or other behavioral issues rather than thirst. One must ask how polyuria and polydipsia interfere with normal activities, including if behaviors are nocturnal, and whether there is a possibility of a psychosocial component (see also Chap. 55).

Once polyuria or polydipsia is established, the next step is to obtain first-morning labs ideally after the child has discontinued drinking including serum osmolality, urinary osmolality, serum sodium, potassium, calcium, glucose, blood urea nitrogen (BUN), and urinalysis [1, 2]. *Appropriate interpretation of these labs requires simultaneous measurement of both urine and serum samples.*

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Serum and Urine Osmolality

Sodium, glucose, and blood urea nitrogen (BUN) are the primary contributors to serum osmolality under normal physiologic conditions. With known concentrations of these three compounds, *calculated serum osmolality* can be estimated by (2 * Serum Na + Serum glucose + BUN), with all concentrations in mmol/L or by ([2 * Serum Na in mmol/L] + [Serum glucose in mg/dL/18] + [BUN in mg/dL/2.8]). When calculated serum osmolality differs from the measured serum osmolality by more than 10 mOsm/kg, this "gap" indicates the presence of another osmotically active compound in circulation, such as ketones, ethanol, or toxins like ethylene glycol.

In the urine, sodium, urea, potassium, and chloride are the primary contributors to osmolality under normal physiologic conditions, with glucose also contributing significantly if glucosuria is present. Urine osmolality is considered a more precise measurement than urine specific gravity, discussed below, although the two are highly correlated when urine has a neutral pH and is "clean" from other substances such as protein, ketones, and bilirubin [3].

Diabetes insipidus is generally characterized by high or high-normal serum sodium and serum osmolality in the presence of hypotonic urine osmolality (see Table 28.1). A serum osmolality greater than 300 mOsm/kg at the same time of urine osmolality less than 300 mOsm/kg is reflective of diabetes insipidus due to inappropriately dilute urine. In contrast, a urine osmolality of greater than 600 mOsm/kg in the setting of normal serum osmolality (<300 mOsm/kg) confirms adequate water reabsorption in the kidneys and strongly suggests against diabetes insipidus. If serum osmolality is greater than 300 mOsm/kg and urine osmolality is less than 600 mOsm/kg, the result is indeterminate and a water deprivation test should be the next step in confirmation of diabetes insipidus diagnosis as discussed in Chap. 55 [1, 2].

In cases of syndrome of inappropriate antidiuretic hormone secretion (SIADH), urine osmolality is usually inappropriately concentrated (greater than 100 mOsm/kg) in the presence of hypotonic serum osmolality (less than

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Table 28.1 Key facts reference box

Diabetes insipidus
May be hypovolemic due to polyuria >2 L/m^2/day
Serum osmolality >300 mOsm/kg in the presence of urine osmolality <300 mOsm/kg
Hypernatremia in the presence of dilute urine
Next steps: water deprivation test (see Part III)
SIADH
Clinical euvolemia
Serum osmolality <275 mOsm/kg in the presence of urine osmolality >100 mOsm/kg
Urinary sodium >40 mmol/L
Hyponatremia in the presence of inappropriately concentrated urine
Next steps: fluid restriction (consult with endocrinology)

275 mOsm/kg, see Table 28.1) [4, 5]. Treatment with fluid restriction is typically preferred and should be performed in consultation with a pediatric endocrinologist or nephrologist.

Sodium

A sodium level assessment and a volume status assessment can also be helpful in obtaining a diagnosis. In patients with hypovolemia and hypernatremia (>145 mmol/L), diabetes insipidus should be suspected [1]. Conversely, hyponatremia (<135 mmol/L) with clinical euvolemia should raise concerns for SIADH [4]. Urinary sodium >40 mmol/L with normal dietary salt intake further suggests SIADH [5].

In the interpretation of serum sodium, it is important to remember that both severe hypertriglyceridemia and severe hypercholesterolemia can cause "pseudohyponatremia" in some types of sodium assays, in which the reported serum sodium concentration is falsely low due to incorrect quantification of the water content of the sample. Additionally, hyperglycemia causes osmotic shifts of water extracellularly, temporarily lowering serum sodium concentrations without lowering total body sodium. A "corrected" sodium concentration can be calculated using the formula: [measured Na] + [1.6 * (serum glucose in mg/dL – [6])].

Urine Specific Gravity

Urine specific gravity can also be helpful in endocrine evaluation although one must keep in mind that the result can be affected by the size of particles in the urine and variations in urine pH. Urine specific gravity is normally between 1.001 and 1.035. A low urine specific gravity helps support the diagnosis of diabetes insipidus or primary polydipsia [7, 8].

Serum Antidiuretic Hormone and Copeptin

Serum concentrations of antidiuretic hormone (ADH, also called vasopressin, arginine vasopressin, or AVP) will not generally be useful in the primary care setting. Measurement of serum ADH is challenging due to several factors, including a very short half-life, small molecular size, instability in plasma or serum, and a high level of binding to platelets [9]. ADH assays are thus difficult and time-consuming and are generally used only in the setting of a water deprivation test (see Chap. 55), in which measurement of ADH may help differentiate central versus nephrogenic DI, with the former having low ADH levels and the latter having very high levels due to resistance at the level of the kidney.

Copeptin, which is part of the precursor peptide of ADH, is secreted along with ADH in equimolar amounts and shows promise as an emerging diagnostic marker for DI. Copeptin has a larger size, greater stability, and longer half-life in serum [9], facilitating easier and more accurate measurement in serum compared to ADH. Although there is limited commercial availability of the copeptin assay at the time of this writing, and pediatric protocols are not well-validated, copeptin is likely to emerge in the next few years as an important diagnostic tool, with very high baseline levels suggestive of nephrogenic DI and levels following diagnostic infusion of hypertonic saline able to distinguish between DI and primary polydipsia.

Excluding Other Causes

Primary polydipsia is a common cause of polyuria, as discussed in Chap. 55. Polyuria can also be caused by osmotic diuresis as most commonly seen in diabetes mellitus, which results in glycosuria [10]. A normal blood glucose value and urinalysis can help rule this out. Other causes of osmotic diuresis include urea and sodium. A urea diuresis can occur in patients recovering from acute kidney injury, whereas sodium diuresis is typically secondary to saline fluid administration or recovery from urinary tract obstruction [11–13]. In these cases, it is necessary to determine specific testing from the history. One should also evaluate for renal abnormalities (e.g. intrinsic renal disease) by measuring BUN and serum creatinine. Hypokalemia and hypercalcemia can also cause polyuria and induce nephrogenic diabetes insipidus [14, 15]. These electrolyte abnormalities should be corrected prior to proceeding with central diabetes insipidus evaluation.

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