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# **A Case of Central Diabetes Insipidus in a Female Patient with Bipolar Disorder, Lithium Consumer over the Last Years**

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## **1. Introduction**

Cade described the effects of lithium on manic episodes in 1949. Schou confirmed these initial observations in 1954. From 1949 until today we can speak of the history of psychopharmacology, in fact it is the oldest drug in mental disorders that is still in full use (Johson, 2006).

The Food and Drug Administration (FDA) approved it in 1970 for the treatment of acute mania and in 1974 for the prophylaxis of bipolar disorder.

Today lithium valid indications remain in force: acute mania, bipolar depression, prophylaxis and maintenance of bipolar disorder and unipolar depression. Moreover, its use has also been extended to many diseases: personality disorders, aggression, anxiety, etc. (Freeman, 2006).

However, it is a drug whose management requires detailed knowledge of their numerous side effects (Table 1), as well as drug interactions (Table 2), contraindications and special situations (Álvarez, 2000). The fact that it is a drug with a very narrow therapeutic window, requires frequent monitoring plasma determinations.

We report a case that has, in principle, one of the most common side effects of using this drug, 25 to 35 percent of patients have polyuria and polydipsia (Sadock, 2004), a person who concurrently also presents serious illnesses which require special surveillance. But a close examination proved to be another slightly different pathology documented.

Central diabetes insipidus (CDI) is a condition characterized by polyuria, polydipsia, and nocturia and is due to deficiency of arginine vasopressin (AVP).

The case has already been published four years ago in a Spanish journal (Gil-Díez, 2007), but we consider it of interest in order to report on the progress of the disease and a bibliographic update.

## **2. Case report**

A 61 year old woman diagnosed with bipolar disorder since the age of 18. She was frequently hospitalized due to depressive episodes and treated with lithium for about 19 years with excellent results.

Cardiovascular system	Sinus Node dysfunction ECG changes Myocardial disorders (myocarditis)
Kidney	On Glomerular Filtration Rate (GFR) On Serum Creatinine On Distal Tubular function Renal Tubular acidosis Proteinuria Morphologic changes
Body weight	Increase
Nervous System	Acute toxicity Permanent cognitive impairment Cognitive functions altered
Haematology	Leukocytosis
Skin & Skin appendages	Skin Rash Psoriasis Acne Alopecia
Endocrinous System	Hypothyroidism Increased Calcium plasma levels Glycemic disorders
Gastrointestinal System	Diarrhea Vomiting Constipation Metalic taste
Sexual function	Sexual dysfunction

Table 1. Main Lithium side effects.

Family history: A mother and a brother diagnosed with affective disorder who died by suicide.

Significant medical history and treatment with various specialists: Primary autoimmune hypothyroidism with an adequate replacement therapy treatment, Diabetes mellitus type 2 with current good metabolic control, hypercholesterolemia and obesity.

She was continuously treated with lithium 600 mg three times a day, with appropriate lithemia plasma levels.

Concomitant treatment: Risperidone 3 (0 - 0 - 1/2), Quetiapine 200 (0 - 0 - 1), Levothyroxine 100 (1 before breakfast), Glycazide 30 (1/2 - 1/2 - 0) and Symvastatine 40 (1 at bedtime).

In July 2006, she was admitted for severe depressive episode with suicidal ideation and Paroxetine was added to her treatment. A few days later she suffered from fever, stupor, and myoclonus. Among the studies carried out a plasma lithemia of 1.03 mEq/l was highlighted. Psychotropic treatment was discontinued and she was referred to the Internal Medicine Department. Facing the possibility of a meningo-encephalitis, laboratory tests and CT scan were performed. She was treated empirically with acyclovir, ceftriaxone, and ampicillin, which lead to the disappearance of the fever and other satisfactory outcomes. Micrococcus sp was isolated from blood cultures.

Drug	Effect	Risk*
Ansilitic - alprazolam, clonazepam	> lithemia due to > oral lithium absortion	3
Anticonvulsivants - carbamazepine/valproate - lamotrigine/gabapentin	> lithemia, neurotoxicity risk ¿?	2 3
Antidepressants - SSRI - Tricyclic - MAOIs	> lithemia, serotonin sd. Risk ¿? lithemia, > tremor ¿? lithemia, serotonin sd. Risk	2 2 2
Antipsychotics - Atypical - Classical	> lithemia ¿?	2 2
Calcium Channel Blockers - verapamil, diltiazem	possible synergism	1
Risk: (1) Interaction risk, use only if necessary, surveillance; (2) potentially hazard, surveillance; (3) safe, mild discomfort		

Table 2. Lithium interactions with other psychotropic drugs

In this context, high blood sodium levels (164 mEq/l), polyuria and polydipsia were presented. The urine had an osmolarity of 369, lower than would correspond to blood osmolarity of 353 mOsm/kg. The values of 24-hour urine cortisol were increased but with normal baseline figures for plasma cortisol. Also presenting: ADH: 2.8 pg/ml, aldosterone: 273 pg/ml, renin: 0.7 ng/ml/h. Abdominal CT is performed to assess adrenal glands and new determinations of urinary cortisol, ACTH and DHEA plasma levels, all within the normal range. It was thought in diabetes insipidus and detailed assessment was made of Nephrology and Endocrinology Services, to confirm whether it was central or nephrogenic diabetes.

The results of analytical determinations carried out are detailed as follows:

Serum chemistries:

- Blood glucose (82 mg/dl.), Urea (38 mg/dl.), Creatinine (0.66 mg/dl.), Uric acid (5.9 mg/dl.), Triglycerides (151 mg/dl.), Cholesterol (265 mg/dl.), HDL-cholesterol (53 mg/dl.), LDL-cholesterol (182 mg/dl.), Electrolytes (BUN, creatinine, Na, K, Cl all within normal range), Calcium (9.2 mg/dl.), Phosphorus (3.6 mg/dl.), transaminases (normal), blood osmolarity (296 mOsm/Kg.), urine osmolarity in 24 hours (197 mOsm/Kg.), diuresis (4500ml.),
- Nugent test: after administration of 1 mg of Dexamethasone, Cortisol levels post-dexametasone 0.63 mcg/dl.
- Thyroid function: thyroxine free (0.75 ng/dl.), TSH (3.75 mIU/l), FSH (14.1 IU/l), LH (3.72 IU/l.)

- Cortisol in urine 24 hours (65 mcg.),
  - Estradiol (29 pg/ml.),
  - Growth Hormone (baseline: 0.4 ng/ml. – After 15’ lower than 0.3 ng/ml.),
  - Prolactin (previous baseline values: 9.1 and 5.8 ng/ml.)
- The water deprivation test (WDT) is performed followed by desmopressin injection (DDAVP test). Both test results (table 3) were compatible with partial central diabetes insipidus, due to the appearance of urine concentration after a desmopressin injection as shown in the following results:
- Blood osmolarity at 08:30 h: 297 mOsm/kg.; at 11:30 h: 304 mOsm/kg.; at 14:00 h: 300 mosm/kg.
  - In urine from 07:30 to 08:30 h: 138 mOsm/Kg.; from 10:30 h to 11:30 h: 197 mOsm/kg.; from 13:30 h to 14:30 h: 154 mOsm/kg.
  - At 14:30 h (with an increased urine osmolality less than 30 mOsm/kg, blood osmolarity> 290 and urine> 300), 2 mcg desmopressin was injected subcutaneously.
  - Urine osmolality from 14:30 to 15:30 h: 300 mOsm/kg; from 15:30 to 16:30 h: 402 mOsm/kg.; from 16:30 to 17:30: 351; from 17:30 to 18:30: 269 mOsm/kg.
  - Osmolality (4 h after desmopressin injecticon): 295 mOsm/kg; ADH: 1.6 pg/ml. Study being compatible with partial central diabetes insipidus presenting partial concentration of the urine after injection of DDAVP.
- In addition, there were no changes in kidney function.

		Blood	Urine
Osmolality		296 mOsm/Kg	197 mOsm/Kg
<b>Water Deprivation Test</b>			
Osmolarity (mOsm/Kg)at	08:30 h.	297	138
	11:30 h.	304	197
	14:00 h.	300	154
<b>DDVP test</b>			
(2 mcgr. Dessmopresin injec.) Osmolarity (mOsm/Kg) at	15:30 h.		300
	16:30 h.		402
	17:30 h.		351
	18:30 h.	295	269

Table 3. Water Deprivation and Vassopresin tests results

In the WDT (Muller test), urine osmolality is not modified neither in Central Diabetes Insipidus nor in Nephrogenic Diabetes Insipidus.

In DDVP test, urine osmolality is increased > 9% in Central Diabetes Insipidus.

MRI of the brain and pituitary findings: Partially empty sella, small laminar pituitary gland covering the sella’s floor, centred pituitary stalk, no abnormalities suggesting a pathology were showed after contrast administration.

The patient medical history was completed with the following diagnosis: Diabetes insipidus. Partially empty sella. Normal pituitary function.

Desmopressin therapy was prescribed 0.1 mg every 8 hours. A few days later, the volume of urine collected in 24 hours was within acceptable range.

Since our first study, four years ago, the patient has continued to balance psychopathologically and no episodes of mental illness were presented. During this time the patient has been treated with lithium and its lithemia plasma levels have always been within therapeutic range.

Current treatment:

Lithium 400 mg (1-1-1), Clonazepan 2 mg ( $\frac{1}{2}$  -  $\frac{1}{2}$  -1), Escitalopram 15 (1-0 -0), Quetiapine 100 (0-0-1), Desmopressin 0.1 mg (1-1-1), Levothyroxine 100 (1-0-0), Simvastatin 40 mg (0-0-1), Gliclazide 30 mg ( $\frac{1}{2}$  tablet od -breakfast-).

During this period the patient attended frequent medical controls with analytical testing. In all cases the patient has remained stable. Related to central diabetes insipidus has remained asymptomatic, with mild polyuria and polydipsia and analytical testing within normal range limits. She continued with desmopressin.

However, the patient was admitted twice for a few days because of respiratory failure and moderate pulmonary hypertension. Treatment includes oxygen therapy, tiotropium 18 mcgr (one puff od), budesonide and formoterol fumarate 160/4.5 mcgr (one puff bd) and torasemide 10 mg (od at breakfast).

### 3. Discussion

Central diabetes insipidus (CDI) is a condition characterized by polyuria and polydipsia due to the presence of inadequate secretion of antidiuretic hormone (ADH) or vasopressin by the neurohypophysis or posterior pituitary; in the absence of ADH polyuria, it occurs because the patient is unable to concentrate urine.

Any cause damaging or altering the neurohypophyseal system can lead to CDI (Casanueva, 1998). Traumatic brain injury or neurosurgery are the most frequent causes, there are also primary and inherited forms (Table 4). However, it should be noted that in 25% of cases in adults the etiology remains unknown (Catalá, 2007).

In nephrogenic diabetes insipidus (NDI) lithium interferes with the action of ADH at distal tubule and collector level by reducing the sensitivity of adenylate cyclase to vasopressin and consequently interfering with the formation of intracellular cAMP. As some authors describe, 10% of patients with the chronic treatment of lithium may develop NDI (Pérez-Blanco, 2000).

Differential diagnosis of diabetes insipidus is complex and involves analytical testing (Table 5) and hypothalamic-pituitary magnetic resonance imaging (MRI), together with the consideration of history and the exclusion of other causes (hyperglycemia, hypercalcemia, etc.).

Whilst nephrogenic diabetes insipidus is considered as a possible and relatively common effect of lithium, this drug in central diabetes insipidus is rarely involved in its origin.

According to other authors, the lithium can induce a partial CDI (Pérez-Blanco, 2000). We have found few cases documented and the mechanism of action is not known. In all references found the population studies are people with lithium treatment who develop symptoms of diabetes insipidus by the simultaneous presence of other pathologies: trauma (Olson, 2004), aortic stenosis (Hensen, 1997), cavernous sinus thrombosis (Kamijo, 2003). The role of lithium in the regulation of ADH release is discussed due to its participation in osmolarity and its action on osmoreceptors as controllers of ADH release (Gold, 1983).



Genetic or familial: autosomal
Dominant (mutations of the gene encoding the AVP-neurophysin II)
Recessive
Gene mutations inactivating AVP
X Q28 linked (gene not identified)
Deletion of chromosome 7q
Wolfram syndrome (WFS gene mutation, region chromosome 4p16)
Congenital
Septo-optical dysplasia
hypogenesis pituitary
Cranial midline defects
Holoprosencephaly
Acquired
Head injury
Neurosurgery
Neoplasms
- craniopharyngioma, pituitary adenoma, pinealoma, dysgerminoma, meningioma,
- metastasis (carcinoma of the lung in male and female breast)
- hematologic: lymphoma, leukemia
- granulomas, histiocytosis, Wegener granulomatosis, sarcoidosis
- infections: chronic meningitis, tuberculosis, syphilis, viral encephalitis,
toxoplasmosis
- vascular diseases: Sheehan syndrome, internal carotid aneurysm, bypass surgery,
hypoxic encephalopathy
- autoimmune: lymphocytic infundibulohypophysitis
- inflammatory: lupus erythematosus, scleroderma
- toxins: Tetrodotoxin, snake venom
- drugs: ethanol, phenytoin, corticosteroids, alpha agonists
- idiopathic

Modified from: Catalá Bouset et al. Guía clínica del diagnóstico y tratamiento de los trastornos de la neurohipófisis. Endocrinol Nutr. 2007;54(1):23-33

Table 4. Etiology of central diabetes insipidus. Modified from Bauset M. (2007)

	Normal	Central Diabetes Insipidus	Nephrogenic Diabetes Insipidus
Plasma Osmolality (mOsm/Kg)	Normal	Increased	Increased
Urine Osmolality (mOsm/Kg)	Normal	Decreased	Decreased
Urine Osmolality (mOsm/Kg) after water deprivation	> 750	< 300	< 300
Urine Osmolality (mOsm/Kg) after AVP	> 750	> 750	< 300
Plasma AVP (pmol/l)	Normal	Decreased or Normal	Normal or Increased
AVP: Vasopressin			

Table 5. Diabetes Insipidus differential diagnoses

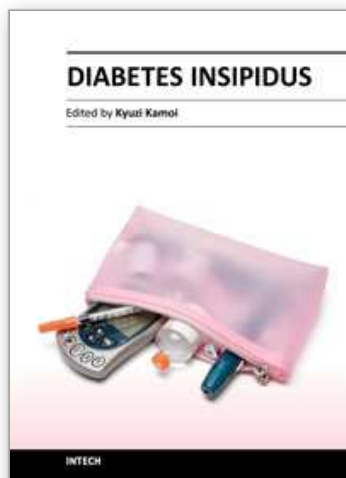
In our case it is appropriate to note the existence of viral encephalitis in the appearance of the picture, so it is worth recalling the pathological images of sella and pituitary findings. Anyway, the case illustrates the difficulties of management of some patients with lithium, and the need for a differential diagnosis in the presence of diabetes insipidus (Posner, 1996). The treatment is also completely different. In central diabetes insipidus desmopressin is the drug of choice for treatment. It is a synthetic analogue of vasopressin, which has a potent antidiuretic effect. In our case, over 4 years has been effective, and did not change the serum sodium levels (one of the risks of use) (Catalá, 2007).

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## **Diabetes Insipidus**

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The first chapter of the book reports on the management of Langerhans cell histiocytosis (LCH)-induced central diabetes insipidus and its associated endocrinological/neurological sequelae in the national survey. The next chapter addresses DI and head injuries. Next, the management of neuroendocrine instability during maintenance of potential organ donors is described. Organ transplants have gradually increased worldwide. To have maintenance of appropriate potential organs, AVP is needed. Furthermore, nephrogenic DI-the potential therapeutic drugs and analysis of membrane protein stability is the topic of the next two chapters, followed by new insights into the diagnosis and management of pregnancy-related DI. The seventh chapter reports on the problems with differential diagnosis in a case of central DI in a female patient with bipolar disorder. The lithium treatment usually resulted in nephrogenic DI. Finally, over the last years, the development of MRI imaging on the pituitary gland with the stalk and hypothalamus has advanced. The final chapter interprets imaging techniques in DI in detail.

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