Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj. 1705329

Anatolian Curr Med J. 2025;7(5):576-582

Differentiating AVP deficiency and primary polydipsia: a clinical and biochemical perspective

Beril Turan Erdoğan[1], Muzaffer Serdar Deniz[1], Belma Özlem Tural Balsak[1], Çağlar Keskin[1], Şefika Burçak Polat[2], Oya Topaloğlu[2], Reyhan Ersoy[2], Bekir Çakır[2]

[1]*Department of Endocrinology and Metabolism, Ankara Bilkent City Hospital, Ankara, Turkiye*

[2]*Division of Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine, Ankara Yıldırım Beyazıt University, Ankara, Turkiye*

Cite this article as: Turan Erdoğan B, Deniz MS, Tural Balsak BÖ, et al. Differentiating AVP deficiency and primary polydipsia: a clinical and biochemical perspective. *Anatolian Curr Med J.* 2025;7(5):576-582.

Received: 23.05.2025 ◆ **Accepted**: 14.08.2025 ◆ **Published**: 15.09.2025

ABSTRACT

Aims: The polyuria–polydipsia syndrome encompasses three major disorders—arginine vasopressin (AVP) deficiency, AVP resistance, and primary polydipsia. This study aimed to differentiate AVP deficiency from primary polydipsia by evaluating clinical features, biochemical markers, and anterior pituitary hormone levels, using the water deprivation test as the primary diagnostic modality.

Methods: This retrospective observational study included 34 adult patients with polyuria–polydipsia syndrome who underwent a standardized inpatient water deprivation test. Patients were categorized into AVP deficiency (complete or partial) or primary polydipsia based on urine osmolality responses to dehydration and desmopressin. Clinical data, daily fluid intake, and nocturia frequency were recorded. Serum electrolytes and anterior pituitary hormones (LH, GH) were analyzed.

Results: AVP deficiency was diagnosed in 76.4% of patients (58.8% complete, 17.6% partial), while 23.5% had primary polydipsia. LH and GH levels were significantly higher in the primary polydipsia group ($p=0.011$ and $p=0.028$, respectively), whereas AVP deficiency was associated with lower gonadotropin levels, especially in postoperative cases. Serum sodium, chloride, and magnesium levels were significantly lower in primary polydipsia ($p<0.05$), reflecting dilutional hyponatremia. Urine osmolality was significantly higher in primary polydipsia ($p=0.011$), indicating preserved concentrating ability. Nocturia occurred in 96.2% of patients with AVP deficiency versus 12.5% in primary polydipsia ($p<0.001$).

Conclusion: The water deprivation test remains a valuable diagnostic tool for differentiating AVP deficiency from primary polydipsia. These retrospective findings may serve as predictive indicators in the differential diagnosis, particularly in clinical settings where water deprivation tests and copeptin testing are not readily available. Incorporating nocturia frequency, serum electrolytes, and anterior pituitary hormone levels particularly LH and GH may improve diagnostic precision and facilitate individualized management.

Keywords: Polyuria–polydipsia syndrome, arginine vasopressin deficiency, primary polydipsia, water deprivation test

INTRODUCTION

The polyuria–polydipsia syndrome encompasses three major disorders characterized by excessive urine production (polyuria) and increased fluid intake (polydipsia): arginine vasopressin (AVP) deficiency (formerly central diabetes insipidus), AVP resistance (previously nephrogenic diabetes insipidus), and primary polydipsia.[1,2] Despite sharing similar clinical presentations, these conditions differ significantly in their pathophysiology and management.[3,4]

AVP deficiency results from impaired AVP synthesis or secretion in the hypothalamic–pituitary axis and typically necessitates treatment with desmopressin to maintain water homeostasis.[1,5] AVP resistance occurs when the renal collecting ducts do not respond to AVP, often due to hereditary receptor mutations or acquired causes such as lithium-induced nephrotoxicity.[6] Primary polydipsia, on the other hand, involves excessive water intake that suppresses endogenous AVP release; management generally consists of fluid restriction and, in some cases, psychological interventions.[2,7]

Although acute excessive water intake in primary polydipsia can lead to hyponatremia, most patients maintain normal sodium levels unless intake exceeds renal excretory capacity. In AVP deficiency or resistance, patients may develop hypernatremia and dehydration if fluid intake is inadequate, but many maintain normonatremia when water access is unrestricted.[6,7] Postoperative AVP deficiency, especially after neurosurgical or pituitary procedures, can compromise AVP secretion and disrupt the adjacent pituitary axis, resulting in

Corresponding Author: Beril Turan Erdoğan, berilturan@hotmail.com

diminished levels of anterior pituitary hormones such as LH and GH.[2] Psychiatric or stress-related factors may influence LH secretion, as stress has been shown to suppress LH pulsatility and reduce basal LH levels.[4,8] Hence, a comprehensive endocrine workup, including both biochemical and hormonal evaluations, is crucial to ensure accurate diagnosis and appropriate management.[4]

The water deprivation test is commonly used to differentiate these disorders by assessing the kidneys' capacity to concentrate urine during dehydration, followed by administration of exogenous desmopressin.[9] Although some centers continue to rely primarily on this test, newer techniques including hypertonic saline infusion and arginine-stimulated copeptin measurement have shown promise in diagnostic accuracy. Additionally, evaluating key serum electrolytes (sodium, chloride, magnesium) and anterior pituitary hormones (LH, GH, ACTH) may help distinguish among different types of polyuria–polydipsia syndromes.[3]

Despite the widespread use of the water deprivation test, differentiating between partial AVP deficiency and primary polydipsia remains challenging in clinical practice, especially in the absence of copeptin assays or when anterior pituitary function is not routinely evaluated. Furthermore, the integration of hormonal markers—such as LH and GH—into the diagnostic framework is not well established in most existing studies. Therefore, this study aims to not only validate traditional clinical and biochemical criteria but also to explore the potential diagnostic utility of anterior pituitary hormones in distinguishing AVP deficiency from primary polydipsia. By addressing these gaps, our 9 findings may enhance diagnostic precision and contribute to more tailored therapeutic strategies.

METHODS

This study has been approved by the Ethics Committee of Clinical Researches No. 1 at Ankara Bilkent City Hospital (Date: 06.09.2023, Decision No: E1-23-3947) and conducted in accordance with the Declaration of Helsinki.

This retrospective observational study included patients presenting with polyuria and polydipsia to the Endocrinology Clinic of Ankara Bilkent City Hospital from February 2019 to December 2024. A total of 35 patients underwent a standardized diagnostic evaluation, including the water deprivation test, conducted in the inpatient endocrinology unit.

Exclusion criteria included patients with significant comorbid conditions that could affect water metabolism or interfere with test interpretation. Specifically, patients were excluded if they had advanced chronic kidney disease (eGFR <30 ml/min/1.73 m^2), decompensated liver disease, uncontrolled diabetes mellitus, active malignancy, severe electrolyte disturbances at baseline (serum sodium <130 or >150 mEq/L), or inability to comply with test protocols due to cognitive or psychiatric disorders.

All patients underwent a standardized water deprivation test following hospital admission, in accordance with established clinical protocols.[10] Participants were instructed to abstain from alcohol, diuretics, and desmopressin use for 24 hours prior to testing. Baseline measurements of body weight, serum sodium concentration, and plasma osmolality were obtained at 8:00 a.m. Urine samples were collected and urine osmolality was measured hourly throughout the dehydration period. The test was terminated upon either a ≥10% increase in urine osmolality between two consecutive samples or a ≥2% reduction in body weight.

After test termination, 2 µg of intranasal desmopressin was administered. Urine osmolality was subsequently assessed at 30-minute intervals over the next two hours. A post-desmopressin increase in urine osmolality of ≥50% was considered consistent with complete AVP deficiency, while an increase between 10% and 50% indicated partial AVP deficiency. Minimal or no change in urine osmolality, in the context of an adequate baseline value (typically >500 mOsm/kg), was considered diagnostic of primary polydipsia.

A single patient met diagnostic criteria for AVP resistance during the water deprivation test and was subsequently excluded from the analysis. In this case, AVP resistance was suspected to be secondary to chronic lithium therapy

For analytical purposes, patients with complete and partial AVP deficiency were merged into a single group (AVP deficiency), due to overlapping clinical features and similar management strategies. This grouping also allowed for enhanced statistical power in between-group comparisons.

Demographic data (age, sex, BMI) and clinical characteristics (symptom duration in months) were recorded. Nocturia frequency was classified as fewer than three, three to five, or more than five occurrences per night. Daily fluid consumption and urine output were categorized into four groups: less than 5 liters, 5–10 liters, 10–15 liters, and more than 15 liters per day.

All participants underwent comprehensive biochemical and hormonal assessment during their initial outpatient endocrinology clinic visit.

All participants underwent comprehensive biochemical and hormonal assessment. Biochemical parameters included fasting blood glucose, blood urea nitrogen (BUN), creatinine, estimated glomerular filtration rate (eGFR), uric acid, albumin, serum electrolytes (sodium, potassium, chloride, calcium, magnesium, phosphorus), and plasma/urine osmolality. Urine specific gravity was also measured.

Hormonal evaluations involved thyroid hormones (TSH, free T4, free T3), gonadotropins (FSH, LH), sex hormones (estradiol, total testosterone), prolactin (PRL), adrenocorticotropic hormone (ACTH), cortisol, insulin-like growth factor-1 (IGF-1), and growth hormone (GH).

Statistical Analysis

All data analyses were conducted using IBM SPSS Statistics version 26.0. The normality of continuous variables was assessed using the Shapiro-Wilk test. Continuous variables with normal distribution were analyzed using the independent samples t-test, while those without normal distribution were compared using the Mann-Whitney U test. Categorical

variables were analyzed using Fisher's exact test. Descriptive statistics were expressed as mean±standard deviation (SD), median (minimum–maximum), or frequencies and percentages as appropriate. A p-value of <0.05 was considered statistically significant for all analyses.

RESULTS

Patient Characteristics

Of the initial 35 patients evaluated, one was excluded due to a diagnosis of AVP resistance based on test findings. The patient had a history of chronic lithium use, suggesting secondary nephrogenic diabetes insipidus.

A total of 34 patients were included in the final analysis. The mean age was 42.7±12.6 years, and 41.2% were male. The mean BMI was 30.5±5.3 kg/m². The average symptom duration was 91.97±155.3 months.

Based on the water deprivation test results, 58.8% (n=20) of patients were diagnosed with complete AVP deficiency, 17.6% (n=6) with partial AVP deficiency, and 23.5% (n=8) with primary polydipsia. Notably, none of the patients in the primary polydipsia group experienced significant weight loss during the dehydration phase, which further supported the diagnosis (Table 1).

Table 1. Demographic, clinical, and etiological characteristics of patients with polyuria and polydipsia (n=34; one patient with AVP resistance excluded)

	Patients n=34
Age (years), (SD)	42.7 (12.64)
Gender, female, n (%)	20 (58.8)
BMI (kg/m²) (SD)	30.5 (5.28)
Duration of polyuria and polydipsia (months) (SD)	91.97 (155.34)
Nocturia	
Yes, n (%)	26 (76.5)
No, n (%)	8 (23.5)
Frequency of nocturia	
<3, n (%)	12 (46.2)
3-5, n (%)	8 (30.8)
>5, n (%)	6 (23.1)
Fluid intake and output	
<5, n (%)	2 (5.9)
5-10, n (%)	20 (58.8)
10-15, n (%)	8 (23.5)
>15, n (%)	4 (11.8)
Diagnosis	
AVP deficiency, n (%)	20 (58.8)
Partial AVP deficiency, n (%)	6 (17.6)
Primary polydipsia, n (%)	8 (23.5)
Etiology	
Idiopathic, n (%)	13 (38.2)
Post-operative, n (%)	7 (20.6)
Psychogenic, n (%)	8 (23.5)
Hypophysitis, n (%)	4 (11.8)
Infundibulum metastasis, n (%)	1 (2.9)
Meningioma, n (%)	1 (2.9)

SD: Standard deviation, BMI: Body-mass index, AVP: Arginine vasopressin

Hormonal Parameters

Significant differences were observed in anterior pituitary hormone levels between groups. LH levels were significantly higher in the primary polydipsia group compared to the AVP deficiency group (11.78±11.99 vs. 5.65±7.77 U/L; p=0.011). Similarly, GH levels were elevated in primary polydipsia (0.43±0.39 µg/L vs. 0.27±0.54 µg/L; p=0.028).

ACTH levels were higher in the AVP deficiency group (31.90±13.70 pg/ml vs. 26.01±9.16 pg/ml), although this difference was not statistically significant (p=0.265). No significant differences were observed in cortisol, IGF-1, thyroid hormones, FSH, PRL, estradiol, or testosterone levels (Table 2).

Biochemical Parameters

Primary polydipsia patients demonstrated significantly lower serum sodium (138±4 vs. 142±3 mEq/L; p=0.030), chloride (105±4 vs. 108±3 mEq/L; p=0.040), and magnesium (1.8±0.1 vs. 2.0±0.2 mg/dl; p=0.010), reflecting dilutional effects from excessive fluid intake.

Urine osmolality was significantly higher in the primary polydipsia group (129±41 mOsm/kg) than in the AVP deficiency group (101±48 mOsm/kg; p=0.011. Plasma osmolality, creatinine, eGFR, calcium, and phosphorus levels did not differ significantly between the groups (Table 3).

Clinical Features

Nocturia was present in 76.5% of the cohort. It was significantly more common in the AVP deficiency group than in primary polydipsia (96.2% vs. 12.5%; p<0.001). All patients reporting more than five episodes of nocturia per night belonged to the AVP deficiency group.

Daily fluid intake ranged from <5 to >15 liters/day. Most patients (58.8%) reported intake between 5–10 liters. Although patients with primary polydipsia tended to consume more fluid than those with AVP deficiency, this difference did not reach statistical significance (p=0.322).

Regarding etiology, psychogenic causes were exclusively observed in the primary polydipsia group. In contrast, AVP deficiency was attributed to idiopathic causes in 26.9%, postoperative causes in 26.9%, neurohypophyseal signal loss in 17.6%, hypophysitis in 11.8%, and rare lesions such as infundibulum metastasis and meningioma in 2.9% each.

Among the postoperative cases (n=9), five had non-functioning pituitary adenomas and two had craniopharyngiomas. All seven developed anterior hypopituitarism after surgery. Additionally, both patients with pituitary stalk meningioma and metastatic infundibular involvement underwent neurosurgical intervention and subsequently developed postoperative anterior pituitary hormone deficiencies. No patient had preoperative hypopituitarism documented prior to intervention (Table 4).

DISCUSSION

This study evaluated the clinical, hormonal, and biochemical profiles of patients with AVP deficiency and primary polydipsia, using the water deprivation test as the principal diagnostic tool. Our findings reinforce the utility of this test for distinguishing between these two conditions based on urinary and hormonal responses. We acknowledge that our study design lacks a comparator based on a current gold standard such as copeptin-based diagnostics. As a result,

Table 2. Comparison of hormonal parameters between AVP deficiency and primary polydipsia groups

	Diagnosis								
	AVP deficiency (n=26)				Primary polydipsia (n=8)				p
	Mean	Min	Max	SD	Mean	Min	Max	SD	
TSH, mIU/L	2.127	0.008	4.750	1.338	1.881	0.010	4.300	1.248	0.648[a]
fT4, ng/dl	1.07	0.67	1.39	0.17	1.20	0.89	2.10	0.41	0.745[b]
fT3, ng/L	3.37	1.90	4.20	0.53	3.57	3.05	4.20	0.40	0.344[a]
FSH, U/L	9.9	0.3	57.6	13.1	17.9	3.4	78.4	25.8	0.626[b]
LH, U/L	5.65	0.07	31.20	7.77	11.78	3.50	39.60	11.99	0.011[b]
E2, U/L	39.3	11.8	205.0	39.2	102.0	11.8	370.0	118.9	0.149[b]
Total testosteron, µg/L	1.3427	0.0700	4.5900	1.6421	2.1763	0.0900	7.3700	2.7889	0.443[a]
PRL, µg/L	15.73	0.60	112.50	21.70	21.03	5.40	48.00	15.71	0.155[b]
ACTH, pg/ml	31.90	5.00	57.30	13.70	26.01	13.30	37.20	9.16	0.265[a]
Cortisol, µg/dl	13.9	3.7	24.4	4.6	17.3	7.7	23.9	5.1	0.087[a]
IGF-1, µg/L	98	15	261	50	132	89	220	47	0.094[a]
GH, µg/L	0.27	0.05	2.20	0.54	0.43	0.10	1.10	0.39	0.028[b]

AVP: Arginine vasopressin, Min: Minimum, Max: Maximum, SD: Standard deviation, TSH: Thyroid stimulating hormone, fT4: Free thyroxine, fT3: Free triiodothyronine, FSH: Follicle- stimulating hormone, LH: Luteinizing hormone, E2: Estrodiol, PRL: Prolactin, ACTH: Adrenocorticotropic hormone, IGF-1: Insulin-like growth factor 1, GH: Growth hormone, a: Independent Samples t-test, b: Mann-Whitney U test

Table 3. Comparison of biochemical parameters between AVP deficiency and primary polydipsia groups

	Diagnosis								
	AVP deficiency (n=26)				Primary polydipsia (n=8)				p
	Mean	Min	Max	SD	Mean	Min	Max	SD	
Duration of polyuria and polydipsia (month)	91	1	660	159	113	1	480	168	0.451[b]
Fasting blood glucose, mg/dl	90	70	110	10	86	74	108	10	0.238[b]
BUN, mg/dl	21	13	30	5	21	14	32	7	0.986[a]
Creatinine, mg/dl	0.75	0.56	1.06	0.15	0.68	0.58	0.87	0.10	0.249[a]
eGFR, ml/min/1.73m^2	104	74	134	16	115	96	132	11	0.215[b]
Uric asid, mg/dl	6.0	4.2	9.4	1.3	5.0	3.0	6.8	1.3	0.058[a]
Albumin, g/L	42.9	36.0	47.0	2.9	42.0	36.0	47.0	3.5	0.487[b]
Na, mEq/L	142	134	147	3	138	130	142	4	0.030[a]
K, mEq/L	4.2	3.6	5.1	0.3	4.2	3.9	4.7	0.3	0.982[a]
Cl, mEq/L	108	102	115	3	105	99	109	4	0.040[a]
Ca, mg/dl	9.5	8.8	10.3	0.4	9.4	8.5	10.4	0.6	0.341[a]
Mg, mg/dl	2.0	1.6	2.2	0.2	1.8	1.8	1.9	0.1	0.010[a]
P, mg/dl	4.0	2.1	5.0	0.6	4.3	3.4	5.0	0.6	0.314[a]
Plasma osmolarity, mOsm/kg	287	189	302	21	290	272	305	11	0.984[b]
Urine osmolarity, mOsm/kg	101	48	299	48	129	99	226	41	0.011[b]
Urine specific gravity	1004	1000	1009	2	1005	1002	1009	2	0.370[a]

AVP: Arginine vasopressin, Min: Minimum, Max: Maximum, SD: Standard deviation, BUN: Blood urea nitrite, eGFR: Estimated glomerular filtration rate, Na: Sodium, K: Potassium, Cl: Chlorine, Ca: Calcium, Mg: Magnesium, P: Phosphorus, a: Independent Samples t-test, b: Mann-Whitney U test

our findings reflect internal consistency rather than external validation. Nevertheless, in many clinical settings where copeptin assays are unavailable, the water deprivation test remains the most feasible diagnostic approach. Our study aimed to assess whether additional clinical and hormonal parameters could enhance the interpretative value of the WDT in such real-world contexts.

Although the water deprivation test has known limitations in differentiating AVP deficiency from primary polydipsia, it continues to be widely used due to its accessibility and simplicity. By integrating clinical indicators—such as nocturia frequency and fluid intake—with biochemical and hormonal findings, we aimed to strengthen the diagnostic utility of this conventional test in routine endocrinology practice.

In our cohort, AVP deficiency was the predominant diagnosis (58.8%), followed by partial AVP deficiency (17.6%) and primary polydipsia (23.5%). This distribution mirrors patterns reported in tertiary endocrinology centers, where a significant portion of patients with polyuria-polydipsia syndrome are ultimately classified as having a complete or partial AVP deficiency.[1,3] The mean age and BMI observed were consistent with previously described cohorts, reinforcing

Table 4. Comparison of nocturia, fluid intake, and etiological factors between AVP deficiency and primary polydipsia groups

		Diagnosis				
		AVP deficiency (n=26)	Primary polydipsia (n=8)	Total	x^2	p
Nocturia	Yes	25 (96.2%)	1 (12.5%)	26 (76.5%)	22.595	0.000[a]
	No	1 (3.8%)	7 (87.5%)	8 (23.5%)		
Frequency of nocturia	<3	11 (44.0%)	1 (100.0%)	12 (46.2%)	1.367	1.000[a]
	3-5	8 (32.0%)	0 (0.0%)	8 (30.8%)		
	>5	6 (24.0%)	0 (0.0%)	6 (23.1%)		
Fluid intake and output (litres)	<5	1 (3.8%)	1 (12.5%)	2 (5.9%)	3.146	0.322[a]
	5-10	17 (65.4%)	3 (37.5%)	20 (58.8%)		
	10-15	5 (19.2%)	3 (37.5%)	8 (23.5%)		
	15-20	3 (11.5%)	1 (12.5%)	4 (11.8%)		
Etiology	Idiopathic	13 (50.0%)	0 (0.0%)	13 (38.2%)	27.070	0.000[a]
	Post-operative	7 (27%)	0 (0.0%)	7 (20.6%)		
	Psychogenic	0 (0.0%)	8 (100.0%)	8 (23.5%)		
	Hypophysitis	4 (15.4%)	0 (0.0%)	4 (11.8%)		
	Infundibulum metastasis	1 (3.8%)	0 (0.0%)	1 (2.9%)		
	Menengiom	1 (3.8%)	0 (0.0%)	1 (2.9%)		

AVP: Arginine vasopressin, a: Fisher's Exact test

the generalizability of our sample.[4] The prolonged duration of symptoms observed in our cohort likely reflects a combination of under-recognition, delayed referral, and the intermittent or nonspecific nature of polyuria–polydipsia presentations. This pattern has been similarly reported in other studies and underscores the diagnostic challenges posed by these syndromes in real-world practice.

We observed significantly higher LH and GH levels in patients with primary polydipsia compared to those with AVP deficiency. These findings are consistent with the hypothesis that chronic psychogenic stress or psychiatric illness may stimulate hypothalamic-pituitary activation, leading to elevated gonadotropin and GH secretion.[2,4,9] Conversely, reduced levels of these hormones in AVP deficiency, particularly among postoperative patients, may reflect impaired hypothalamic input or direct surgical injury to the pituitary stalk.[2]

Although ACTH levels were not statistically different between groups, their tendency to be elevated in AVP deficiency aligns with prior observations of hypothalamic–pituitary–adrenal (HPA) axis compensation in the context of chronic free water loss.[5,11]

These findings suggest that selected anterior pituitary hormones—particularly LH and GH—may serve as adjunctive markers in the differential diagnosis of polyuria–polydipsia syndromes, especially in settings where copeptin measurement is not available.[8] GH secretion is known to exhibit significant interindividual variability and is influenced by multiple factors, including age, body composition, and comorbidities such as diabetes mellitus. While our study did not perform multivariate adjustment for these variables, the lack of significant difference in IGF-1 levels between groups supports the possibility that observed differences in GH may not reflect a true endocrine disturbance, but rather context-dependent variability.[12]

We considered menopausal status in the interpretation of LH values. While elevated LH levels in some primary polydipsia patients may reflect postmenopausal physiology, the overall trend observed—particularly in male patients and premenopausal women—suggests that additional factors such as psychogenic stress may also play a role.

The observed reduction in LH and GH levels in patients with AVP deficiency was particularly pronounced in those with a history of neurosurgical intervention. In our cohort, nine patients underwent surgery for sellar or suprasellar lesions, including pituitary adenomas, craniopharyngiomas, meningioma, and metastatic lesions. All of these patients developed anterior hypopituitarism postoperatively, whereas none had documented pituitary hormone deficiencies prior to surgery. These findings highlight the impact of surgical disruption of the hypothalamic–pituitary axis on anterior pituitary hormone secretion, particularly gonadotropins and GH. Therefore, when interpreting hormonal patterns especially in postoperative patients acquired pituitary insufficiency should be considered as a potential confounder in the differential diagnosis of polyuria–polydipsia syndromes.

Estradiol and testosterone levels are known to vary with age and reproductive status. Although we recorded these parameters, our analysis did not include age-adjusted stratification due to limited subgroup size. Importantly, these hormones were not central to the primary aim of the study and were analyzed for descriptive purposes. Future studies may incorporate age- and sex-specific hormone reference ranges to improve interpretability.

Patients with primary polydipsia exhibited significantly lower serum sodium, chloride, and magnesium levels, consistent with dilutional effects of excessive water consumption.[9,13] While hyponatremia may suggest primary polydipsia, particularly in acute presentations, it is not always sufficient to establish a definitive diagnosis. Some patients presented

with chronic, fluctuating symptoms or overlapping features, prompting further evaluation. In our cohort, water deprivation testing was conducted to clarify diagnosis and exclude other etiologies, especially in cases where clinical and biochemical findings were inconclusive at baseline. In contrast, the relative elevation of sodium and chloride levels in AVP deficiency reflects free water loss and the risk of hypernatremia if untreated.[1,7,14]

Interestingly, urine osmolality was significantly higher in the primary polydipsia group despite persistent polyuria. Although absolute urine osmolality values remained low in both groups, the relatively higher levels observed in primary polydipsia may reflect a partially preserved concentrating ability. This is consistent with previous studies suggesting that renal concentrating capacity may improve under supervised fluid restriction in chronic polydipsia cases. This suggests that at least partial concentrating ability is preserved in these patients and may become apparent during supervised fluid restriction. This observation supports previous reports indicating reversibility of renal concentrating dysfunction in primary polydipsia when excessive intake is curtailed.[11,14]

The absence of a significant difference in plasma osmolality between groups highlights a potential limitation of static plasma values in differentiating AVP deficiency from primary polydipsia, particularly at baseline.

Nocturia was found to be a highly discriminative symptom in our cohort, occurring in 96.2% of patients with AVP deficiency but only 12.5% of those with primary polydipsia. These findings align with the physiological role of AVP in promoting nocturnal antidiuresis and support prior reports that highlight nocturia as a clinical hallmark of AVP deficiency.[2,11] Moreover, all patients reporting >5 nocturnal episodes belonged to the AVP deficiency group, suggesting that frequent nocturia may serve as a clinically useful, albeit non-specific, diagnostic indicator.

Although daily fluid intake tended to be higher in primary polydipsia, this difference did not reach statistical significance—potentially due to overlapping behavior patterns and subjective variability in intake reporting.

From an etiological standpoint, our findings confirmed that psychogenic factors underlie all cases of primary polydipsia, while AVP deficiency was associated with a heterogeneous set of causes, including idiopathic, postoperative, inflammatory, and neoplastic conditions. These results underscore the need for comprehensive diagnostic evaluation including neuroimaging and clinical history in cases suggestive of AVP deficiency.

While the water deprivation test has limitations,[3] it remains accessible in most clinical settings. Our findings suggest that integrating clinical parameters such as nocturia frequency and anterior pituitary hormone levels may enhance diagnostic confidence in routine practice.

In recent years, the water deprivation test has been increasingly challenged by novel diagnostic methods such as copeptin-based testing. Among these, arginine-stimulated copeptin measurement has emerged as a promising alternative with notable advantages. Recent studies show that hypertonic saline-stimulated copeptin testing yields a sensitivity of 93.2% and a specificity of 100% in differentiating primary polydipsia from central diabetes insipidus, whereas the traditional water deprivation test offers an accuracy of only 73.3%.[8] Similarly, the arginine-stimulated test demonstrates a diagnostic accuracy of 93% (sensitivity 93%, specificity 92%) along with superior safety and patient comfort.[15] Unlike the water deprivation test, which requires prolonged inpatient monitoring (8–16 hours) and poses a risk of severe dehydration, copeptin assays can be performed in outpatient settings within 2–3 hours, with minimal side effects.[8,15] However, broader adoption of copeptin measurement remains limited due to its higher cost, requirement for specialized laboratory infrastructure, and restricted accessibility in many healthcare systems. In settings where copeptin testing is unavailable, our findings indicate that the diagnostic performance of the traditional water deprivation test may be improved by incorporating additional clinical indicators such as nocturia frequency and anterior pituitary hormone levels.

Limitations

We acknowledge the inherent limitation of relying solely on the WDT without external validation such as copeptin-based assays. Second, the relatively small sample size and unequal group distribution (26 patients with AVP deficiency vs. 8 with primary polydipsia) may limit the statistical power and generalizability of our findings. However, our study was not designed to re-validate the WDT itself, but rather to identify additional clinical and biochemical features that may aid interpretation in routine endocrinology settings where copeptin testing is unavailable. In this context, parameters such as nocturia frequency, serum electrolytes, and anterior pituitary hormone levels—particularly LH and GH—may improve diagnostic confidence when applied alongside the WDT.

Future research should focus on validating the diagnostic utility of anterior pituitary hormones particularly LH and GH as potential adjunctive markers in resource-limited settings. Moreover, large-scale, multicenter studies are needed to evaluate the long-term prognostic implications of these hormonal and biochemical patterns, and to refine diagnostic algorithms for polyuria–polydipsia syndrome.

CONCLUSION

In summary, this study highlights the continued relevance of the water deprivation test in differentiating AVP deficiency from primary polydipsia and suggests that selected anterior pituitary hormones may provide additional diagnostic insight. Clinical features such as nocturia frequency and biochemical markers including serum sodium and urine osmolality remain essential components of a comprehensive diagnostic approach. Tailoring diagnostic strategies to include endocrine and behavioral context may enhance accuracy and lead to more effective, individualized management plans.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study has been approved by the Ethics Committee of Clinical Researches No. 1 at Ankara Bilkent City Hospital (Date: 06.09.2023, Decision No: E1-23-3947).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Refardt J, Winzeler B, Christ-Crain M. Diabetes insipidus: an update. *Endocrinol Metab Clin North Am*. 2020;49(3):517-531. doi:10.1016/j.ecl.2020.05.012
2. Sailer CO, Winzeler B, Christ-Crain M. Primary polydipsia in the medical and psychiatric patient: characteristics, complications and therapy. *Swiss Med Wkly*. 2017;147:w14514. doi:10.4414/smw.2017.14514
3. Teare H, Argente J, Dattani M, et al. Challenges and improvement needs in the care of patients with central diabetes insipidus. *Orphanet J Rare Dis*. 2022;17(1):58. doi:10.1186/s13023-022-02191-2
4. Atila C, Yıldız BO, Güler S, et al. Psychopathological characteristics in patients with arginine vasopressin deficiency (central diabetes insipidus) and primary polydipsia compared to healthy controls. *Eur J Endocrinol*. 2024;190(5):354-362. doi:10.1093/ejendo/lvae040
5. Itagaki E, Ozawa S, Yamaguchi S, et al. Increases in plasma ACTH and cortisol after hypertonic saline infusion in patients with central diabetes insipidus. *J Clin Endocrinol Metab*. 2001;86:5749-5754.
6. Flynn K, Thomas L, Jackson P, et al. Central and nephrogenic diabetes insipidus: updates on diagnosis and management. *Front Endocrinol (Lausanne)*. 2025;15:1479764. doi:10.3389/fendo.2024.1479764
7. Bologna K, Cesana-Nigro N, Refardt J, et al. Effect of arginine on the hypothalamic-pituitary-adrenal axis in individuals with and without vasopressin deficiency. *J Clin Endocrinol Metab*. 2020;105(3):e884-e892. doi:10.1210/clinem/dgaa157
8. Fenske W, Refardt J, Chifu I, et al. A copeptin-based approach in the diagnosis of diabetes insipidus. *N Engl J Med*. 2018;379(5):428-439. doi:10.1056/NEJMoa1803760
9. Pires BF, Andrade M, Silva T, et al. Primary polydipsia and sIDH Type D due to water-electrolytic disturbance in a schizophrenic patient: a case report and systematic review. *Open J Psychiatry*. 2025;15(1):1-15.
10. Pedrosa W, Drummond JB, Soares BS, Ribeiro-Oliveira A Jr. A combined outpatient and inpatient overnight water deprivation test is effective and safe in diagnosing patients with polyuria-polydipsia syndrome. *Endocr Pract*. 2018;24(11):963-972. doi:10.4158/ep-2018-0238
11. Pivonello R, Faggiano A, Filippella M, et al. Hypothalamus-pituitary-adrenal axis in central diabetes insipidus: ACTH and cortisol responsiveness to CRH administration. *J Endocrinol Invest*. 2002;25(10):932-937. doi:10.1007/BF03344064
12. Ho KK; 2007 GH Deficiency Consensus Workshop Participants. Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: a statement of the GH Research Society in association with the European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia. *Eur J Endocrinol*. 2007;157(6):695-700. doi:10.1530/EJE-07-0631
13. Atila C, Lustenberger S, Yıldız BO, et al. Relationship between plasma urea and copeptin in response to arginine stimulation in healthy adults, patients with vasopressin deficiency, and primary polydipsia. *Pituitary*. 2025;28(1):18. doi:10.1007/s11102-024-01489-7
14. Trimpou P, Olsson DS, Ehn O, Ragnarsson O. Diagnostic value of the water deprivation test in the polyuria-polydipsia syndrome. *Hormones (Athens)*. 2017;16(4):414-422. doi:10.14310/horm.2002.1762
15. Winzeler B, Cesana-Nigro N, Refardt J, et al. Arginine-stimulated copeptin measurements in the differential diagnosis of diabetes insipidus: a prospective diagnostic study. *Lancet*. 2019;394(10198):587-595. doi:10.1016/S0140-6736(19)31255-3