

Case Report: An interesting case of a patient who presented with increasing thirst and polyuria in a district general hospital in the UK

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Abstract

A gentleman presented with polyuria and polydipsia to the Endocrine Clinic in late 2020. The patient was investigated extensively. Diabetes Mellitus was excluded, and the patient was investigated for Diabetes Insipidus (DI). The patient was passing more than 3L of urine/day. A Water deprivation Test (WDT) was done, and it suggested Partial Central Diabetes Insipidus (Partial Arginine Vasopressin Deficiency), which is a rare disorder. Various blood tests looking for the aetiologies such as Sarcoid, Germinoma, IgG4 Disease and Vasculitis were negative. MRI scan of the Pituitary carried out twice showed no abnormality. The patient's distressing symptoms were alleviated with proper treatment (nasal Desmopressin). Thus, it is important to diagnose this treatable condition which is often confused with Primary Polydipsia. The patient has since then been clinically and biochemically well.

Keywords: Polyuria; Polydipsia; AVP; Diabetes Insipidus; Pituitary

1. Introduction

Diabetes insipidus results from problems relating to a hormone called Arginine Vasopressin Peptide (AVP), also known as Antidiuretic hormone (ADH). It is produced in the hypothalamus and then passes from the hypothalamus to the posterior pituitary gland, where it's stored until needed. The posterior pituitary gland releases AVP when the amount of water in the body becomes too low (1). AVP acts on the distal convoluted tubules of the kidneys and helps to retain water in the body by reducing the amount of water filtered out through the kidneys, and thus the kidneys produce more concentrated urine (1). In Central Diabetes Insipidus, there is deficient production of AVP whereas in more rare cases, called Nephrogenic Diabetes Insipidus, the kidneys do not respond to the circulating AVP. Patients feel thirsty as the body tries to compensate for the increased loss of water by increasing the amount of water intake (1). In Central Diabetes Insipidus some individuals may have a severe form of the disorder (Complete CDI) with little or no vasopressin activity and others may have a mild form of the disorder (Partial CDI) with residual vasopressin activity. Individuals with CDI are at risk of developing dehydration and cardiovascular symptoms including irregular heartbeats, fever, dry skin and mucous membranes, confusion, seizures, change in consciousness, and potentially coma.

2. Case Report

A 69-year-old gentleman was referred by his GP to the Endocrinology Out- Patients Department with excessive thirst and polyuria. His background history included: Vitamin D deficiency, potential hypertension, non-alcoholic fatty liver disease, actinic keratosis and solar elastosis and Varicose veins of the legs. The patient was only on Omeprazole at the time of referral.

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He underwent a number of investigations: Urea and Electrolytes- Normal (done several times with serum sodium always > 137 mmol/L), (2) Bone profile- Normal (checked several times), (3) HBA1C 37 mmol/mol and 36 mmol/mol checked twice, (4) Thyroid Function- Normal, (5) Cortisol- Normal, (6) B-HCG Normal : < 2 U/L (Normal <10), Alfa-fetoprotein done twice- Normal: 2.6 and 3.0 KU/L (Normal <6.7), (6) ACE <12 U/L (Normal 20-70), (7) CXR- Normal, (8) IgG- Normal: 8.35g/L (Normal: 6-16), (9) Vasculitis screen: Normal.

A Water Deprivation Test (WDT) was organised at our Planned Investigation Unit. The results were as follows:

Table 1 Results of the WDT

Time	Urine Osmolality in mosmol/kg	Urine sodium in mmol/L	Serum Osmolality in mosmol/kg (N: 275-295)	Serum sodium in mmol/L (N: 133-145)
9 AM	365	43	295	137
9.30 AM	470	54		
10.30 AM	429	49		
11.30 AM	462	52	289	139
12.30 PM	510	60		
13.30 hrs	536	66		
14.30 hrs	573	69		
15.30 hrs	584	71	289	138
16.30 hrs *	634	75	290	140
22.30 hrs (after Desmopressin)	731	82		

*Desmopressin injection 2 mcg was given at this time

Table 2 Interpretation of the Water Deprivation Test (2)

Interpretation	Urine (mosmol/kg) after Deprivation	Osmolality after Water	Urine (mosmol/kg) after Desmopressin injection
Normal	>750		>750
Central Diabetes Insipidus	<300		>750
Nephrogenic Diabetes Insipidus	<300		<300
Primary Polydipsia	300-750 (A low or low-normal Serum sodium is expected)		<750
Partial Diabetes Insipidus	300-750		<750

Ideally during the WDT, the patient is deprived of fluids for 8 hrs, followed by Desmopressin 2 mcg IM.

The diagnosis here was challenging; the differential diagnosis was between Primary Polydipsia and Partial Diabetes Insipidus (DI). Initial Urine Osmolality was 365mosmol/Kg and following Desmopressin injection it went up to 731mosmol/Kg. The patient had never suffered from hyponatraemia (low Serum sodium); hence the possible diagnosis was Partial Diabetes Insipidus and not Primary Polydipsia. Partial Central Diabetes insipidus is diagnosed in patients who have a maximum urine osmolality of 300 to 800 mOsm/Kg (750 according to some) and an increase in urine osmolality of 9 to 50% after administration of Desmopressin. Primary polydipsia is diagnosed in patients who have a

maximum urine osmolality of 300 to 800 mosm/Kg (750 according to some) and an increase in urine osmolality of less than 9% after administration of Desmopressin (Ref:3,4).

Our patient had $>15\%$ $[(731-634)/634 \times 100 = 15.3\%]$ rise in urine osmolality following Desmopressin injection; hence the diagnosis was Partial Central Diabetes Insipidus.

However, the test required to distinguish between the two conditions is stimulated Copeptin test (with hypertonic saline or arginine). Copeptin is the C-terminal peptide of the prohormone for AVP (Arginine Vasopressin) and is produced by the posterior pituitary on an equimolar basis with AVP. This test is not done in our hospital.

Stimulated Copeptin Test is done with hypertonic saline (2). Initially 250 ml of 3% Saline is infused at 0.15 ml/Kg/min. Blood samples for osmolality, sodium, urea, and glucose are checked every 30 mins until a plasma sodium level of 150 mmol/l is reached. Copeptin is measured before and at peak sodium.

Interpretation (2, 5, 6): A Copeptin value (blood test done any time) of >21.4 pmol/l establishes the diagnosis of Nephrogenic DI (Ref: 3, 4). This stimulated test is carried out if the Copeptin value is <21.4 pmol/l. Plasma Copeptin <4.9 pmol/l indicates Complete or Partial Central Diabetes Insipidus.; Plasma Copeptin >4.9 pmol/l indicates Primary Polydipsia.

The second Stimulated Copeptin test is the Arginine stimulation test (7) where 0.5 g L-Arginine-Hydrochloride/kg body weight, is infused over 60-120 minutes. A Copeptin level, 60 minutes after Arginine infusion, of <3.8 pmol/l suggests Central Diabetes Insipidus and a level of >3.8 pmol/l suggests Nephrogenic Diabetes Insipidus.

The patient had MRI Pituitary done twice, with the second one 1 year after the first one, MRI of the pituitary gland before and after intravenous contrast injection showed no convincing abnormality on both occasions.

A normal scan at presentation requires repeat imaging at 6-12 months to check for Germinoma (2). The commonest finding in Cranial Diabetes Insipidus is an absent posterior pituitary bright spot. In case of a sellar mass with Cranial DI, Craniopharyngioma or Granuloma needs to be considered. A thickened Pituitary stalk can be found in autoimmune hypophysitis (2).

A low Serum ACE and normal CXR excluded Sarcoid; also, IgG (looking for IgG4 disease), B-hCG and AFP (looking for Germinoma) and Vasculitis screen were normal. Thus, our patient had Idiopathic Partial Central Diabetes Insipidus.

3. Discussion

Central Diabetes Insipidus (CDI) is due to deficient production of Antidiuretic Hormone (ADH) or Arginine Vasopressin Peptide (AVP). It is clinically characterised by polydipsia, nocturia and polyuria of dilute urine. It is the result of a defect involving the hypothalamic osmoreceptors or the posterior pituitary gland (8). The most common causes are neoplasms of the hypothalamic-pituitary axis (25%), surgery (20%), head trauma (15%) or familial causes (10%). No cause is identified in up to 30% of cases (8)

In Diabetes Insipidus or DI there is production of >3 L/24 hrs of urine (can be up to 20 L/24 hrs) which is dilute (<300 mOsmol/Kg).

Classification: (1) Cranial or Central DI, also called Arginine Vasopressin Deficiency or AVP-D (9): It is due to a deficit of AVP synthesis; 80% of AVP secreting hormones must be lost to cause Complete Cranial DI, (2) Nephrogenic DI: This is due to renal resistance to circulating AVP

Causes of Central DI (2):

- Genetic including DIDMOAD (DI, DM, Optic Atrophy, Deafness) Syndrome, (2) Tumours like Craniopharyngiomas, Germinomas, Metastases, (3) Trauma like Head Injury, Surgery for Pituitary adenoma, (4) Inflammatory like Hypophysitis, Sarcoidosis, Chronic Multifocal Langerhans -cell -Histiocytosis (Hand-Schuller- Christian Disease), ANCA- associated Vasculitis, (5) Infections: Meningitis, Encephalitis, HIV disease, (6) Vascular: Subarachnoid haemorrhage, Sheehan's syndrome, (7) Idiopathic including Autoimmune
- Nephrogenic DI, also called Arginine Vasopressin Resistance or AVP- R(9) Causes: (1) Genetic -AVPR2 gene mutation in 90% cases and AQP2 gene mutation in 10% cases (1), (2) Drugs: Lithium, Demeclocycline,

Colchicine, Amphotericin B, (3) Metabolic: Hypercalcaemia, Hyperglycaemia, Hypokalaemia, (4) Chronic kidney disease, (5) Post-obstructive uropathy.

Partial Nephrogenic Diabetes Insipidus results from partial resistance of the kidneys to the action of AVP

A high serum osmolality of >300 mosmol/Kg in the presence of polyuria with dilute urine is highly suggestive of Diabetes Insipidus.

- Gestational DI (10): Gestational DI occurs during pregnancy usually during the third trimester. During pregnancy, Vasopressinase produced from placental trophoblasts breaks down AVP or ADH. Gestational DI is thought to occur with excessive production and/or impaired clearance of Vasopressinase as in Pre-eclampsia, HELLP syndrome and acute fatty liver of pregnancy.

3.1. Treatment

3.1.1. Central Diabetes Insipidus

Desmopressin in 1- 2 divided doses: (1) Nasal Spray: 10-40 mcg daily, (2) Desmopressin Injection 2-4 mcg IM or S/C daily, (3) Desmopressin Oral- Initially 100 micrograms 3 times a day; maintenance 100–200 micrograms 3 times a day; usual dose 0.2–1.2 mg daily, Sublingual: Initially 60 micrograms 3 times a day, adjusted according to response; usual dose 40–240 micrograms 3 times a day

3.1.2. Nephrogenic Diabetes Insipidus

(1) Adequate Fluid intake and Reduced Salt intake, (2) Discontinuation of drugs like Lithium or Demeclocycline, (3) Thiazide diuretics like Bendroflumethiazide or Hydrochlorothiazide and Thiazide like diuretic Indapamide- for reduction in urine output and increase in urine concentration, (4) Amiloride is useful in Lithium- induced Nephrogenic DI, (5) Prostaglandin synthetase inhibitors like Ibuprofen and (6) Carbamazepine and Clofibrate may be effective in mild cases.

Treatment of our patient: Desmopressin Nasal Spray: 10 mcg in one nostril daily- Patient has remained well. Polyuria and Polydipsia have resolved, Serum sodium and Osmolality have remained normal.

4. Conclusion

Our patient had Idiopathic Partial Central Diabetes Insipidus (Idiopathic Partial Arginine Vasopressin Deficiency). The reasons were as follows:

- Following Desmopressin injection during the Water Deprivation test, the Urine Osmolality increased by 15.3 %,
- The patient's symptoms responded to a small dose of Desmopressin without Thiazide diuretics (hence not Partial Nephrogenic DI).

This article aims to help the society in understanding that patients with increasing thirst, polyuria and nocturia may need investigation by an Endocrinologist and a small dose of a drug, Desmopressin, may sometimes be useful in mitigating the distressing and troublesome symptoms of such patients.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest.

Statement of informed consent

Informed consent was obtained from the patient for the purpose of writing up this manuscript.

References

- [1] Diabetes Insipidus: NHS; Last reviewed Oct 13 2022.<https://www.nhs.uk/conditions/diabetes-insipidus/>
- [2] Diabetes Insipidus. Oxford Handbook of Diabetes and Endocrinology. Edited by Owen K, Turner H, Wass J, 2022; Edition 4: 230-234
- [3] Fenske W, Refardt J, Chifu I, Schnyder I, Winzeler B, Drummond J, Ribeiro- Oliveira A Jr, Dreschar T, Stefan B, Vogt DR, Malzahn U, Kroiss M, et al. A Copeptin-Based Approach in the Diagnosis of Diabetes Insipidus, *N Engl J Med* 2018; 379:428-439 <https://www.nejm.org/doi/full/10.1056/NEJMoa1803760>
- [4] Kotagiri R, Sridharan GK. Primary Polydipsia. National Library of Medicine. Last updated. July 20, 2022 <https://www.ncbi.nlm.nih.gov/books/NBK562251/>
- [5] Investigation of Diabetes Insipidus using Copeptin. Royal United Hospitals Bath NHS Foundation Trust; updated May25,2021 https://www.ruh.nhs.uk/pathology/documents/clinical_guidelines/DIAB_ENDO_020_Copeptin_Protocol.pdf
- [6] Christ-Crain M, Refardt J, Winzeler B. Approach to the Patient: “Utility of the Copeptin Assay” *J. Clinical End & Metabol*; 107(6):1727–1738 <https://academic.oup.com/jcem/article/107/6/1727/6524226>
- [7] Winzeler B, NigroCesana N, Refardt J, Vogt DR, Imber C, Morin B, Popovic M, Steinmetz M, Sailer C, Szinna G, Chifu I, Fassnacht M, Christ-Crain M Arginine-stimulated copeptin measurements - a new test for diabetes insipidus. *ECE* 2019. Oral Communications. Anterior and posterior Pituitary 2 *Endocrine Abstracts* (2019) 63 OC13.1
- [8] Adams NC, Farrell TP, O'Shea A, O'Hare A, Thornton J, Power S, Brennan P, Looby S. *Neuroradiology of Central Diabetes Insipidus- when, how and findings* *Neuroradiology*. 2018; 60(10): 995-1012
- [9] Arima H, Cheetham T, Christ-Crain M, Cooper D, Gurnell M, Drummond JB, Levy M, McCormack AI, Verbalis J, Newell-Price J, Wass JAH. Changing the name of diabetes insipidus: a position statement of The Working Group for Renaming Diabetes Insipidus, *Endocr J*. 2022; 69(11):1281-1284.
- [10] Kalelioglu I, Kubat Uzum A, Yildirim A, Ozkan T, Gungor F, Has R. "Transient gestational diabetes insipidus diagnosed in successive pregnancies: review of pathophysiology, diagnosis, treatment, and management of delivery". *Pituitary*. 2007; 10(1): 87–93