**Case report**

**SODIUM VALPROATE INDUCED NEPHROGENIC DIABETES INSIPIDUS;**

**A CASE REPORT**

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ABSTRACT

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| **Nephrogenic Diabetes Insipidus (NDI) is a rare but serious renal complication of long-term lithium therapy, characterized by renal resistance to Anti-Diuretic Hormone (ADH), leading to persistent polyuria and polydipsia. If unrecognized, it can cause severe dehydration and electrolyte imbalances. Sodium valproate, the other mood stabilizer in widespread use, is reported to cause transient central diabetes insipidus in cases of drug overdose. However, NDI due to sodium valproate is not reported in the literature. Here we present a 64-year-old male on prolonged valproate therapy who developed polyuria and polydipsia. Further evaluation confirmed NDI after a water deprivation and desmopressin challenge test. His condition improved after valproate discontinuation and hydrochlorothiazide initiation. This case highlights a very rare complication of prolonged valproate therapy which is not reported so far. Hence, clinicians should maintain a high index of suspicion in long-term valproate users so that timely intervention to avoid further complications can be employed**. |

*Keywords: [****Valproate, Nephrogenic Diabetes Insipidus, Anti-Diuretic Hormone, Polyuria, Desmopressin Challenge Test, Water Deprivation Test*** *}*

**1. INTRODUCTION**

Diabetes insipidus (DI) is a polyuria and polydipsia syndrome caused by insufficient secretion of arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), or a reduced renal response to AVP[1]. This results in dilute urine (<300 mOsm/L), excessive urine output (>50 mL/kg), and compensatory polydipsia, which can reach up to 20 L/day. [2] Nephrogenic diabetes insipidus (NDI) may be congenital or acquired, with causes including infiltrative diseases, electrolyte imbalances, vascular conditions, and certain medications (e.g., lithium, demeclocycline, cisplatin, amphotericin B, and ifosfamide)[3].Although rare, valproic acid has been reported to cause severe hyponatremia due to SIAD (Syndrome of Inappropriate Anti Diuresis) possibly due to its effect on tubular cell function and hypothalamic osmoreceptors[4]. Cases of Valproate linked Fanconi syndrome from tubular dysfunction have been documented [5,6]. NDI due to valproate is so far not reported in the literature and here we present a case of NDI induced by prolonged valproate therapy in a patients with mood disorder.

**2. CASE PRESENTATION**

A 64-year-old man arrived at the outpatient department complaining of an increased amount of urine volume. The symptom had an insidious onset, and severity worsened over the last two weeks. Excess thirst, dryness of mouth, fatigue, and decreased sleep were reported as associated symptoms. His medical history includes Type 2 diabetes, systemic hypertension, and BPAD (Bipolar Affective Disorder). Diabetes and hypertension were well controlled with glipizide and cilnidipine, respectively. He had been taking sodium valproate, quetiapine, fluoxetine, and lorazepam for the previous four years for BPAD. On examination he was conscious and oriented. Oral mucosa and tongue were dry, and his sitting BP was 100/70 mmHg. Clinical examination was otherwise unremarkable. Labs showed a slight increase in blood urea. Blood glucose was within normal limits. Urine specific gravity was 1.002. Detailed lab reports are summarized in Table 1. To confirm polyuria, his 24 hour urine output was measured which was found to be 4.3L. Subsequently he underwent water deprivation test (Table2).

The water deprivation test showed a progressive increase in serum osmolality from 280 to 298 mOsm/kg and plasma sodium levels from 142 to 145 mmol/L. However, the patient failed to concentrate his urine despite creating maximum stimuli for endogenous AVP release, and urine osmolality remained persistently low (<300 mOsm/kg). Thus, primary polydipsia was ruled out. Following administration of desmopressin, there was no significant improvement in urine osmolality, suggesting nephrogenic diabetes insipidus (NDI).

In the absence of other potential causes of NDI, valproate is considered the offending drug. The valproate dose was reduced and later stopped in consultation with the psychiatrist. He was also started on hydrochlorothiazide. He was kept under close follow up with regular monitoring of serum electrolytes and urine output. He reported symptomatic improvement, including a reduction in urine output, by the end of the second week. Hydrochlorothiazide was stopped after one month. He has now been under regular follow up for the past 4 months and is completely asymptomatic at present.

**3. DISCUSSION**

Nephrogenic diabetes insipidus (NDI) is a rare but significant adverse effect of long term lithium therapy. In BPAD patients on lithium therapy, regular monitoring of urine output is necessary to identify this complication in the early stage. Lithium is absorbed through the epithelial sodium channel (ENaC) and decreases the sodium absorption. The natriuresis induced by lithium has multiple adverse effects on the kidney, ultimately leading to NDI and chronic kidney disease. The expression of ENaC is regulated by aldosterone by the pathway that involves phosphorylation of Nedd4-2 (neural precursor cell expressed, developmentally down-regulated 4-2). This pathway is downregulated in patients on chronic lithium therapy. In addition, lithium inhibits GSK3-beta (glycogen synthase kinase 3-beta) and reduces the expression of aquaporin 2 (AQP2) channels on the luminal side of the cortical collecting duct(CCD) leading to decreased water reabsorption in response to vasopressin[7]. Apart from lithium induced NDI, the other important cause for polyuria in patients with psychiatric illness is primary polydipsia. We could not find any reported association between valproate and NDI even after an extensive literature review. Valproate is known to cause renal tubular injury. Fanconi syndrome had been reported in children who had been on valproate for the long term as an antiepileptic drug. It can present as serious electrolyte imbalance, low molecular weight proteinuria, metabolic acidosis, and sometimes reduced renal function. Some cases are nearly asymptomatic and were detected only by screening[6]. Valproate inhibits the beta oxidation and impairs mitochondrial function[8]. Proximal tubular mitochondrial dysfunction is the proposed mechanism of tubular injury. Carnitine therapy is said to ameliorate the toxic effect of valproate, although not proven in clinical trials[9]. Syndrome of inappropriate antidiuresis (SIAD) can rarely occur in valproate therapy and can present as hyponatremia. An interesting case of hypernatremia correction after starting valproate therapy in a patient suffering from central DI due to head injury has been reported [10]. But the occurrence of DI is difficult to explain, as the pathophysiology is exactly opposite to that of SIAD. A single case of valproate poisoning associated with transient central DI is reported in the literature. However, the case was not confirmed by a water deprivation test, and the authors could not explain the exact mechanism of this complication[11]. Another case of nephrogenic DI has been reported in a patient who had been switched to valproate from lithium immediately before the complication[12].

Our patient had a classical presentation of DI, which was confirmed by a water deprivation test. He had complete resolution of the symptoms after the drug withdrawal. Nevertheless, at present we don’t have enough data in the literature to explain the cause of this rare phenomenon.

**4. CONCLUSION**

NDI due to valproate was not reported earlier. Further research is needed to understand the pathophysiology of this rare complication. It is imperative that patients on any long term drug therapy should be strictly monitored for similar complications.

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Table 1. LABORATORY FINDINGS

|  |  |  |  |
| --- | --- | --- | --- |
| Test | Result | Units | Reference range |
| Blood urea | 57  | mg/dL | 10 – 50 |
| Creatinine | 1.12 | mg/dL | 0.7 - 1.3 |
| Sodium | 142 | mEq/L | 135 - 145 |
| Potassium  | 3.2  | mEq/L | 3.5 - 5.1 |
| Chloride  | 106  | mEq/L | 96 – 106 |
| Magnesium  | 2.1 | mg/dL | 1.7 - 2.2 |
| Uric acid  | 8.4 | Mg/dL | 3.5 - 7.2 |
| Cortisol | 168.67 | ng/mL | 50 – 230 |
| TSH | 1.39 | µIU/mL | 0.5 - 5.0 |
| Calcium | 9.4 | mg/dL | 8.5 - 10.5 |
| RBS  | 112 | Mg/dL | <140 |
| HbA1C  | 6.8  | % | 5.7 - 6.5 |
| Complete hemogram  | TC 6570  | Cells/cu.mm | 4000 - 11,000 |
| DC N 84% L8% | % | N: 40 - 75 %,L: 20 - 45 % |
| PLT 2.56 | Lakhs/cu.mm | 1.5 - 4.5 lakhs/cu.mm |
| Hb -14.1  | g/dL | M: 13 - 17, F: 12 – 15 |
| ESR - 22 | mm/hr | M: 0 - 15,F: 0 – 20 |
| Urine Analysis  | Specific gravity – 1.002pH Protein – nilWBC – 1-2 /HPFRBC – 0-1/HPF Casts –nil Crystals – nil Nitrates- neg  | 24 hour urine (Reference range)1. Protein : 284 (<300 mg/day)
2. Calcium : 185 (100 – 300 mg/day)
3. Sodium : 100 (40 – 220 mEq/day)
4. Potassium : 48 (25 – 125 mEq/day)
5. Magnesium : 102 (73 – 122 mg/day)
6. Uric acid : 458 (250 – 750 mg/day)
7. Phosphate : 584 (400 – 1300 mg/day)
8. Glucose : 0 mg/dl
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| USG abdomen  | Normal KUB area  |
| Arterial blood gas  | Within normal limits |

Table 2. WATER DEPRIVATION TEST & DESMOPRESSIN CHALLENGE TEST

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Time (hrs) | Urine Volume (ml/hr) | Urine Osmolality (mOsm/kg) | Serum Osmolality (mOsm/kg) | Plasma Sodium (mmol/L) | Body weight (kg) |
| 0 | 100 | 192 | 280 | 142 | 71.0 |
| 01:00 | 170 | 192 | 282 | 141 | 71.0 |
| 02:00 | 170 | 195 | 282 | 142 | 70.7 |
| 03:00 | 150 | 194 | 284 | 143 | 70.3 |
| 04:00 | 155 | 196 | 288 | 143 | 70.0 |
| 05:00 | 150 | 206 | 294 | 143 | 70.0 |
| 06:00 | 140 | 206 | 298 | 145 | 69.4 |
| Desmopressin challenge test |
| 00:30 | 150 | 210 | 295 | 145 | 69.8 |
| 01:00 | 145 | 210 | 296 | 144 | 69.5 |
| 01:30 | 140 | 208 | 296 | 145 | 69.5 |
| 02:00 | 150 | 206 | 295 | 146 | 69.3 |