Case report

Arginine Vasopressin Resistance (AVP-R)

Falabella Petra[1], Večerić-Haler Željka [2,*]

1. Division of Internal Medicine, General hospital dr. Franca Derganca Nova Gorica, Slovenia
2. Department of Nephrology, University Medical Cebnter Ljubljana, Slovenia

* Correspondence: zeljka.vecerichaler@kclj.si

Citation: Falabella P, Večerić-Haler Ž. Arginine Vasopressin Resistance (AVP-R). Proceedings of Socratic Lectures. **2024**, 11, 1-5. https://doi.org/10.55295/PSL.11.2024.1

Publisher's Note: UL ZF stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Abstract:
Arginine vasopressin resistance (AVP-R) previously known as nephrogenic diabetes insipidus is a rare disorder characterised with large fluid output due to resistance to arginine vasopressin in kidneys. It can be caused by different etiologies, including hereditary causes. In diagnosis we must determine the reason for polyuria (vasopressin deficiency, resistance, or primary polydipsia). Treatment is mostly symptomatic with adequate water consumption in combination with low-salt and low-protein diet. The main drugs used to treat AVP-R are thiazide diuretics, non-steroidal anti-inflammatory drugs (NSAIDs) and amiloride. In the article we present an illustrative clinical case.

Keywords: Arginine vasopressin resistance (AVP-R), polyuria, thiazide diuretics, non-steroidal anti-inflammatory drugs (NSAIDs), amiloride, acute kidney impairment

1. Introduction

Arginine vasopressin resistance, previously known as nephrogenic diabetes insipidus (till 2022 when endocrinologists decided to change the name (Hui et al., 2024)) is a disorder that results in an inability to concentrate urine due to failure of the kidneys to respond to antidiuretic hormone (Kavanagh and Uy, 2019).
In its broader sense, it can occur quite frequently when the concentration ability of the kidneys is decreased due to acute or chronic kidney disease. In the narrow sense, it is a very rare disorder characterized with polyuria (>50 mL/kg), dilute urine (osmolality <300 mOsm/L), and increased thirst with the intake of up to 20 L/day fluid intake (Hui et al., 2024).

2. Epidemiology

AVP-R is far less prevalent than arginine vasopressin deficiency (AVP-D, previously called central diabetes insipidus), which is estimated to be present in 1 of 25,000 individuals. Congenital AVP-R represents less than 10% of all conditions previously known as diabetes insipidus.(Christ-Crain & Gaisl, 2021)
In congenital AVP-R the X-linked hereditary pattern due to mutations in the AVPR2 gene accounts in 90% of cases and occurs with a frequency of 4–8/1 million male live births. For the remaining cases of congenital nephrogenic diabetes insipidus (DI), autosomal recessive and dominant hereditary patterns due to mutations in the aquaporin - 2 (AQP2) gene are responsible.(Christ-Crain & Gaisl, 2021).

3. Pathophysiology

Under normal circumstances, vasopressin is secreted from the pituitary gland when osmolarity rises above 280-290 mOsm/kg. It is then bound to vasopresin 2 receptor (V2R) in the distal tubule of the nephron, which stimulates a signaling cascade that leads to the insertion of AQP2 channels on the apical side and enables water reabsorption (Kavanagh and Uy, 2019). In AVP-R, there is a defect in the signaling pathway for urine concentration in distal tubule. Congenital AVP-R is a result of mutation in AVPR2 (dysfunction of the V2R receptor) or AQP2 genes (dysfunction of aquaporin 2 water channels) (Kavanagh & Uy, 2019).

4. Etiology

AVP-R can be caused by:

- Medications - predominately lithium which can cause irreversible state after long term use (Garofeanu et al., 2005)
- Hypercalcemia (Rosen et al., 1990)
- Hypokalemia (Marples et al., 1996)
- Kidney disease:
    - Autosomal dominant polycystic kidney disease (Valenti & Tamma, 2021)
    - Chronic kidney disease(Tannen et al.,1969)
    - Infiltrating lesions (Christ-Crain & Gaisl, 2021)
    - Sjögren's syndrome (Patel, 2021)
- Urinary tract obstruction (Carpenter et al., 2018; Frokiaer et al., 1996)
- Hereditary (Kavanagh & Uy, 2019)

5. Clinical manifestation

The most important clinical symptoms are polyuria and polydipsia. People with AVP-R are prone to dehydration and hypernatremia due to extreme urine secretion (Kavanagh and Uy, 2019).
If the disorder is congenital, it usually manifests in the first year of life. Infants may refuse milk, prefer water, may vomit and fail to thrive (Lopez-Garcia et al., 2020).

6. Diagnosis

It must first be determined whether polyuria is present, which is characterized by a urine output of more than 3 L/day or more than 40 to 50 mL/kg/day in an adult (Christ-Crain et al., 2021a). This can be determined with a 24-hour urine collection. There are several age-

dependent limits for children. The osmolarity of the urine is then measured, which must be less than 300 mOsm/kg or between 300and 600 mOsm/kg if the calculated total daily solute excretion is less than 1000 mOsm (Christ-Crain et al., 2021a).
Once the inability to concentrate urine has been established, it should be determined if there is vasopressin deficiency, resistance, or primary polydipsia (Christ-Crain et al., 2021a). To differentiate, a water restriction test and an evaluation of the response to desmopressin should be performed. If AVP-R is detected, it is important to determine the etiology, which may be based on the patient's medical history (medication use, known kidney disease, family history) or laboratory findings (electrolyte disturbances).
The measurement of copeptin can also help with the diagnosis. Copeptin is formed from the precursor protein pre–pro-vasopressin together with AVP and neurophysin II. It has been shown that Copeptin reflects the AVP concentration (Christ-Crain et al., 2021a). As it is more stable than AVP, measurements are easier in clinical practice (Christ-Crain et al., 2021a). In children, genetic testing is performed (Milano et al., 2017).

7. Treatment

There is no specific treatment for AVP-R (Milano et al., 2017). Symptomatic treatment includes adequate fluid intake in combination with a low-salt and low-protein diet to minimize mandatory water excretion (Christ-Crain et al., 2021a). The main drugs used to treat AVP-R are thiazide diuretics, non-steroidal anti-inflammatory drugs (NSAIDs) and amiloride, which are used individually or in combination (Christ-Crain et al., 2021a). Thiazide diuretics are effective in reducing urine output when combined with a very low sodium diet (Christ-Crain et al., 2021a). Potassium-sparing agents such as amiloride may have an additional effect with thiazide diuretics via a mechanism probably related to inhibition of thiazide-induced potassium loss (Christ-Crain et al., 2021a). Ibuprofen and indomethacin improve urinary concentrations in AVP-R patients, where urinary excretion can be reduced by 25-50% (Milano et al., 2017). However, a small study found no significant effect of ibuprofen on urinary excretion of urine osmolarity (Libber et al., 1986). In children with genetic AVP-R, early symptomatic treatment is crucial to prevent developmental disorders caused by hypernatremia and dehydration (Lopez-Garcia et al., 2020).

8. Presentation of an illustrative clinical case

A 43-year old man was admitted to the nephrology department due to an acute kidney impairment with anasarca.
He had seen a pediatric endocrinologist regularly throughout his childhood, and the treatment of choice was symptomatic with regulated hydration. He drank about 20 liters of water per day and urinated about 18 liters of fluid per day. He never had problems with electrolyte imbalance, including a normal serum sodium in the normal range, and his kidney function was normal (i.e. last normal serum creatinine before admission was 78 μmol/l). He has also been diagnosed with type 2 diabetes mellitus and arterial hypertension in the last 10 years. His brother also had a congenital form of AVP-R and his daughter had Abernethy syndrome.
The current medical problem began about a month before hospitalization when he sustained a muscle injury to his leg for which he was prescribed ibuprofen (400 mg three times a day) for pain relief. Due to his work as a butcher, he was unable to rest and took the medication a maximum of three times a day as prescribed, and if the pain was too severe, he took one or two more tablets. After about a week, he noticed increasing swelling and reduced urine output, so he instinctively reduced his water intake by half. At the end of the month, he noticed that he was suffering from a persistent cough and shortness of breath. By restricting his water intake, he lost 3 kg, but the edema was still present, his urine output dropped to less than 10% of his usual daily urine output (though by strict definition he was never oliguric, i.e. he had a daily output of more than 400 ml) and he felt extremely tired. He went to the emergency room, where laboratory results showed severely impaired kidney function with severe hyponatremia, whereupon he was admitted to the hospital. The laboratory findings after admission showed hyponatremia with Na concentration 111 mmol/l and a deterioration in kidney function with an increase in creatinine up to 700 mcmol/l. The urine sediment was unremarkable. We decided to

perform a kidney biopsy, which revealed signs of diffuse acute tubular damage and diabetic nephropathy. The kidney biopsy suggested drug- or ischemia-induced tubular damage.

Fluid restriction and a loop diuretic were initiated, after which diuresis gradually improved and polyuria gradually returned. During this time, the sodium concentration gradually increased into the normal range. The patient lost a total of 20 kg of water in 4 days. On the day of discharge, diuresis was about 9 liters per day with a normal and stable sodium concentration and a creatinine level of 320 μmol/l. The patient was satisfied with the fluid loss and the disappearance of symptoms.

This report discusses a multifactorial Acute Kidney Injury (AKI) in a patient with a congenital AVP-R.

The presented case is an indication of the strong effect of NSAIDs on urinary excretion in patients with congenital AVP-R. The case is very illustrative because of the contrast between the extreme polyuria in the compensated state and the severely reduced urine output in the phase of AKI, which, however, could not be so obvious as the patient rarely reached the criteria for oliguria. It is known that NSAIDs can reduce urine output by 25% to 50% in these patients (Milano et al., 2017).

The reason for the deterioration of kidney function in the present case could be an overdose of NSAIDs that caused acute kidney injury with a reduction in urine output. With the reduced urine output and maintaining the normal fluid intake of 20 L per day, the patient entered the volume overload phase. As a result, his hypertension became out of control and he developed congestion and mild pulmonary edema. The mild hyponatremia was probably due to hypervolemia. Fortunately AKI resolved with symptomatic medical treatment without the need for dialysis and eventually with fool recovery of kidney function.

This case emphasizes the importance of careful monitoring when prescribing new drugs for patients with specific conditions such as congenital AVP-R. NSAIDs, thiazides and potassium-sparing diuretics can reduce urine output in patients with congenital AVP-R (Milano et al., 2017), which can be counterintuitive in some cases. Patients with AVP-R, while accustomed to regulating increased urine output, are not accustomed to regulating fluid intake when urine output is suddenly reduced. When they are prescribed a new medication or start a new diet, they should always be advised to monitor their body weight and reassess fluid intake if they suddenly gain weight.

9. Conclusion

AVP-R is a quite rare disease, and its characteristics may pose many challenges when treating patients who have it. Firstly, there is an enormous required fluid intake and fluid waste which have to be accounted for, and secondly, commonly prescribed drugs such as NSAIDs and thiazide diuretics can impose additional challenges as they interfere with water balance.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Carpenter CP, Rawson A, Hains DS, Giel DW. Resolution of Diabetes Insipidus After Pyeloplasty: A Case Report and Review of the Literature. Urology. 2018;115:168-170. DOI:10.1016/j.urology.2018.02.017
2. Christ-Crain M, Gaisl O. Diabetes insipidus. Presse Med. 2021; 50:104093. DOI:10.1016/j.lpm.2021.104093
3. Christ-Crain M, Winzeler B, Refardt J. Diagnosis and management of diabetes insipidus for the internist: an update. J Intern Med. 2021a; 290:73-87. DOI:10.1111/joim.13261
4. Frokiaer J, Marples D, Knepper MA, Nielsen S. Bilateral Ureteral Obstruction Downregulates Expression of Vasopressin-Sensitive AQP-2 Water Channel in Rat Kidney. The American Journal of Physiology. 1996; 270: F657-668. https://doi.org/10.1152/ajprenal.1996.270.4.F657
5. Garofeanu CG, Weir M, Rosas-Arellano MP, et al. Causes of reversible nephrogenic diabetes insipidus: a systematic review. Am J Kidney Dis. 2005 ;45:626-637. DOI:10.1053/j.ajkd.2005.01.008
6. Hui C, Khan M, Khan Suheb MZ, et al. Arginine Vasopressin Disorder (Diabetes Insipidus) [Updated 2024 Jan 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470458/

7. Kavanagh C, Uy NS. Nephrogenic Diabetes Insipidus. Pediatric Clinics of North America. 2019; 66: 227–34. DOI:10.1016/j.pcl.2018.09.006
8. Lopez-Garcia SC, Downie ML, Kim JS, et al. Treatment and long-term outcome in primary nephrogenic diabetes insipidus. Nephrol Dial Transplant. Published online December 26, 2020. DOI:10.1093/ndt/gfaa243
9. Marples D, Frøkiaer J, Dørup J, Knepper MA, Nielsen S. Hypokalemia-induced downregulation of aquaporin-2 water channel expression in rat kidney medulla and cortex. J Clin Invest. 1996; 97:1960-1968. DOI:10.1172/JCI118628
10. Patel Jigar K. Distal Renal Tubular Acidosis due to Primary Sjögren's Syndrome: Presents as Hypoakalemic Paralysis with Hypokalemia-Induced Nephrogenic Diabetes Insipidus. Saudi Journal of Kidney Diseases and Transplantation. 2021; 32:851-854. DOI: 10.4103/1319-2442.336782
11. Rosen S, Greenfeld Z, Bernheim J, Rathaus M, Podjarny E, Brezis M. Hypercalcemic nephropathy: chronic disease with predominant medullary inner stripe injury. Kidney Int. 1990; 37:1067-1075. DOI:10.1038/ki.1990.87
12. Libber SMD, Harrison H, Spector D. Treatment of Nephrogenic Diabetes Insipidus with Prostaglandin Synthesis Inhibitors. The Journal of Pediatrics. 1986; 108: 305-311. https://doi.org/10.1016/s0022-3476(86)81010-1
13. Milano S, Carmosino M, Gerbino A, et al. Hereditary Nephrogenic Diabetes Insipidus: Pathophysiology and Possible Treatment. An Update. Int J Mol Sci. 2017; 18:2385. DOI:10.3390/ijms18112385
14. Tannen RL, Regal EM, Dunn MJ, Schrier RW. Vasopressin-resistant hyposthenuria in advanced chronic renal disease. N Engl J Med. 1969; 280:1135-1141. DOI:10.1056/NEJM196905222802101
15. Valenti G, Tamma G. The Vasopressin-Aquaporin-2 Pathway Syndromes. Handbook of Clinical Neurology. 2021; 181:249–59. https://doi.org/10.1016/B978-0-12-820683-6.00018-X.