

Posterior reversible encephalopathy syndrome (PRES) in a patient with long-term lithium intake and non-toxic serum lithium levels

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Summary

We report a case of posterior reversible encephalopathy syndrome (PRES) in which lithium may have played a role in its development and the maintenance.

A patient with stable schizoaffective disorder under long-term lithium therapy was admitted to a general hospital after suffering an accidental fall at her home. For 2 weeks prior to admission, she had been treated for minor infections. Two days after admission, she developed an encephalopathy, which was diagnosed as PRES radiographically. Lithium was identified as a possible contributor to the development of PRES and consequently discontinued, even though the serum lithium levels never exceeded the predefined norm. After discontinuation of lithium, the patient recovered under further treatment.

The course of the case and documentation in current literature suggest that lithium may be seen as a risk factor in the development of PRES.

Keywords: PRES, RPLS, lithium, encephalopathy, conciliar and liaison psychiatry, psychosomatics, geriatric psychiatry, interdisciplinary

Introduction

The posterior reversible encephalopathy syndrome (PRES), also commonly referred to as reversible posterior leukoencephalopathy syndrome (RPLS), is a syndrome affecting various organs [1]. Clinical findings commonly include a wide number of symptoms, ranging from fatigue, headache and nausea to changes in consciousness and dysarthria, ataxia and seizures [2]. Since the definition of PRES by Hinchey et al. in 1996 it has been well established, with numerous case reports and studies confirming its validity. It is referred to by some researchers as possibly one of the most common causes of encephalopathy seen in intensive care units (ICUs) today [3]. To date, no diagnostic criteria for the clinical detection of PRES have been established [4, 5]. It is commonly diagnosed by radiographic findings via magnetic resonance imaging (MRI) when several of the above-mentioned symptoms point to PRES.

Since its description in the mid-1990s, PRES has been identified as a consequence of many factors, mainly chemotherapy and immunosuppressive therapy, but also eclampsia and malignant hypertension. Less common aetiologies include uraemia, septic infection, hypomagnesaemia and drugs such as amphetamines, clonidine and kratom [1, 2, 6].

The leading hypothesis for the development of PRES is a nonspecific rise in blood pressure, leading to a loss of the auto-regulatory capabilities of the central nervous system blood vessels. This leads to a breakdown of the blood brain barrier, which further induces capillary leakage and interstitial oedema [7]. However, markedly elevated blood pressure does not seem to be present in roughly 25% of the cases of the syndrome [1, 8, 9].

Currently, therapy takes place in an ICU and consists of strict control of the mean blood pressure, prophylaxis for epileptic seizures and pharmacological reduction of the oedema. In addition, the possible cause of PRES is treated and contributing factors, if identifiable, are eliminated [5].

Case description

A chronological overview of the development of symptoms and diagnostic procedures beginning with the admission to hospital is summarised in table 1.

We report a female patient, age 70, who was admitted to the Stadtspital Waid Zürich in 2019. She had been in good physical and mental health since at least 2016. Pre-existing conditions included type 2 diabetes and schizoaffective disorder, diagnosed first in 1995. The patient's medication had been established for a long time and consisted of metformin, lithium and flupentixol. In addition she was prescribed cholecalciferol. The patient reported a discrete tremor of both hands since she started taking lithium.

Two weeks prior to admission, the patient suffered from self-limiting diarrhoea. Two days prior to the admission, she visited her family doctor because of an uncomplicated lower urinary tract infection. On that occasion she complained of fatigue, loss of appetite and an increase in the tremor in her hands. The family doctor's physical exami-

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nation report states that her body temperature was 38.5°C, otherwise there were no notable findings. The urinary tract infection was treated with sulfamethoxazole and trimethoprim, along with paracetamol. Serum lithium levels were not measured.

On the day prior to the admission, the patient fell at home and was not able to get up because of fatigue. She had lain on the floor for 8 hours when her partner found her. On admission to the emergency room of the Stadtsptal Waid, the patient was dehydrated, exhausted, febrile (38.5°C) and presented a discrete tremor of the upper extremities which was more pronounced in her left arm. Otherwise she was deemed to be in good health and showed no disturbances in thought or orientation. Blood pressure was 112/56 mm Hg.

Blood samples showed hypernatraemia (152 mmol/l) due to dehydration, moderately raised creatine kinase (238 U/l) and leucocytosis with a slightly elevated C-reactive protein. The ECG showed T-wave depression, cardiac ischaemia was ruled out by a non-elevated troponin. Microbiological cultures showed no growth. A head computed tomography (CT) scan showed cortical atrophy in the frontal lobes, otherwise findings were normal. The serum lithium level was not elevated (0.55 mmol/l).

Two days after admission the patient suddenly experienced confusion, dysarthria and ataxia. There was no focal paresis and/or meningism. She was disoriented with regard to time and place, and showed inhibited thought processes

and increased agitation. Her language was reduced to one-word sentences and difficult to understand. With respect to psychomotility, fumbling, elevated muscle tone, tremor and postural instability were observed, and the patient was unable to walk, stand or sit in her hospital bed. The patient was afebrile at that time, blood pressure was slightly/intermediately elevated (144/70 mm Hg; 167/77 mmHg). Flupentixol was discontinued and quetiapine to control the agitation was administered.

A follow up CT scan was no different from the one on admission. In a psychiatric examination, encephalopathy, with delirium a possible comorbidity, was ruled as the most likely cause for the patient's condition. The serum lithium level was 0.68 mmol/l. Electroencephalography (EEG) was normal. An examination of cerebrospinal fluid (CSF) showed an increase in cell count, especially lymphocytes, without evidence of bacteria or viruses. A follow up CSF sample showed a reduced cell count, a breakdown of the blood-brain barrier and intrathecal synthesis of IgG and IgM. An extensive serological examination, including bacteriology and virology, of the CSF did not reveal further findings. MRI detected extensive, symmetrical oedema of the brain, mostly posterior and particularly involving parietooccipital and thalamic regions and the cerebellum. This led to the diagnosis of PRES (fig. 1).

After a neurological examination it was hypothesised that the PRES occurred because of neuroinflammation, but a direct infection of the central nervous system was ruled out

Table 1: Chronological overview of patient's condition, diagnostic tests and results.

Day	Diagnostic tests/ location	Result
1–2	Initial examination emergency room: ECG, blood-sample, head CT, urine and blood culture (2×2). Patient febrile, dehydrated, but oriented and adequate in speech. BP 112/56 mm Hg Transfer to regular ward	– T wave depressions without previously known ECG – Leucocytosis, slightly elevated CRP, high sensitivity troponin-I normal, slight hypernatraemia (152 mmol/l), slight elevated creatine kinase (238 U/l), otherwise normal. – Frontal brain atrophy, no bleeding, no fracture, no tumour. – No growth on cultures (antibiotic treatment present at time of sampling)
3–10	Patient non-febrile, but newly disoriented, with dysarthria, ataxia, no meningism. BP elevated, but not exceeding 160/90 mm Hg follow-up head CT, psychiatric exam, follow-up blood-culture, EEG, CSF sample, head MRI (agitated)	– In head CT scan: no ischaemia, no bleeding, no fracture. additional finding: struma nodosa – Suspicion of encephalopathy in psychiatric exam., possible comorbidity: delirium – No growth on follow-up cultures – EEG normal – Pleocytosis in CSF, mostly lymphocytes. Protein 0.48 g/l, PCR tests for varicella zoster virus, herpes simplex virus, human betaherpesvirus 5, tick-borne encephalitis negative – Head MRI could not be completed
11	Patient confused, agitated, disoriented, with postural instability, ataxia, dysarthria. Intermittent BP peaks up to 188/118 mm Hg Head MRI (sedated), neurological exam	– Neuroradiographic findings specific for PRES diagnosis of PRES in neurological exam, possibly due to inflammation or medication. Infection of the CNS later ruled out by extensive bacteriological and virological testing
12–19	Transfer to ICU, intubation, sedation, treatment for PRES Follow up CSF-sample, blood sampling BP strictly controlled under 160/100 mm Hg	– In CSF: normal cell count at 14/ µl. PCR on human betaherpesvirus 5, Epstein-Barr virus, herpes simplex virus 1+2, varicella zoster virus and cultures negative. PCR on bacteria negative. Metagenomic-virus-sequencing negative. Borrelia, tick-borne encephalitis negative, <i>Treponema pallidum</i> , cryptococcus negative. – Medium-grade dysfunction of blood-brain-barrier, intrathecal production of IgG/IgM. Protein 0.61 g/l – Auto-antibodies against CNS, ganglioside, myelin-associated-glycoprotein, voltage-gated potassium channel, n-methyl-d-aspartic-acid receptors: negative – Blood sampling: human immunodeficiency virus and anti-nuclear/anti-cytoplasmic/anti-thyroid peroxidase antibodies: negative
20	Encephalopathy responding to treatment, still agitated, less confused. Extubation and transfer to regular ward. BP not exceeding 140/90 mm Hg Follow up head MRI	– Decreased oedema in head MRI. Radiographic findings still specific for PRES
21–26	Blood sampling. Treatment is continued on regular ward	– Aquaporin-4 and myelin oligodendrocyte glycoprotein antibodies: negative
27–30	Patient adequate and oriented again, still slight ataxia, dysarthria, postural instability. Follow up head MRI Transfer to rehabilitation facility on day 30	– Posterior oedema clearly reduced. No new findings in cMRI

BP = blood pressure; CNS = central nervous system; CRP = C-reactive protein; CSF = cerebrospinal fluid; CT = computed tomography; EEG = electroencephalogram; MRI = magnetic resonance imaging; PCR = polymerase chain reaction; PRES = posterior reversible encephalopathy syndrome

by the negative CSF test results. From the current literature, lithium was identified as a possible cause. The lithium therapy was therefore terminated. At this stage, elevated blood pressure values with intermittent peaks as high as 188/118 mm Hg were recorded.

Treatment continued in the ICU, where the patient was intubated and sedated for 7 days. She received levetiracetam against possible seizures, prednisone for the central nervous system oedema, urapidil for control of the elevated blood pressure; quetiapine, oxazepam and biperiden were used for symptom control of the encephalopathic neuropsychiatric state of agitation. In addition, the patient received aciclovir and ceftriaxone for a total of 6 days until the results of the extensive virological and bacteriological examination showed this medication to be unnecessary.

Over the course of treatment, levetiracetam was replaced by lamotrigine, both for seizure control and as a long-term alternative to the discontinued lithium. Quetiapine, biperiden and oxazepam were reduced with the goal of discontinuation in the near future. After improvement, the patient was transferred to a regular ward, where treatment continued. Blood pressure during this time never exceeded 140/90 mm Hg.

Two follow up MRIs further confirmed the diagnosis of PRES over time and also showed a reduction of the oedema (fig. 2). The patient's confusion and agitation declined in parallel with the reduced oedema, as did her dysarthria and ataxia.

After the patient's condition improved, she was moved to a rehabilitation facility for further neurorehabilitation. Dur-

Figure 1: Cranial MRI scan (day 11) showing oedema of the occipital part of the central nervous system, in both sides of the thalamic region and partially in the cerebellum. Note the additional finding of bifrontal and bitemporo-parietal atrophy of mostly grey matter. (Image courtesy of Dr Nikola Nikolic, Department of Radiology, Stadtspital Waid und Triemli Zürich.)

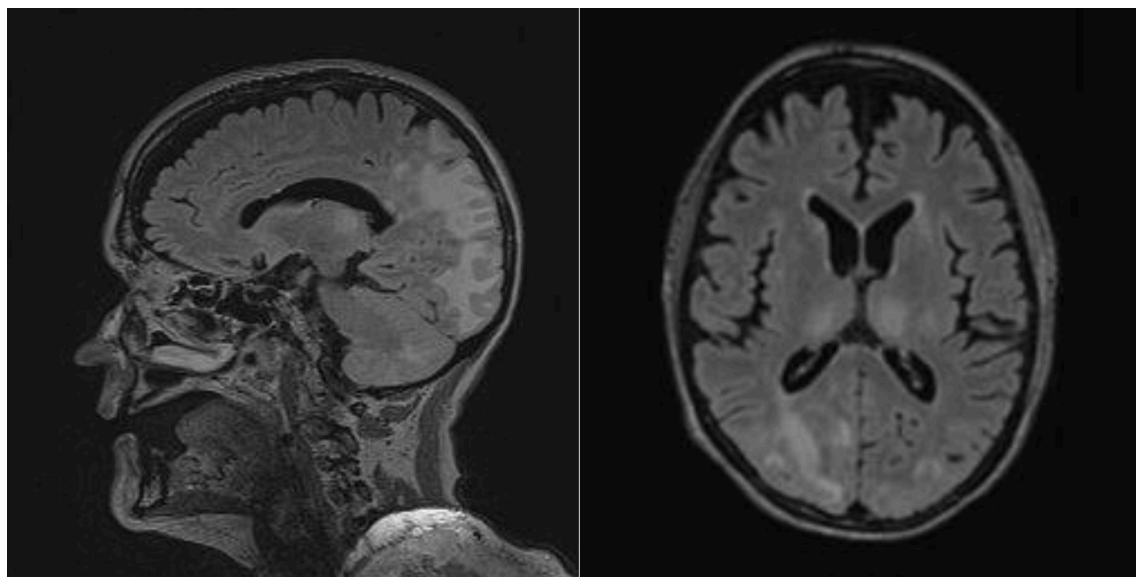
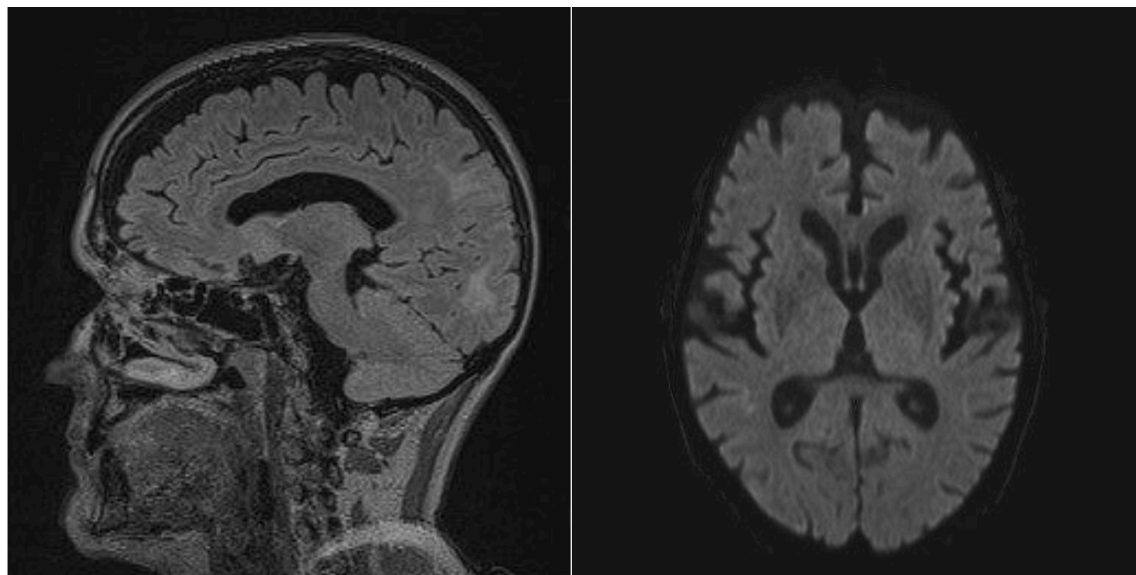


Figure 2: Cranial MRI scan (day 27) showing the reduced oedema, with a slight residue in the occipital part of the central nervous system. Note the additional finding of bifrontal and bitemporo-parietal atrophy of mostly grey matter. (Image courtesy of Dr Nikola Nikolic, Department of Radiology, Stadtspital Waid und Triemli Zürich.)



ing her stay at the hospital, CSF pressure was not measured.

Discussion

It is most likely that a multitude of factors contributed to the development of PRES in our patient. Nevertheless, the role of lithium – and flupentixol for that matter – in the occurrence of PRES is mostly unknown.

Two reports, consisting of three cases in total, state a possible role of lithium in the origin of PRES. Two cases of PRES developed following lithium intoxication [10]. One case of PRES developed after lithium was discontinued because of a lithium intoxication; the resulting PRES decreased when antipsychotics were administered again [11]. No report showing a connection with flupentixol exists as of July 2020 [12]. In the case presented above, there is great uncertainty about the aetiopathogenesis of PRES.

Initially, her mean blood pressure was normal and her long-term medication had not been changed for a long time. However, prior to admission to the hospital, the patient suffered from diarrhoea and a lower urinary tract infection with a febrile temperatures of 38.5°C, which was treated with sulfamethoxazole and trimethoprim. Due to the infection, but also to the stress-levels caused by lying on the floor in her home for 8 hours, elevated blood pressure levels are plausible. The elevated blood pressure could have been counteracted by the dehydration that followed, thus remaining undetected at the time of admission. Serum lithium levels were possibly initially increased owing to the diarrhoea. It is also possible that PRES was already present shortly before admission, shown by the fatigue, which led to the patient's accidental fall and the subsequent inability to raise herself up again.

The current leading hypothesis for the pathogenesis of PRES is a collapse of the blood-brain barrier. It has been shown in a number of scientific studies that lithium leads to a shrinking of endothelial layers in blood vessels, both due to exceeding concentration [13] and long-lasting administration [14], thus weakening the blood-brain-barrier. Loens et al. discuss this possibility in their case report cited above [11]. In addition, lithium may alter vascular endothelial growth factor expression [15], thus predisposing to a heightened risk of capillary leakage, which was hypothesised to be a contributor to PRES in the report of two cases by Fitzgerald et al. [10].

The patient in our case had taken lithium for a long time before developing PRES, and serum lithium levels never exceeded the norm when tested.

It has been shown that systemic inflammation leads to a further dysfunction of the blood-brain barrier via production of cytokines [16]. A lower urinary tract infection, as seen in our patient, could cause such a systemic inflammation. This could have led to a further uptake of lithium across the blood-brain barrier, thus elevating CNS concentrations of lithium relative to the measured serum concentrations, which stayed within predetermined boundaries. For the lower urinary tract infection, the patient was treated with trimethoprim prior to admission. There have been cases of symptoms of lithium intoxication when lithium and trimethoprim were administered together, even without elevated serum lithium levels [17].

Lithium can also produce symptoms of intoxication in patients with normal serum-levels [18], especially with fever and/or inflammation present and with old age as an independent risk factor [19].

All these factors coming together may have pushed the blood-brain barrier over the threshold, thus leading to the development of PRES in our patient, even if blood pressure was not elevated initially as one might have expected. The patient's age, dehydration, infection, inflammation and pre-existing medication, with the addition of trimethoprim, possibly contributed to the development of the encephalopathy, maybe influencing each other over the course of its pathogenesis.

Conclusion

Lithium, especially when prescribed over a long time, may lead to a situation that makes the occurrence of PRES under certain circumstances more likely. In our discussion, we suggest that lithium may be seen as a risk factor in the development of PRES.

To what extent lithium is able to originate PRES on its own (for example, when highly elevated), and by which pathological mechanism, remains unclear. Given the current knowledge, lithium as a single cause for PRES seems unlikely. There is little evidence to support this, with only two case reports in the literature, which deal with the possible involvement of lithium in PRES as a risk factor. We thought it necessary to add our own clinical findings to the ones cited above, in the hope of contributing to a further understanding of PRES and its multitude of possible pathogenetic pathways, and to highlight lithium as a possible risk factor in the development of PRES.

Acknowledgements

Special thanks to Dr Daniel Schröpfer, Chefarzt Medizinisch-Soziale Ambulatorien der Stadt Zürich for formal support, Dr Beate Sidau for language consultation and Dr Nikola Nikolic, Leitender Arzt Radiology Department Stadtspital Waid und Triemli Zürich for the MRI scan images.

Disclosure statement

No financial support and no other potential conflict of interest relevant to this article was reported.

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