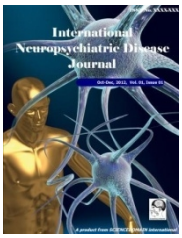

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Sub-acute Posterior Reversible Encephalopathy Associated with Extrapyramidal Signs Induced by Primary Hyperparathyroidism: A Case Report and a Revision of Literature

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Authors' contributions

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Case Study

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ABSTRACT

Aims: We present the case of a subacute psycho-motor deterioration in the context of a hypercalcemic state due to primary hyperparathyroidism inducing a posterior reversible encephalopathy.
Presentation of Case: a 78 year-old man, affected by parkinsonism, developed a subacute psycho-motor deterioration in the course of a month and presented to our attention with generalized seizures. Biochemical analysis revealed hypercalcemia due to primary hyperparathyroidism. After the surgical removal of a hyperfunctioning parathyroid gland, we assisted to a dramatic improvement. Alongside with characteristic MRI findings, the picture was compatible with a posterior reversible encephalopathy syndrome (PRES).
Discussion: To date, this is the third reported case of PRES caused by primary hyperparathyroidism. Our case appears peculiar because of the subacute onset of the syndrome, and of the accompanying progressive worsening of a pre-existing extrapyramidal syndrome. Also, the specific setting of radiologic findings and hormonal anomalies points to a prominent role of endothelial dysfunction in the still debated pathogenesis of PRES.

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Conclusion: Our case presents a rare combination of hyperparathyroidism, PRES and parkinsonism. We propose that the Blood-Brain barrier plays a central role in this setting.

Keywords: Posterior reversible encephalopathy syndrome; hyperparathyroidism; primary; hypercalcemia; parkinsonian disorders; blood-brain barrier.

1. INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is a clinic-radiological entity, which has been described since the mid-90's [1]. It is a known cause of acute alteration of consciousness frequently accompanied by headache, seizures and focal neurological signs, such as visual field defects. This syndrome has been described in a wide variety of settings, mostly solid organ transplantation, hypertensive crisis, immunosuppressive drugs administration. Nevertheless, the physiopathologic mechanisms of this condition are still debated. On the other hand, hypercalcemia is a common metabolic disturbance, often due to primary hyperparathyroidism, that is an excessive secretion of parathormone by a hyperfunctioning parathyroid gland. Hypercalcemia can induce gastrointestinal symptoms (nausea, anorexia, constipation, or pancreatitis), bone pain or pathologic fractures, electrocardiographic changes and neuropsychiatric symptoms (ranging from trouble concentrating to coma) [2]. Here we report a case of PRES caused by primary hyperparathyroidism.

2. PRESENTATION OF CASE

A 78 year-old man was brought to our ED for 2 sequential tonic-clonic generalized seizures. He was previously diagnosed with an extrapyramidal syndrome, hypertension and osteoporosis with multiple lumbar vertebral fractures. He had no history of neoplasia, autoimmune disorder, transplantation, immunosuppressive or antiblastic therapy. His home medication comprised L-DOPA + Benserazide, Tamsulosin, Esomeprazole, Domperidone, unchanged for more than 6 months. He had never suffered from seizures before. In the previous month, he had appeared slowed and confused, with fluctuating alterations of alertness, and worsening of his extrapyramidal syndrome.

At presentation he was drowsy, he opened his eyes in response to loud vocal stimuli, emitted incomprehensible sounds, moved spontaneously his right limbs. He showed signs of right hemispheric dysfunction (absence of spontaneous movements and brisk reflexes in the left limbs, asymmetry of the face, and left Babinski's sign). His temperature was 37.4 °C, blood pressure was 210/140 mmHg, cardiac frequency 114. CT imaging was negative for acute events. He was found to have a severe hypercalcemia (total calcium 14.3 mg/dl, normal albumin), and 15210 WBC/mm3. The remaining of his blood tests was unremarkable. The hypertension was successfully treated with nitroglycerin in the ED; during the entire following hospital stay, blood pressure levels were in normal range, without any need for treatment.

To correct the calcium imbalance, we put him on forced diuresis with continuous intravenous saline infusion (at 100 ml/h) and furosemide (10 mg every 500 ml of saline). In adjunction, we administered parenteral clodronic acid, and obtained a progressive reduction of calcium concentrations, stabilizing at around 12 mg/dl, with a parallel although modest improvement regarding the patient's responsiveness and alertness.

An EEG performed at the admission, within 24 hours of seizure onset, showed a background activity characterized by arrhythmic theta-delta slowing, more pronounced on left temporal leads. Epileptic activity was also present, consisting of frontal bilateral sharp-slow waves. Total calcium at the time was 13.7 mg/dl.

A brain MRI obtained 2 days after admission and initiation of medical therapy showed, alongside a condition of chronic vascular encephalopathy with deep hemispheric gliotic scars, diffuse symmetrical subcortical lesions, mainly posterior in distribution (although some also appeared in the frontal lobes and in the cerebellar hemispheres). These lesions were hyperintense in T2w images, and showed no alterations in DWI.

In the meantime we found he had PTH levels of 256 pg/ml (upper reference value: 65), and thus diagnosed him as having a primary hyperparathyroidism. A Sestamibi parathyroid scintigraphy demonstrated a focal hypercaptation near the lower left lobe of the thyroid gland. On the basis of these findings the patient underwent a surgical resection of an enlarged parathyroid gland located in the left neck. Soon after the resection the PTH levels dropped to 11 pg/ml and total Calcium concentration stabilized at around 8.5 mg/dl within 3 days.

In a repeated brain MRI executed 7 days after the surgery and the correction of hypercalcemia the subcortical and cerebellar lesions had disappeared (figure 1), thus confirming the suspect of a reversible encephalopathy.

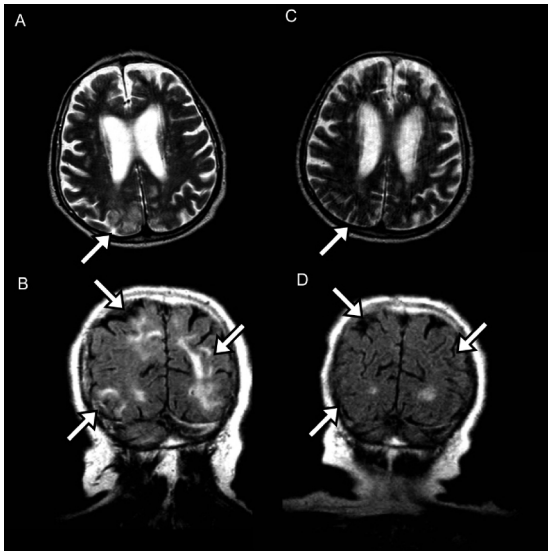

Fig. 1. MRI images after 2 days of medical therapy of hypercalcemia (A, T2 axial section; B, FLAIR coronal section) and 7 days after parathyroidectomy (C, T2 axial section; D, FLAIR coronal section): white matter hyperintense cerebral and cerebellar lesions have disappeared soon after surgery.

After the surgery the patient showed a dramatic improvement regarding the alertness, spatiotemporal orientation and motility. He was then sent to another structure for a cycle of physical therapy. Two months after the operation, the patient had regained full motor

functionality, cognitive functions, and autonomy in the daily life activities. Also extrapyramidal signs and symptoms described since about two years were largely reduced with a quite complete removal of the L-DOPA intake.

3. DISCUSSION

The case presented is consistent with the diagnosis of Posterior Reversible Encephalopathy Syndrome (PRES). This condition has been well described since the mid-90s as a clinically recognizable syndrome associated with characteristic neuroimaging findings: patients present with headache, decreased alertness, altered mental functioning, seizures, visual changes, motor signs. Symptoms develop sub-acutely or acutely, often with seizures at onset. Imaging studies (both CT and MRI) show edema in the brain white matter, mostly posterior in the parieto-occipital regions, although additional areas can be involved, such as the brain stem and cerebellum.

PRES has been more frequently associated with eclampsia, cyclosporine treatment, solid organ or bone marrow transplantation, and severe hypertension. However, a wide variety of conditions have been reported as causes of PRES (Table 1) [3].

In our case, PRES was attributed to hypercalcemia due to primary hyperparathyroidism, as confirmed by the resolution of the clinical and radiological abnormalities subsequently to the surgical removal of a hyperfunctioning parathyroid gland and the normalization of calcemia. To our knowledge, eight cases of hypercalcemia-related PRES have been reported in literature [4-10], only 2 of which were due to parathyroid adenoma (Table 2) [8,9].

Our patient presented also with a two-year history of parkinsonism deteriorating in the few months before admission, but greatly ameliorated after hyperparathyroidism correction. This close temporal correlation suggests a possible negative effect of the leukoencephalopathy or of the metabolic disturbance on the extrapyramidal motor system. While parkinsonism has not been reported in the setting of PRES, few records have described the association between primary hyperparathyroidism and parkinsonism with reversible features after adenoma removal [11,12].

As for the pathogenesis of PRES, two main theories have been proposed, one focusing on severe hypertension overcoming the autoregulation of cerebral blood vessels and inducing “overflow” edema, and the other calling for altered blood-brain barrier functioning caused by a combination of endothelial dysfunction, hypoperfusion, vasoconstriction [13]. In our patient, blood pressure at presentation was at the upper limit of autoregulation. However, in the next days, in spite of normal blood pressure values, no significant clinical changes were observed until the correction of hypercalcemia. We did not perform angiographic studies of the intracranial circulation, but considering the MRI findings suggestive of vasogenic edema, we could hypothesize a dysfunction of the blood-brain barrier rather than in the vasomotility. In fact, it has been shown that both hypercalcemia and elevated PTH levels can act on endothelium inducing the production of substances, such as VEGF and NO, capable of altering vascular permeability [14,15,16]. Interestingly, Rite et al. [17] have shown that VEGF can induce degeneration of nigral dopaminergic neurons through disruption of the Blood-Brain barrier.

Table 1. Conditions at risk for PRES

Toxemia of pregnancy (preeclampsia/ eclampsia)
Post-transplantation:
Allogenic Bone Marrow Transplantation
Solid Organ Transplantation
Immune suppression:
Cyclosporine
Tacrolimus
Infection/sepsis/shock:
Systemic inflammatory response syndrome
Multiorgan dysfunction syndrome
Autoimmune diseases:
Systemic lupus erythematosus
Systemic sclerosis
Wegener's disease
Polyarteritis nodosa
Status-post cancer chemotherapy:
Combination high-dose chemotherapy
Reported miscellaneous drugs:
Cytarabine
Cisplatin
Gemcitabine
Tiazofurin
Bevacizumab
Miscellaneous reported associations:
Hypomagnesemia
Hypercalcemia
Hypocholesterolemia
Intravenous immunoglobulin
Guillain-Barré syndrome
Ephedra overdose
Dislysis/erythropoietin
Triple-H therapy
Tumor lysis syndrome
Hydrogen peroxide
Dimethyl sulfoxide stem cells

Table 2. Cases of Hypercalcemia-related PRES in literature

Case	Cause	MRI	Angiographic studies	Therapies
Kaplan 1998	Myeloma + calcium containing antacids	Hyper T2	SPECT: hypoperfusion	Pamidronate, phenytoin
Kastrup 2002 case 1	Oral calcium supplementation for postoperative hypoparathyroidism	Hyper FLAIR, DWI	MRA: normal	Fluid, furosemide
Kastrup 2002 case 2	Plasmocytoma	Hyper T2, FLAIR, low ADC	Angiography: normal	Fluid, diuretics

Chen 2004	Breast cancer, high PTH	Hyper T2, FLAIR, DWI	MRA: focal disappearance right posterior cerebral artery. Angiography: segmental narrowing and beading of right posterior cerebral artery	Fluid, Magnesium, diazepam, phenytoin, valproic acid
Choudhary 2005	Mycobacterium avium-granulomatous disease	Hyper T2	MRA: normal	Steroids
Kim 2005	Parathyroid adenoma	Hyper FLAIR, DWI, normal ADC	MRA: normal	Fluid, calcitonin, pamidronate
Au 2012	Parathyroid adenoma	Hyper T2	CT angiography: prominence in size and number of vessels to the right cerebral hemisphere	Furosemide, calcitonin, haemodialysis, cinacalcet, pamidronate, phenytoin, levetiracetam, midazolam, propofol
Ahmed 2012	Oral calcium and alfacalcidiol for postoperative hypoparathyroidism	Hyper T2		Fluid, biphosphonate

4. CONCLUSION

Our patient had been affected by a parkinsonian syndrome for about two years before his admission to the hospital, but in the last month, his extrapyramidal symptoms had worsened, along with minor neuropsychological complaints. This latter period of time likely represents a subacute onset of PRES, in which the leukoencephalopathy caused a worsening in the extrapyramidal motor system functioning. To our knowledge, this is a unique presentation of PRES.

As the pathophysiology of PRES is still unclear, we hope that this case can give a contribution to the understanding of this syndrome. The leukoencephalopathy in our patient was probably caused by an action of parathormone or calcium on the endothelium and the Blood-Brain barrier. Moreover, it is not remote that such an action might contribute to the pathogenesis of other neurological disorders.

CONSENT

All authors declare that written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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