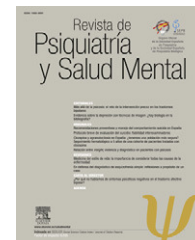




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## SCIENTIFIC LETTER

### Severe hypernatraemia associated with lithium treatment<sup>☆</sup>

#### Hipernatremia grave en relación con un tratamiento con litio

Dear Sir,

Nephrogenic diabetes insipidus (NDI) is characterised by an incapacity to concentrate urine despite normal or elevated levels of antidiuretic hormone (ADH).<sup>1</sup> It can be genetic or acquired. The main causes of acquired are electrolyte imbalances, chronic renal insufficiency and various drugs,<sup>2</sup> the most frequent of which is lithium, where NDI appears in 10–40%<sup>3</sup> of patients treated. Because of the banal symptoms (polydipsia and polyuria) of NDI, it frequently goes unnoticed until there is fluid restriction. In this case, the resulting hypernatraemia can produce a potentially lethal confusional syndrome.

We present the case of a 69-year-old man with bipolar disorder treated with lithium (currently 1200 mg/day) for the last 14 years, sent to the Emergency Department for respiratory infection and oscillations in consciousness. Significant amongst his personal antecedents were the existence of osteoarthritis and metabolic syndrome with hypertension, obesity and mixed dyslipidemia; the patient was under treatment with enalapril 20 mg/day, atorvastatin 40 mg/day, acetylsalicylic acid 100 mg/day, alprazolam 4 mg/day and non-steroidal anti-inflammatory drugs (NSAIDs) on demand. In addition, following an ischaemic stroke 2 years earlier, he presented a right hemiparesis and frequent bronchial aspiration pneumonia. From the psychiatric viewpoint, the most striking incident was a suicide attempt when he was 58. The lithium dose had been maintained stable for the last year. The family indicated that the patient followed the treatment strictly, given that they administered it to him. The biochemical analyses performed in the emergency department showed serious hypernatraemia (sodium [Na]: 161 mmol/l), with increased plasma osmolality ( $Osm_p$ ) (313 mOsm/kg), decreased urinary osmolality ( $Osm_u$ ) (300 mOsm/kg) and hyponatruia (49 mmol/l). In spite of fluid therapy, the analytic alterations and cognitive

deterioration intensified. The fluid balance showed polyuria of 4.5 l/day; the family reported that this was what it had usually been for years and that they considered it to be normal given that the patient drank over 4 l of liquid a day. They had always attributed this behaviour to his underlying pathology, so it had not been studied. Lithaemia was 0.73 mmol/l and ADH plasma levels were 2 pg/ml (both within normal value ranges). Because DI was suspected, the desmopressin (DDAVP) test was performed, after which the  $Osm_p$  increased less than 10%; the diagnosis of NDI secondary to chronic lithium treatment was established. The lithium was suspended and treatment with hydrochlorothiazide (50 mg/day) and ketorolac (50 mg/8 h) was instituted. The hydro-electrolytic imbalances and the confusional syndrome resolved 48 h later.

Patients with psychiatric pathology (mainly schizophrenia) often present fluid balance alterations.<sup>4</sup> The most frequent is primary polydipsia,<sup>5,6</sup> in which there is a faulty regulation of the mechanism for stimulating thirst, frequently intensified by various antipsychotic drugs. It usually occurs together with hyponatraemia and low ADH levels, and the polyuria normally respects sleeping. However, it should be remembered that renal toxicity from lithium is common<sup>3,7</sup> and that NDI is its most frequent complication; consequently, polyuria can also be due to an NDI secondary to lithium treatment. This is related with the treatment duration and dosage.<sup>3</sup> Furthermore, although lithium is considered a normally reversible cause of NDI, persistent symptoms can appear, up to 10 years after lithium withdrawal.<sup>8</sup> Due to the stimulation of thirst from the hyperosmolality, the existence of a severe hypernatraemia is rare, but it can appear when there are decreases in the level of consciousness in which patients become dehydrated because they cannot ask for water, as in our case. The mechanism through which lithium induces the appearance of an NDI has been discussed widely, with there being several physiopathological proposals<sup>3</sup>:

- (1) Lithium provokes a negative regulation (of up to 95%) of aquaporin 2 and even the remaining 5% is not transported appropriately to the collecting duct membrane; as a consequence, the response to ADH drops and intense water loss is produced.
- (2) There is a decrease in the density of ADH receptors.
- (3) There is a decrease in the activity of adenylate cyclase.

Treatment lies in maintaining an appropriate fluid intake, with gradual correction of hypernatraemia and a low-sodium

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diet. If it is possible, lithium treatment should be suspended. The thiazides (50–100 mg/day) present a paradoxical beneficial antidiuretic effect,<sup>9</sup> although they increase lithaemia by some 25–40%. Amiloride<sup>10</sup> (5–20 mg/day) is the drug of choice, particularly when it is necessary to continue lithium treatment (as it decreases its entry into the cells of the distal tubule) or to counteract the thiazide-induced hypokalaemia. In persistent cases, it is also useful to add NSAIDs,<sup>11</sup> especially 100–150 mg/day of indomethacin.

In conclusion, alterations in fluid balance are frequent in psychiatric patients and attributable to very diverse causes, so such alterations require appropriate assessment. In patients with an unaltered thirst mechanism, NDI secondary to lithium treatment often goes unnoticed and remains underdiagnosed. However, given that it is a frequent complication, the possible existence of an NDI should always be considered in patients that have been or are in treatment with lithium (even if they have normal lithaemia); it is necessary to be vigilant and report the appearance of symptoms (polyuria, polydipsia) and to maintain appropriate fluid balance to avoid a severe hypernatraemia that is potentially lethal.

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Alma M. Prieto Tenreiro

*Sección de Endocrinología y Nutrición, Hospital El Bierzo, Ponferrada, León, Spain*

*E-mail address: [almaprietotenreiro@hotmail.com](mailto:almaprietotenreiro@hotmail.com)*