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Case Series

Posterior Reversible Encephalopathy Syndrome Due to Hypocalcemia: A Very Rare Clinical Association

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Abstract

Introduction: Posterior reversible encephalopathy syndrome (PRES) is a clinicoradiographic neurovascular disorder. Recognized risk factors for PRES include hypertension, renal disease, autoimmune disorders, preeclampsia, sepsis, and exposure to cytotoxic or immunosuppressive therapies. Hypomagnesemia and hypercalcemia, are very rarely associated with PRES. Here, we report three patients with severe hypocalcemia that presented with PRES syndrome that improved with calcium replacement.

Case Summary: In this prospective case series, we describe the clinical, biochemical, and radiological characteristics of PRES associated with hypocalcemia in the absence of classical risk factors. Three patients presented with PRES with significant hypocalcemia secondary to vitamin D deficiency. All cases demonstrated favorable clinical outcomes following standard management of PRES along with correction of the underlying hypocalcemia.

Conclusion: The study identifies hypocalcemia as a potential cause for PRES. It further expands existing literature of hypocalcemia as a rare contributory risk factor.

Key Message: Hypocalcemia is a novel and important, treatable metabolic cause of PRES that should be looked in during evaluation of PRES.

Keywords: *Hypocalcemia, PRES, Seizures, Encephalopathy.*

Introduction

Posterior Reversible Encephalopathy Syndrome (PRES) is a clinico-radiological syndrome. It is most commonly associated in context of severe hypertension, hypotension, renal failure, eclampsia, renal transplant autoimmune disorders, sepsis, and immunosuppressive or cytotoxic therapies.[1,2] The most common presenting symptoms include seizures (80%), headache (50%), encephalopathy (28%), quadrantanopia(39%), visual disturbances like binocular diplopia, vision loss, hemianopia and focal neurological deficits (10-15%). [2] Hypercalcemia is a known risk factor for the onset of PRES; however, this article emphasizes a collection of cases where hypocalcemia appeared as a possible and often overlooked triggering factor for PRES.

Case Summary

Case 1

A 33 years female patient of primi gravid post LSCS day 1 presented with sudden onset of altered sensorium with 1 episode of generalized tonic clonic seizure (GTCS) type of seizures. She did not have any history of hypertension prior or during pregnancy. On examination, Glasgow coma scale (GCS) of E1 V1 M2 with pupils dilated and fixed not reacting to light with one and half syndrome (restriction of movements in the Right eye with abduction paresis in the left eye), patient developed aspiration pneumonia with poor respiratory drive for which invasive mechanical ventilation support was taken. BP was 150/100 on admission. MRI brain showed areas of T2 FLAIR hyper intensity noted in bilateral hippocampus, right half of midbrain, pons, bilateral posterior thalami, right middle cerebellar peduncle and right superior cerebellar hemisphere with corresponding areas of restriction diffusion and areas of blooming noted in susceptible weighted image (SWI) in bilateral hippocampus extending into bilateral lateral ventricles. Also, bilateral sulcal FLAIR hyper intensity noted in the paritooccipital areas [Figure 1] indicating, atypical PRES with hemorrhagic component. At the time of admission serum calcium was low [Table1]. Urine and blood culture were sterile. She was treated with antiepileptics, antiedema measures, hypertensive medications to maintain BP below 140/90 mm of Hg, along with vitamin D correction and calcium supplements. Patient showed clinical improvement with GCS score 15/15 and was discharged on day 8.

Case 2

24 years female without any prior history of hypertension, presented with headache in the occipital region of moderate intensity for 5 days followed by GTCS type of seizures of 3 episodes in last 4 hours with each episode lasting for 3 to 4 min with partial regain of conscious intermittently and was associated with tongue bite. Her B.P was 158/100 mm of Hg, pulse rate of 112 per min, temperature 98.7F with GCS of E2V3M3.MRI brain showed gyriform T2 and FLAIR hyper intensities involving the cortex and subcortical white matter in bilateral temporo occipital, occipital including parasagittal, bilateral high frontal and high parietal regions. Also, focal T2 and FLAIR hyperintensities in bilateral corona radiata, parietal and occipital deep white matter and right half of splenium of corpus callosum. Areas of T2 and FLAIR hyperintensity were also noted in bilateral cerebellar hemispheres [Figure 1]. All these areas show T2 shine through suggesting vasogenic edema suggestive of atypical PRES. Patient was treated with antiepileptics, anti-hypertensive, antiedema measures. Her serum calcium and vitamin D levels were low [Table 1] which were treated appropriately. Patient GCS gradually improved to E4 V5 M6, power of both upper limbs 4-/5 and lower limbs of 3/5 with seizure free in subsequent days. She was discharged on day 7.

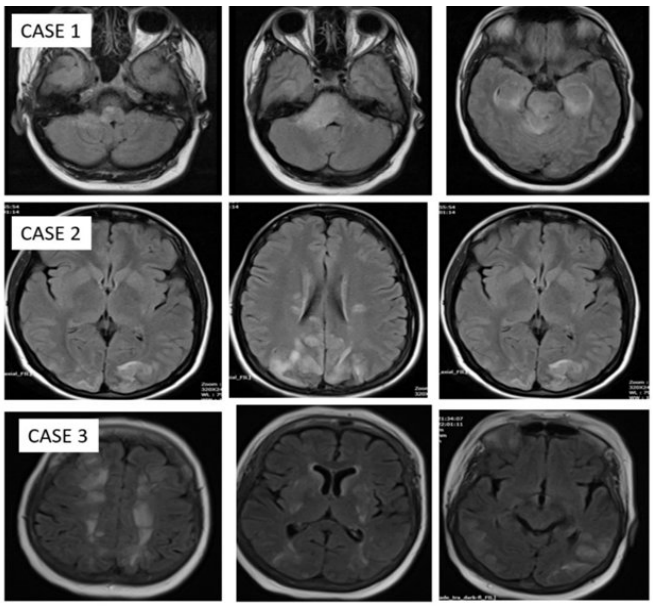

Figure 1. Showing MRI brain axial sequences showing hyperintensity in brainstem and temporal lobe (central PRES) in case 1, and hyperintensity in T2 flair in subcortical parieto-occipital region (classical PRES) in case 2 and case 3.

Case 3

A 26 year female with prior hypothyroidism on medication presented with headache for 2 days continuous that lasted for more than 24 hours and was not relieved by medication. Headache was followed by GTCS type of seizures total 4 episodes over a period of 3 hours with each episode lasting for 2 to 3 minutes. Patient was brought to the emergency department in a state of altered sensorium with GCS of E2 V3 M5, B.P 170/110 mm Hg, pulse rate 95/ min, SPO2 97% on room air, and temperature 99.2 F. MRI Brain showed hyper intensities without restricted diffusion in the cortical and subcortical regions of left parietal, occipital including the para sagittal region, left caudate nucleus and bilateral corpus callosum suggesting PRES [Figure 1]. EEG done day 2, was normal. Blood investigations showed low serum calcium levels and low vitamin D levels [Table 1]. Patient was treated with antiseizure medication, vitamin D, calcium supplements and short course of antihypertensive. GCS improved to E4V5M6 with no active seizures during the hospital stay and discharged on day 5.

Table 1. Showing laboratory parameters of study cases.

	Case 1		Case 2		Case 3	
Blood parameters with (units) and (normal range)	During admission	During discharge	During admission	During discharge	During admission	During discharge
Hb (gm/dL) [11-14.5]	10.4	11.1	10.4	11.1	11.6	11.4
WBC (cell/cumm) [4000 – 11000]	23800	13500	23800	13500	12100	8600
Platelet count lakh cells /cumm [150000 – 450000]	1.3	4.4	1.3	4.4	3.4	2.8
S. Calcium mg/ dl[8.8 – 10.8]	**7.9**	8.9	**7.4**	8.1	**7.6**	8.5
S. Magnesium (mg/dl) [1.6 -2.3]	1.84		1.90		1.60	
S.Sodium (mEq/L) [136 – 145]	146.3	139.7	138.5	141.6	141.3	142.8
S . Potassium (mmol/L) [3.5 -5.0]	3.85	4.55	4.3	4.6	3.60	3.87
S. Chloride (mEq/L) [95 -105]	111.0	102.3	101.4	99.8	105.4	100.4
S.Urea (mg/dl) [10 -45]	24	26	41	34	38	32
S.Creatinine (mg/ dL)[0.6 -1.5]	0.6	0.6	0.9	0.6	0.6	0.6
S. Albumin (g/dl) [3.5 – 5]	3.3	3.9	4.3	4.0	3.4	3.7
Vitamin D (nmol/L) [>30]	11.4		12		18	
Parathyroid hormone (pg/ ml)(10-65)	29.8		45		44	

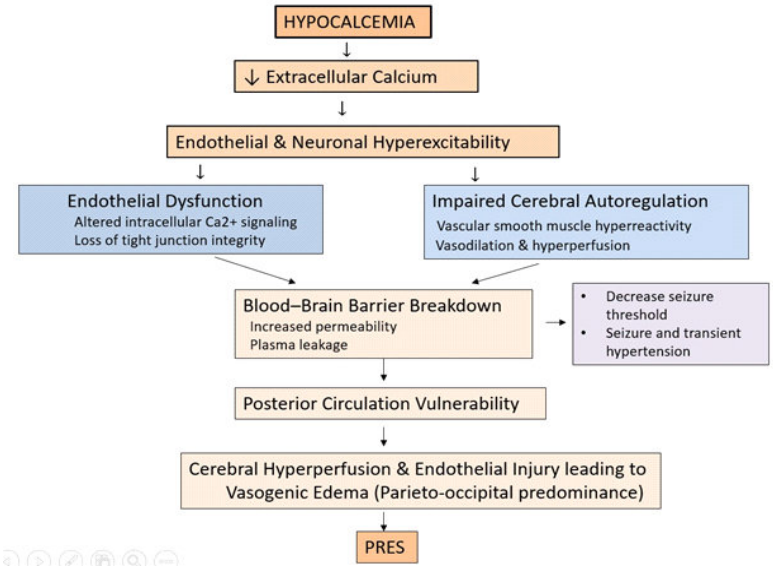

Figure 2. Showing pathophysiology of hypocalcemia causing PRES.

Discussion

PRES was first described in 1996 in a group of 15 patients identified retrospectively in the records of the New England Medical Center in Boston and Hospital Sainte Anne in Paris. [3] The name was revised in 2000 from "leukencephalopathy" to "encephalopathy" by Casey et al, as the former suggested that it only affects the white matter of the brain, which is not the case. [4] Other names for PRES are reversible posterior cerebral edema syndrome, posterior leukoencephalopathy syndrome, hyper perfusion encephalopathy or brain capillary leak syndrome. The name 'reversible' derives from the fact that both neurological and neuroimaging findings spontaneously recover within a few hours or 7-8 days after the initiation of treatment. [5, 6]

Classically, two main theories for the pathogenesis of PRES have been proposed. [3, 7, 8, 9] The first is severe hypertension that leads to disruption of the brain auto regulation system, resulting in endothelial edema or injury. PRES is frequently found in patients with reversible cerebral vasoconstriction syndrome (RCVS), characterized by segmental vasoconstriction and vasodilatation in small cerebral vessels arising from cerebral vascular tone deregulation. The abrupt blood pressure surge associated with RCVS may play a pivotal role in the pathogenesis of PRES in these patients. This theory is supported by the fact that hypertensive crisis leads to PRES. The second is endothelial dysfunction caused by circulating endogenous or exogenous toxins. This hypothesis provides a plausible reason why patients with preeclampsia/ eclampsia, sepsis, immunosuppressant medications, and cytotoxic drugs have a higher probability of developing PRES. Among the various risk factors, the activation or disruption of the immune system has recently been recognized as a key initial factor in the development of PRES and is crucial in the progression of the disease. [10] PRES due to hypocalcemia may occur with normal or mildly elevated blood pressure, Seen in conditions such as hyperparathyroidism, post-thyroidectomy states, vitamin D deficiency, chronic kidney disease and massive transfusion. Our case atypical PRES was seen in 2 cases. Atypical PRES shows either cytotoxic edema, contrast enhancement, central PRES (location in brainstem and cerebellum), and hemorrhagic conversion of lesion on MRI brain than classical vasogenic edema of subcortical parieto-occipital region. [11]

Very rarely electrolyte abnormality such as hypomagnesemia and hypercalcemia has been associated with PRES. [12, 13, 14] Hypercalcemia-related PRES is frequently associated with cancers or severe hyperparathyroidism, marked by symptoms such as seizures, headaches, and changes in mental status. The literature on hypocalcemia causing PRES is very sparse. Till date there is only one case, reported from Russia where severe hypocalcemia was secondary to extirpation of parathyroid gland that led to recurrent PRES. [15] Other causes of hypocalcemia are chronic renal failure, hypoparathyroidism and vitamin D deficiency. Present case series hypocalcemia was due to vitamin D deficiency. Low calcium impairs vascular smooth muscle contraction, leading to cerebral vasodysregulation, endothelial dysfunction, and breakdown of the blood–brain barrier.

This results in vasoconstriction, hypertension and vasogenic edema, particularly in the posterior circulation, characteristic of PRES. Pathophysiological mechanism linking hypocalcemia to PRES has been depicted in Figure 2.

Conclusion

Our case series showed that hypocalcemia, may predispose to PRES, presenting with seizures and encephalopathy; early detection and correction of calcium improve outcomes. Case series underscores the importance of evaluating serum electrolytes in patients with PRES to better elucidate their pathogenic role. Study further adds to this rare cause in literature.

Conflict of Interest Statement

The authors declare no conflict of interest.

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