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RAPID COMMUNICATION

Challenges and unmet needs in diagnosing polyuria-polydipsia syndrome: National survey by the Italian Society of Endocrinology

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Abstract

Purpose Symptoms and baseline laboratory results often fail to identify the underlying cause of polyuria–polydipsia syndrome (PPS). A copeptin-based approach has recently been proposed for the differential diagnosis in adults. Given the rarity and complexity of PPS, national endocrinology societies should provide guidance to minimize diagnostic delays and ensure patients receive the most accurate evaluation.

Methods The Hydro-Saline Club conducted a 22-question web-based survey targeting all endocrinologists registered with the Italian Society of Endocrinology in 2024. Data were collected from July 18 to September 22, 2024.

Results A total of 120 endocrinologists from 75% of Italian regions completed the survey. 60% worked in university hospitals, while the remainder worked in peripheral hospitals and outpatient clinics. Copeptin testing was available in 58.3% of facilities. However, a basal copeptin evaluation was infrequently requested in PPS, mainly due to assay availability ($p<0.001$) and low confidence in results interpretation, which correlated with clinical experience ($p=0.007$). The WDT remained the most used stimulation test, with preference driven by personal experience ($p=0.020$) rather than facility type. Familiarity with each diagnostic test increased with use, and test choice was apparently not influenced by concerns over potential side effects or accuracy. Rather, the main barrier identified was the perceived caregiving burden associated with the diagnostic process, leading many clinicians to prefer a stepwise diagnostic approach.

Conclusion Endocrinological societies should promote awareness of novel, accurate diagnostic tools for PPS and support streamlined referral pathways to centers offering reliable, appropriate testing.

Keywords Arginine vasopressin deficiency · Resistance · Primary polydipsia · Diabetes insipidus · Hypertonic saline · Copeptin

Introduction

The polyuria-polydipsia syndrome (PPS) is characterized by urinary output exceeding 40–50 ml/kg/day (or >250 ml/h for more than 2 consecutive hours) and excessive water intake (usually defined as >3000 ml/day), resulting from an increased sense of thirst [1–3]. The precise incidence of the syndrome is unknown, and symptoms are often insufficient to distinguish the underlying etiology; this is also true for baseline laboratory values, such as serum sodium and plasma osmolality.

The initial step in differential diagnosis involves identifying cases due to osmotic diuresis (e.g., urinary excretion of glucose, mannitol, or urea) and other pathological conditions, such as electrolyte disturbances (i.e., hypercalcemia or hypokalemia), resolution of renal failure, diuretic use, or

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isotonic saline hydration [1–3]. Upon confirming hypotonic polyuria (urine osmolality < 800 mOsm/kg), arginine vasopressin deficiency (AVP-D), also known as central diabetes insipidus, should be suspected within the appropriate clinical context [4]. Additionally, two other conditions must be considered: peripheral resistance to AVP (AVP-R or nephrogenic diabetes insipidus) and primary polydipsia (PP).

Recently, experts have proposed a copeptin-based approach for the differential diagnosis of PPS in adults, drawing on available literature to provide clear diagnostic guidance for clinical practice [1]. According to this consensus, the water deprivation test (WDT) is reserved for cases where copeptin measurement is unavailable. In other situations, after excluding AVP-R with a single basal copeptin value [4, 5], the hypertonic saline test is recommended as the gold standard for distinguishing between AVP-D (particularly partial forms) and PP [6]. In cases with contraindications to the hypertonic saline test [7], or when appropriate monitoring is not feasible, the arginine stimulation test - less accurate, but simpler to perform [8, 9] - remains a viable alternative. The characteristics of main stimulation tests for the differential diagnosis of PPS are resumed in Table 1.

The Italian clinical landscape is marked by significant regional variability, highlighting the need for the scientific community to bridge gaps among specialists, improve understanding of the pathological spectrum of PPS, address recent literature recommendations, and promote the establishment of collaborative networks. These efforts are essential to streamline, secure, and enhance diagnostic and therapeutic pathways for patients with rare conditions such as AVP-D and AVP-R. This need is underscored by the persistently long diagnostic delays in this field, which contribute to a dual burden: on one hand, the overuse of unnecessary and costly investigations (e.g., pituitary magnetic resonance imaging), and on the other, limited access to advanced diagnostic evaluations and structured follow-up in more complex cases—particularly those involving idiopathic AVP deficiency (AVP-D) [10].

Materials and methods

Taking this into account, Hydro-Saline Club of the Italian Society of Endocrinology conducted a web survey on the diagnostic approach to PPS aimed at all the endocrinologists registered in 2024. The survey was composed of 22 questions and is provided in Supplementary Table 1. Data were collected from July 18 to September 22, 2024. The results are presented as median and interquartile range or absolute values and percentage. The Chi-square test and Fisher's exact test assessed associations between binary variables, and Spearman's rank test evaluated correlations between continuous variables. Statistical analysis was conducted using Stata 18 software (StataCorp. 2023. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC).

Table 1 Comparison of the main stimulation tests for the differential diagnosis of polyuria–polydipsia syndrome

Test	Procedure	Cut-off	Diagnostic accuracy
Indirect water deprivation test	- Water deprivation ≥ 16 h - Regular assessment of s-Na, p-Osm, u-Osm, diuresis, weight - Stop if: u-Osm > 800 mOsm/kg, s-Na > 150 mmol/L or weight loss > 3% - Administration of dDAVP (2–4 µg iv/sc) if u-Osm max < 800 mOsm/kg	- Complete AVP-D: u-Osm < 300 mOsm/kg + increase > 50% after dDAVP - Partial AVP-D: u-Osm max 300–800 mOsm/kg + increase > 9% after dDAVP - PP: u-Osm > 800 mOsm/kg, or 300–800 mOsm/kg + increase < 9% after dDAVP	76.6% [6]
Hypertonic saline stimulation test	- Water deprivation 2 h - Hypertonic saline 3% infusion (250-ml bolus over 15 min, followed by infusion at a rate of 0.15 ml/kg/min) - Measurement of s-Na every 30 min - Stop if s-Na ≥ 150 mmol/L − 500-ml infusion of 5% glucose + oral water load (30 ml/kg) within 60 min	- PP: copeptin > 4.9 pmol/L	96–97% [6,9]
Arginine stimulation test	- Water deprivation 2 h - Infusion of arginine 21% (0.5 g/kg - max 40 g) diluted in 500 ml of sodium chloride 0.9% over 30 min - Copeptin measurement 60 min after the start of infusion	a. PP: copeptin > 5.2 pmol/L b. AVP-D: copeptin ≤ 3.0 pmol/L	a. Sp of 91.4% in the diagnosis of PP [9] b. Sp of 90.9% in the diagnosis of AVP-D [9]

Abbreviations: dDAVP: 1-deamino-8-D-arginine vasopressin; AVP-D: arginine vasopressin deficiency; iv: intravenous; PP: primary polydipsia; s-Na: serum sodium; p-Osm: plasma osmolality; sc: subcutaneous; Sp: specificity; u-Osm: urine osmolality

Results

A total of 120 endocrinologists participated in the survey. Of these, 51.7% were under 40 years of age, and 52.5% had less than 16 years of experience since obtaining their medical degree. Participants were from 15 of the 20 Italian regions, representing approximately 75% of the country. 60% of the endocrinologists were employed at university hospitals, while the remaining participants worked in peripheral hospitals and outpatient clinics. Copeptin determination was available in 58.3% of the facilities where they practiced.

Most participants (50.8%) reported having seen fewer than three patients with PPS in the past three months. Additionally, 45.8% used to request a baseline copeptin evaluation in such cases, while 54.2% reported doing so "never," "rarely," or "sometimes". Notably, neither the number of patients nor the availability of copeptin assays was associated with the type of facility where the participants were employed. In contrast, the decision to request a baseline copeptin evaluation to rule out AVP-R was primarily influenced by the availability of the copeptin assay at the center where the clinician worked ($p < 0.001$).

Coherently, more than one-third of clinicians reported feeling unconfident in interpreting basal copeptin values to exclude AVP-R, with 40.9% responding that their confidence was "low" or "very low." Confidence in test interpretation was positively correlated with clinical experience, measured by the number of years since obtaining their medical degree ($p = 0.007$).

Most of the interviewed endocrinologists reported that they did not refer patients to another tertiary care center for diagnosis (50.8% responded "never"). The decision to refer patients to a specialized referral center appeared to be primarily influenced by the type of facility where the endocrinologists were employed, with those working in hospitals less likely to make referrals ($p = 0.007$). The availability of the copeptin assay at their workplace also significantly influenced the decision to refer the patient to a tertiary center, showing a strong association ($p < 0.001$).

They infrequently diagnosed AVP-D *ex juvantibus* through a therapeutic challenge with desmopressin acetate, with 77.5% reporting that they did so "never" or "rarely." This approach did not appear to be associated with the availability of the copeptin assay at the center where they worked.

In relation to the recommended stimulation tests for differentiating AVP-D from PP - namely, the hypertonic saline test, arginine stimulation test, and WDT - interviewed endocrinologists reported the highest confidence in interpreting the WDT, with 45.8% expressing "high" or "very high" confidence. In contrast, lower confidence levels were reported for the hypertonic saline test, despite its higher accuracy, with 57.5% of respondents indicating "low" or "very low" confidence, and for the arginine stimulation test, where 59.2% indicated similarly low confidence.

Further analysis demonstrated that confidence in interpreting the WDT was significantly associated with the endocrinologists' years of post-graduate experience ($p = 0.020$). Additionally, higher confidence in interpreting each test significantly correlated with both the number of patients with PPS evaluated over the past three months and the frequency of its use in differential diagnosis ($p < 0.001$ for each test).

Overall, the endocrinologists rarely performed the hypertonic saline test (67.5% responded "never" or "rarely"), despite it being considered the new gold standard in diagnosis, and even less frequently performed the arginine stimulation test (70.1% responded "never" or "rarely"). In contrast, they still relied on the less accurate WDT in nearly half of cases (47.5% responded "always," "almost always," or "sometimes"). These preferences were not associated with the years since obtaining their medical degree nor with the type of facility in which they were employed.

Consistent with their limited confidence in the hypertonic saline test and the high healthcare resources it requires, the endocrinologists rarely used its high accuracy to reassess previous diagnoses, with 96.7% reporting "never," "rarely," or "sometimes" for this practice. In fact, the decision to reevaluate previous cases using the osmotic test was significantly associated with both the number of tests performed and the confidence expressed in interpreting the test ($p < 0.001$ for both).

Regarding recognized limitations in improving the routine clinical practice of each test, clinicians expressed a high level of uncertainty, which may stem from concerns about potential side effects associated with the hypertonic saline test (40.8% responded uncertain) or the low accuracy of the arginine test (50.8% responded uncertain). Similarly, opinions were divided on whether the low accuracy of the WDT was a significant concern, with 47.5% responding strongly disagree/disagree/uncertain and 52.5% agreeing/strongly agreeing.

In contrast, the recently abandoned stepwise approach - where the hypertonic saline test was limited to doubtful cases - still received considerable support within the analyzed cohort, with 56.7% agreeing or strongly agreeing. This preference did not appear to be associated with the type of facility where participants worked, nor with concerns about potential side effects during the hypertonic saline test or the low accuracy demonstrated by the WDT in this differential diagnosis. Conversely, support for the stepwise approach was strongly correlated with the clinicians' perceptions of the reliability of the results obtained from the arginine test ($p < 0.001$).

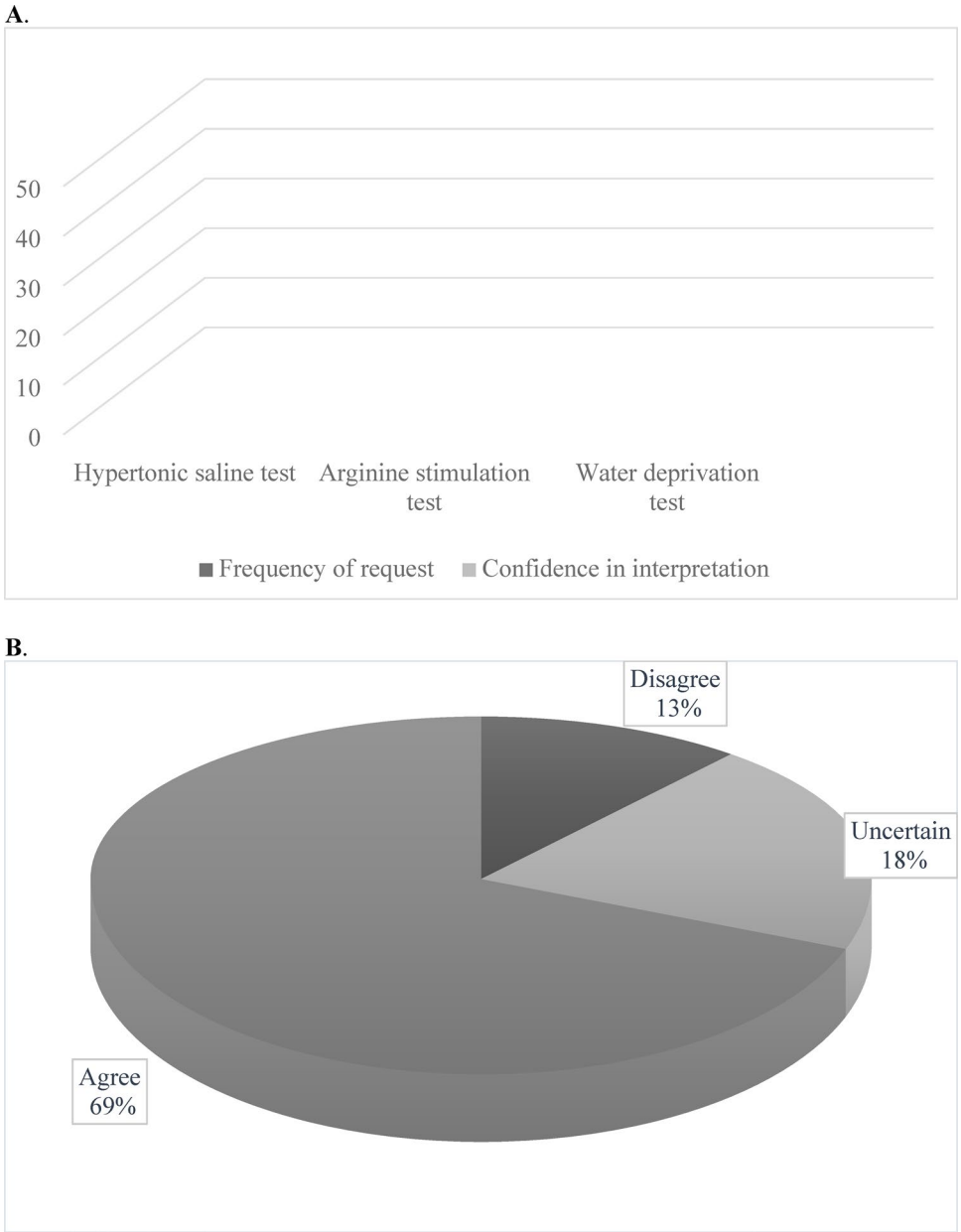

Fig. 1 Frequent utilization of available stimulation tests (responses "always" or "almost always" to questions 9, 11, and 13) with high confidence in their interpretation (responses "high" or "very high" to questions 10, 12, and 14) (**A**). Perceived impact of caregiving burden on test selection for diagnosing polyuria-polydipsia syndrome (responses of "strongly disagree" and "disagree" as well as "strongly agree" and "agree" were combined) (**B**)

This reflects an acknowledgment of the significant influence of the associated caregiving burden on the current approach to the differential diagnosis of PPS, with 69.2% agreeing or strongly agreeing (Fig. 1B).

Notably, the answer to these last two questions were not associated with the type of facility where participants worked, the availability of the copeptin assay, or the frequency with which they referred patients with PPS to another center.

Discussion

The results of this National survey offer several valuable insights into endocrinological clinical practices related to the differential diagnosis of PPS in Italy.

First, the availability of copeptin assays is now widespread in nearly half of the facilities, extending beyond just referral centers. Moreover, the presence of copeptin testing in the facility where clinicians work significantly influences their decision to request a basal copeptin measurement to rule out AVP-R cases or to refer patients with PPS to a specialized center. However, our data suggests that a key challenge remains the confidence in interpreting these results, which could benefit from improved dissemination

of knowledge about this diagnostic tool, particularly among younger clinicians.

Second, the WDT remains the most used stimulation test among Italian endocrinologists (Fig. 1A), partly due to a lack of recognition regarding its limited accuracy and the healthcare burden it entails. This preference is largely shaped by extensive experience accumulated over the past decades, during which the WDT was the gold standard for PPS differential diagnosis in the absence of more accurate tests. Notably, this preference is not associated with the type of hospital facility in which the specialist is employed but rather with clinicians' confidence in the test, which is influenced by their years of experience and the number of patients they have seen.

In this regard, it is noteworthy that the survey did not collect specific data on the respondents' level of expertise in neuroendocrinology, which may represent a limitation worth acknowledging. Overall, the most significant finding from our data is that expertise with each diagnostic test increases with its use (Fig. 1A). The choice of which test to prioritize does not appear to be driven by concerns about potential side effects during hypertonic saline infusion or the perceived low accuracy of the arginine test. Rather, the primary concern expressed by endocrinologists was the perceived caregiving burden associated with the PPS diagnostic process, with 69.2% expressing agreement, 18.3% uncertain, and 12.5% in disagreement (Fig. 1B). As a result, many clinicians favored a stepwise approach, emphasizing the use of a quicker, more accessible test like the arginine stimulation test, rather than a direct path to diagnosis involving referral to a specialized center.

This case exemplifies how the application of recent evidence in the diagnosis of rare diseases often depends more on the expertise of healthcare personnel and the availability of appropriate diagnostic tools than on consensus recommendations alone. Reducing the latency between the generation of scientific evidence and its implementation in clinical practice remains a key objective of scientific societies. Based on the results of our survey, the primary role of endocrinological societies should be to raise awareness of the varying accuracies of the novel diagnostic options for PPS and to support the development of streamlined pathways that guide patients toward referral centers. These centers can then provide a reliable diagnosis using the most accurate and appropriate tests for each individual case.

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Data availability Some or all data sets generated during and/or analyzed during the present study are not publicly available but are available from the corresponding author on reasonable request.

Declarations

Consent for publication All authors have read and agreed to the published article.

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent to participate Informed consent was obtained from all individual participants included in the study.

References

1. Atila C, Refardt J, Christ-Crain M (2024) Arginine vasopressin deficiency: diagnosis, management and the relevance of oxytocin deficiency. Nat Rev Endocrinol. https://doi.org/10.1038/s41574-024-00985-x
2. Refardt J, Atila C, Christ-Crain M (2024) New insights on diagnosis and treatment of AVP deficiency. Rev Endocr Metab Disord 25:639–649. https://doi.org/10.1007/s11154-023-09862-w
3. Newell-Price J, Drummond JB, Gurnell M et al (2024) Approach to the patient with suspected hypotonic polyuria. J Clin Endocrinol Metab dgae565. https://doi.org/10.1210/clinem/dgae565
4. Fenske W, Quinkler M, Lorenz D et al (2011) Copeptin in the differential diagnosis of the Polydipsia-Polyuria Syndrome—Revisiting the direct and indirect water deprivation tests. J Clin Endocrinol Metabolism 96:1506–1515. https://doi.org/10.1210/jc.2010-2345
5. Timper K, Fenske W, Kühn F et al (2015) Diagnostic accuracy of copeptin in the differential diagnosis of the polyuria-polydipsia syndrome: a prospective multicenter study. J Clin Endocrinol Metab 100:2268–2274. https://doi.org/10.1210/jc.2014-4507
6. Fenske W, Refardt J, Chifu I et al (2018) A copeptin-based approach in the diagnosis of diabetes insipidus. N Engl J Med 379:428–439. https://doi.org/10.1056/NEJMoa1803760
7. Refardt J (2020) Diagnosis and differential diagnosis of diabetes insipidus: update. Best Pract Res Clin Endocrinol Metab 34:101398. https://doi.org/10.1016/j.beem.2020.101398

8. Winzeler B, Cesana-Nigro N, Refardt J et al (2019) Arginine-stimulated copeptin measurements in the differential diagnosis of diabetes insipidus: a prospective diagnostic study. Lancet 394:587–595. https://doi.org/10.1016/S0140-6736(19)31255-3
9. Refardt J, Atila C, Chifu I et al (2023) Arginine or hypertonic saline-stimulated copeptin to diagnose AVP deficiency. N Engl J Med 389:1877–1887. https://doi.org/10.1056/NEJMoa2306263
10. Atila C, Loughrey PB, Garrahy A (2022) Central diabetes insipidus from a patient's perspective: management, psychological co-morbidities, and renaming of the condition: results from an international web-based survey. Lancet Diabetes Endocrinol 10:700–709. https://doi.org/10.1016/S2213-8587(22)00219-4