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Testing for Arginine Vasopressin Deficiency

John Newell-Price, Ph.D., M.B., B.Chir.

Accurate classification of patients with hypotonic polyuria is essential because management differs for the three main causes[1]: arginine vasopressin (AVP) deficiency (formerly called central diabetes insipidus), AVP resistance (also known as nephrogenic diabetes insipidus),[2] and primary polydipsia, in which excess fluid intake suppresses AVP secretion. Primary polydipsia is the most common cause of hypotonic polyuria, whereas AVP deficiency is less common.

Nerve bodies in the hypothalamus synthesize a prohormone precursor peptide to vasopressin. During axonal transport to termini in the posterior pituitary, this peptide is cleaved to form AVP and a nonactive C-terminal portion, copeptin. AVP and copeptin are then released into the circulation, predominantly in response to increased plasma osmolality.[3] Since copeptin is more stable than AVP and is easily measured, it acts as a reliable circulating biomarker for AVP secretion. AVP resistance is accurately identified by a high basal serum copeptin level (>21.4 pmol per liter), which reflects resistance to AVP in the kidney.[4] In contrast, basal copeptin levels overlap in adults with both AVP deficiency and primary polydipsia, which renders the differential diagnosis challenging, with stimulated higher values found in those with primary polydipsia.[5] Limited data obtained from hospitalized children have shown that copeptin levels after overnight fasting can identify AVP deficiency.[6] Independent studies of copeptin stimulation in adults by infusion of either hypertonic saline[7] or arginine[8] have shown that both are superior to assessment by the time-honored water deprivation test, in which urine and plasma osmolality responses are assessed. The diagnostic accuracies of these three tests have been reported to be 95.2% for hypertonic-saline stimulation, 93% for arginine stimulation, and 70% for water deprivation.[5,7,8]

The arginine-stimulation test is simpler and has a better side-effect profile than the hypertonic-saline test, but questions remain about its reliability. In this issue of the *Journal*, Refardt and colleagues[9] address this issue in their careful prospective, multicenter head-to-head trial to assess the noninferiority of the arginine-stimulation test as compared with the hypertonic-saline test. A total of 158 adult patients underwent both testing procedures on different days. In accordance with previous studies,[7,8] the investigators enlisted two expert endocrinologists to make the final diagnosis of AVP deficiency or primary polydipsia 3 months after the tests had been performed. The expert reviewers were unaware of the results of the arginine-stimulation testing and based their diagnoses on a combination of the patients' medical history, imaging, laboratory data, results of the hypertonic-saline test, and response to treatment.

The final diagnosis was determined to be AVP deficiency in 69 patients (41 with complete deficiency and 28 with partial deficiency) and primary polydipsia in 89 patients. Surprisingly, the diagnostic accuracy of the arginine-stimulation test was only 74.4% in this trial, whereas the excellent performance of the hypertonic-saline test was confirmed at 95.6%. Although both the tests had acceptable side effects, 72% of the patients preferred the arginine-stimulated

test. Thirst and mild headache were common symptoms during both tests, but the intensity and frequency were reported as lower for arginine stimulation.

How practical is each of these tests? The arginine-stimulation test is straightforward in that it requires a short intravenous infusion and sampling at 60 minutes for copeptin. In contrast, the hypertonic-saline test is more cumbersome and requires bolus doses, longer infusions, and repeated testing of venous samples for plasma or serum sodium levels until the levels reach more than 149 mmol per liter, at which point sampling for copeptin is performed. Moreover, hypertonic saline is an irritant that requires good venous access for administration. Furthermore, at the end of the hypertonic-saline test, both an oral water load and a 5% intravenous dextrose infusion are used to lower the serum sodium level to a normal level. Such fluid loads and electrolyte shifts are contraindicated in some patients (e.g., those with heart failure or epilepsy).

Given the simplicity of the arginine-stimulation test, it is a shame that it was found to be inferior. But why did it have a poorer performance than what had been previously reported? Here, the authors offer several possibilities. The difference may relate to the inclusion of patients with primary polydipsia who had a reduced baseline osmolality, resulting in lower stimulated copeptin levels. In addition, the dose of arginine that was administered may have been insufficient in some patients with obesity. Furthermore, the comparator in the current trial was the high-performing hypertonic-saline test rather than the water deprivation test. The performance of the arginine-stimulation test might have been improved by including an overnight fluid restriction in carefully selected patients to increase plasma osmolality or by administering a higher arginine dose, but these hypotheses need empirical evaluation.

How should these tests be used in clinical practice? Not every patient who presents with hypotonic polyuria needs to undergo stimulation testing. For example, in patients with pituitary or hypothalamic disease, especially with mild hypernatremia, the diagnosis of partial or complete AVP deficiency is highly likely, and an analysis of matched plasma and urine osmolalities or basal copeptin levels may be sufficient for diagnosis. Conversely, in patients who present with no previous diagnosis and who have no contraindications, hypertonic saline is clearly the superior test to discriminate between AVP deficiency and primary polydipsia. However, regardless of which test is used, practitioners need to be aware that the cutoffs for appropriate copeptin levels are not generalizable among copeptin assays.[10] Among patients in whom the use of hypertonic saline is contraindicated, or because of patient preferences, the arginine-stimulation test is the next best option. However, reliance on the less accurate water deprivation test will still be needed in practices without access to copeptin assays.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From the School of Medicine and Population Health, University of Sheffield, Sheffield, United Kingdom.

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