Intern Emerg Med (2014) 9:661–664
DOI 10.1007/s11739-014-1084-5

IM - CASE RECORD

An alarming deterioration of neurological status

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Received: 28 March 2014 / Accepted: 5 May 2014 / Published online: 23 May 2014

Keywords Lithium intoxication · Central myelinolysis · Nephrogenic diabetes insipidus · Vasogenic oedema

Case presentation

Dr Frizzi and Dr Bruni: A 75-year-old woman was admitted to the emergency department for lithium intoxication manifested acutely with diffuse weakness and slurred speech. Some days earlier the patient had presented serious symptoms of diarrhoea. The patient had been under treatment with carbolithium (300 mg once daily) for several years due to major depressive syndrome. On arrival vital parameters were stable, Glasgow Coma Scale (GCS) was 15/15, there were no focal neurological deficits, and no meningeal signs (Table 1). The patient denied alcohol consumption, or recent trauma. Brain CT scan, chest and abdominal X-ray and abdominal ultrasound examinations performed on admission showed no significant alterations. An EKG showed sinus rhythm at 65 bpm, normal atrioventricular conduction, normal electrical axis, normal depolarization; and normal ventricular repolarization. Laboratory studies showed renal impairment (urea 66 mg/dl and creatinine 1.71 mg/dl), elevated sodium (152 mEq/l) and lithium (2.36 mmol/l; n.v. 0,5-1 mmol/l) levels, and a mild macrocytic normochromic anemia (Hb 10.6 g/dl). Other laboratory tests performed were in the normal ranges (Table 2).

Differential diagnosis and clinical approach

Prof. Pastorelli and Dr Bocchi: First we performed an arterial blood gas analysis (BGA) to rule out any possible underlying metabolic and respiratory disorders: BGA showed anion gap metabolic acidosis (pH 7.26, bicarbonate 16.1 mmol/l, AG 15.6 mEq/l), abnormal sodium levels (156 mEq/l) and severe hyperosmolarity (317.3 mmol/kg).

We then administered hydration with half-normal saline solution and 5 % dextrose solution in accordance with international guidelines, and opted for a period of clinical observation. Since serum levels of lithium were in initial reduction after therapy, haemodialysis was deemed unnecessary.

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Table 1 Clinical data

	1st day	2nd day	3rd day	4th day	5th day
GCS	15/15	11/15	4/15	3/15	3/15
PA (mmHg)	110/70	100/60	80/40	70/30	68/35
FC (bpm)	66 sr	70 sr	98 sr	137 a	132 a

sr sinus rhythm, *a* arrhythmic

Table 2 Laboratory tests

	1st day	2nd day	3rd day	4th day	5th day
I pH	7.26	7.42	7.4	7.43	7.41
HCO_3^- (mmol/l)	16,1	22,9	21,1	21,3	21,2
AG	15,6	11,3	10,1	11	11,7
Osm (mmol/kg)	317	320	318	310	303
Creat. (mg/dl)	1,71	1,93	2,34	3,3	–
BUN (mg/dl)	66	–	–	80	–
Sodium (mEq/l)	152	154	150	146	–
Lithium (mmol/l)	2,36	–	–	1,28	–
Hb (g/dl)	10,6	–	–	10,1	–

On the second day, the patient's neurological status worsened GCS 11/15 (E2+V4+M5): therefore, searching for an unidentified cerebral problem, we ordered an electroencephalogram (EEG) considering that a severe metabolic encephalopathy was becoming increasingly plausible. As we feared, the EEG showed diffuse paroxysmal activity with triphasic voltage consistent with metabolic encephalopathy. The same evening the patient presented a fever (auricular temperature 39°C).

Since the patient had a bladder catheter, we collected blood and urine samples for culture looking for a possible complicated urinary tract infection (UTI) in a patient with a bladder catheter. A broad spectrum antibiotic piperacillin/tazobactam iv titrated to renal function was initiated. The same day, urinalysis showed hypoconcentrated urine (a specific gravity of 1,004) and signs of bacterial growth: these findings supported a diagnosis of renal diabetes insipidus [1] and UTI.

On the third day, the patient became critical: vital parameters were worsening (arterial blood pressure was 80/40 mmHg), GCS was 4/15 (E1+V2+M1) and neurological examination showed flaccid paralysis in all limbs and the absence of reflexes. BGA showed initial sodium and osmolarity reduction while lactate increased (1.6 mmol/l).

On the fourth day, the GCS was 3/15 (E1+V1+M1) and the arterial blood pressure was 70/30 mmHg: we started norepinephrine IV infusion (0.2 μg/kg/min). BGA showed moderate improvement in oxygenation, sodium concentration (151 mEq/l) and osmolarity (310 mmol/kg). Creatinine was 3.3 mg/dl, urea was 208 mg/dl and inflammatory markers were rising (C-Reactive Protein 16.14 mg/dl; procalcitonin 36.36 ng/ml), whereas lithium levels were reduced (1.28 mmol/l) and electrolytes and osmolarity were improving (sodium 148 mEq/l and osmolarity 303.9 mmol/kg).

On the fifth day, there was an onset of atrial fibrillation with a fast ventricular response, which was treated with digoxin. At this point there were two emerging problems: (1) a septic state, which could not entirely justify the worsened neurological condition, and (2) a worsening encephalopathy, which was not consistent with the improvement in blood electrolytes, osmolarity and lithium, levels. At this point, because of the possibility of an osmotic demyelination syndrome, we decided to perform a brain MRI imaging study. The patient died about 4 h after the MRI execution because of cardio-respiratory and arrest, resuscitation attempts were unsuccessful.

Radiological diagnosis

Dr. Romano: Central pontine and extra-pontine osmotic demyelinating syndromes (CPM-EPM) can be seen on CT scan, but magnetic resonance imaging (MRI) is the imaging technique of choice, having a greater sensitivity for CPM than CT scan, and superior capacity for the demonstration of the lesions of EPM. Hyperintense lesions can be seen on T2, FLAIR, as well as hypointense lesions on T1 weighted images. The lesions are non-contrast enhancing. Diffusion weighted imaging (DWI), performed in early phases, may have the capability of detecting unidentified lesions on T2 and FLAIR. A finding of irreversible vasogenic edema in the DWI sequences is a signal alteration at b-1,000 DWI without restriction in ADC. The timing of the appearance of lesions on the MRI may be significantly delayed: a repeated MRI after 10–14 days may reveal lesions that weren't visible on earlier scans (Fig. 1). The lesions are always symmetrical and localized in the cerebellum, lateral geniculate body and less frequently in the claustrum, midbrain, internal medullary lamella, mammillary body, and medulla oblongata.

In our case the MRI, on the second day, showed in FLAIR, T2 and DWI b-1,000 sequences a symmetrical lesion in midbrain at the level of the inferior colliculus, without contrast enhancement in post-Gadolinium IV administration [2, 3].

General information on lithium use and side effects

Prof Gonnelli and Dr Bocchi: Lithium salts were introduced in 1949 for the treatment of mania, but the

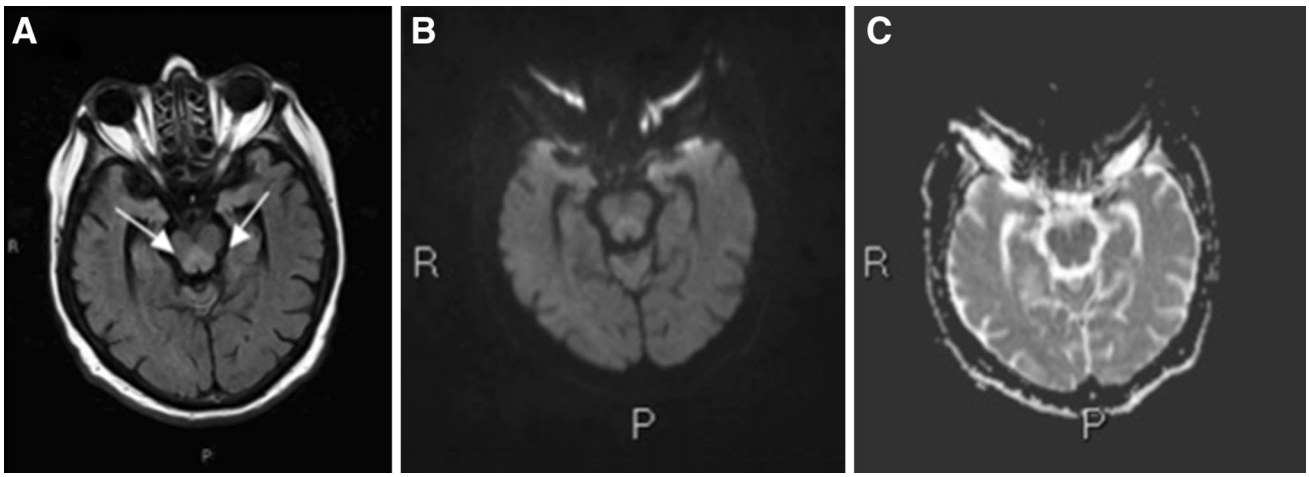

Fig. 1 1.5 T MRI of the brain shows a symmetric subtle high-intensity signal alteration on fluid attenuated inversion-recovery images (**a**) and diffusion-weighted (**b**: 1,000 s/mm^2) images (**b**) of the mid-posterior portion of the midbrain (*arrows*), without restricted diffusion at apparent diffusion coefficient maps (**c**). These findings are consistent with vasogenic oedema, and thus with myelinolysis

exact pharmacodynamics mechanism of Li^+ as a mood stabilizer remains unclear. Li^+ competes with similar weight ions such as sodium, potassium, calcium and magnesium in various intra and extracellular molecular reactions, and this explains the diversity of its effects [4]. In cells Li^+ tends to accumulate in place of potassium altering the normal potassium gradient, and causing malfunction of the sodium–potassium pump resulting in intracellular accumulation of sodium. In the brain, lithium slows down calcium-mediated norepinephrine and dopamine release, and also modifies adenylate ciclase and phospholipase-C mediated responses. Despite recent advances in pharmaceutical treatment of psychiatric disorders, lithium salts remain frequently used particularly for the treatments of bipolar disorders and major depression. Use of lithium is limited by its narrow therapeutic index. The therapeutic concentration that is considered safe ranges from 0.5 to 1.1 mEq/l; however, serum lithium concentrations do not reflect tissue levels, and the correlation between lithium levels and toxicity is poor. Therefore, long-term use of lithium presents several side effects, such as mild hypercalcemia, thyroid disorders, hypotension and dysrhythmias. Moreover, up to 20–30 % of long-term treated patients may develop nephrogenic diabetes insipidus (NDI.) Lithium is the most common cause of acquired NDI, which is usually reversible after the withdrawal of the drug. Literature suggests that lithium inhibits the ADH induced expression of the aquaporins in the renal collecting ducts, mainly aquaporin 2, by mechanisms still not fully understood. Sometiimes in lithium treated patients, chronic renal failure is present, and also, though rarely, acute renal failure may occur.

Lithium and myelinolysis: review of literature

Dr Borselli and Dr Sartini: Central pontine and extrapontine osmotic demyelinating syndromes (CPM, EPM) are very uncommon disorders characterized by non-inflammatory lesions involving the pons, and sometimes spreading to other areas. In CPM, the lesions are confined to the pons, while in EPM are located to the basal ganglia, cerebrum and cerebellum. The pathogenesis of this disease is complex, and involves the inability of brain cells to respond to rapid changes in osmolality of the interstitial (extracellular) compartment of the brain, leading to dehydration of energy-depleted cells with subsequent axonal damage that occurs in characteristic areas. Overly rapid correction of hyponatremia has been considered as the main cause of osmotic demyelination syndromes, particularly in patients with conditions leading to nutritional or electrolyte stress.

Khan et al. [5] made the first mention of the correlation between lithium intoxication and central pontine myelinolysis. Fabisiak et al. [6] report a case in which a psychiatric patient in treatment with lithium, manifested blindness due to overdose of the drug. In this case, central pontine myelinolysis with involvement of the lateral geniculate nucleus was demonstrated to be the aetiology. In the same issue of the journal, a contribution by Swartz et al. [7] is published, which mentions the same case, and states that the central pontine myelinolysis may be a rare but possible complication of lithium intoxication. Bejot et al. [8] report a case of a young pregnant woman who developed pontine and extrapontine myelinolysis due to lithium intoxication. In this case, the pathogenic mechanism reported is attributed to the rapid correction

of hyponatremia in consequence of renal diabetes insipidus induced by lithium.

Discussion

Prof. Pastorelli and Dr Frizzi: the final diagnosis of the case here reported was extra-pontine myelinolysis in a patient with lithium intoxication and NDI. In this case report, the *primum movens* was likely an accidental overdose of lithium as a consequence of dehydration due to an episode of severe diarrhea. As described in the literature, lithium intoxication may cause NDI, and this may explain the low urinary specific gravity, and the worsening renal function [1].

This sequence of events may have caused rapid increase of sodium levels and plasmatic osmolarity (probably following a pre-existing diarrhoea induced hyponatremia); Moreover, because of the sodium–potassium pump alteration caused by lithium overdose, the true value of intracellular sodium concentration is greater than in plasma. Neurological symptoms were likely caused by hyperosmolar impairment of cortico-bulbar tracts, and subsequent flaccid paresis due to impairment of cortico-spinal tracts [9, 10]. The extra-pontine myelinolysis could be an explanation for the severe alteration of neurological status, which progressed despite a progressive reduction of lithium, sodium and osmolarity alteration. The fever pathogenesis may have been from a central origin combined with the urinary tract infection.

This clinical case should make us reflect on the potential dangers of lithium, often too readily prescribed by non-expert physicians to elderly, and often poorly compliant, patients. There also needs to be very close monitoring of plasma lithium levels, in addition to paying attention to clinical signs, such as a persistent polyuria or hyperosmolarity, because these could be important early warning signs. It is therefore useful to reiterate that, in case of lithium intoxication with altered neurological status despite improvement blood tests, it is necessary to consider pontine or extra-pontine myelinolysis as a rare but possible complication.

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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