ISSN- O: 2458 - 868X, ISSN–P: 2458 – 8687
Index Copernicus Value: 68 . 16
PubMed - National Library of Medicine - ID: 101731606

International Journal of Medical Science and Innovative Research (IJMSIR)
IJMSIR : A Medical Publication Hub
Available Online at: www.ijmsir.com
Volume – 4, Issue – 6, December - 2019, Page No. : 169 - 175

Posterior Reversible Encephalopathy Syndrome due to Hypercalcemia associated with Ectopic Hyperparathyroidism in a low socio-economic setting: a case report

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Type of Publication: Case Report

Conflicts of Interest: Nil

Abstract

Background: Posterior Reversible Encephalopathy Syndrome (PRES) is a leuko-encephalopathy that usually presents with seizures. There are a wide variety of conditions that are associated with PRES. Hypercalcemia due to ectopic production of parathyroid hormone (PTH) is a relatively rare etiology of this syndrome.

Case: We report a rare case of a 45 year old female who presented with epigastric pain for five days along with several episodes of vomiting and fits. On physical examination she was severely hypertensive and dehydrated. Laboratory investigations revealed raised serum amylase and lipase levels, significant hypercalcemia and hypophosphatemia, along with elevated PTH and Vitamin D levels.

All relevant investigations for hyperparathyroidism proved negative in our patient. A Magnetic Resonance Imaging (MRI) of the brain with contrast revealed typical features that were indicative of PRES. The hypercalcemia was treated with a combination of intravenous Pamidronate with aggressive hydration and the patient improved significantly. However, she relapsed a month later with persistent hyperparathyroidism and concomitant hypercalcemia. She was not rendered stable for a surgical neck exploration and succumbed to aspiration pneumonia which advanced to a cardiopulmonary arrest.

Conclusion: Although quite rare, PRES can occur in a setting of hypercalcemia and must be considered in patients who present with neurological signs and symptoms. Immediate correction of the underlying cause yields speedy recovery without any major sequelae.

Through our report, we intend to highlight the importance of diagnosing ectopic hyperparathyroidism in a low socioeconomic setting such as ours, where improved resources and surgical expertise can help physicians achieve effective patient care.

Keywords: Posterior reversible encephalopathy syndrome; Parathyroid hormone; Hypercalcemia; Hypertension; Seizures; Magnetic Resonance Imaging

Introduction

Posterior Reversible Encephalopathy Syndrome (PRES) is a leuko-encephalopathy that encompasses various neurological features like headaches, altered mental status, visual disturbances and seizures. On Magnetic resonance imaging (MRI) of the brain, it

shows characteristic bilateral subcortical and cortical edema predominantly involving the parietal and occipital lobes. [1] Chronic kidney disease, hypertension and eclampsia are just a few of the wide variety of conditions that are associated with PRES.[2] Hypercalcemia due to ectopic production of parathyroid hormone (PTH) is a relatively rare etiology of this syndrome. Ectopic parathyroid glands are classically located within the mediastinum, typically between the vagus nerve and recurrent laryngeal nerve.[3] In this case report we discuss a patient who presented to us with hypercalcemia induced PRES in a background of idiopathic primary hyperparathyroidism. To the best of our knowledge, such a case report has not been published previously.

Case Report

A 45 year old female presented with complaints of epigastric pain for five days along with several episodes of vomiting. Prior to her admission, she also developed a headache with slight blurring of vision but no diplopia. Our patient also reported three episodes of fits but there was no history of loss of consciousness, urinary or fecal incontinence or frothing from the mouth. She was prescribed 25mg Losartan by her primary care doctor for the last two months but was non- compliant. All other systems were unremarkable. On physical examination she was severely hypertensive (210/110mm Hg) and dehydrated. The abdomen was non-distended and markedly tender in the epigastrium. A CNS examination revealed a GCS of 14/15 (E4V4M6) and no other signs of neurological dysfunction were noted.

Baseline investigations were performed, the results of which lay within the normal range. To evaluate the cause of epigastric pain, serum amylase and lipase levels were done, both of which were markedly elevated. A Computed tomography (CT) scan with pancreatic protocol indicated cholelithiasis with peri-pancreatic fat stranding, suggestive of acute pancreatitis. Laboratory investigations also revealed significant hypercalcemia (16.1mg/dl) and hypophosphatemia (1.6mg/dl). We then noted a rise in the PTH level from 145pg/ml on admission to 188pg/ml within a span of two weeks. Vitamin D levels were also found to be elevated (160ng/ml). In order to evaluate the cause of primary hyperparathyroidism, all necessary investigations were performed, including ultrasound and CT scan of neck with contrast, which revealed a left sided thyroid adenoma with coexistent cervical lymphadenopathy and right maxillary sinusitis. A parathyroid scintography was done which proved to be negative for any functioning parathyroid adenoma in the neck and mediastinum. To rule out an ectopic production of PTH, a CT scan of chest and abdomen with contrast was also performed, but no malignancy was found.

To investigate the cause of seizures, we opted for a brain MRI with contrast. This indicated an iso -intense to hypo intense lesion in T1 and a hyper intense signal intensity of lesion in T2 and FLAIR in the deep white matter of the bilateral frontal lobes, cortical and sub cortical regions of right post central parietal, and occipital lobes (Figure 1).

There was no diffusion restriction on Diffusion Weighted MRI (DWI) and pituitary glands appeared normal. These findings were suggestive of PRES. We then planned for a symptomatic management and treated the patient with intravenous Pamidronate followed by aggressive hydration. Soon, the serum calcium, amylase and lipase levels began to improve and the patient recovered gradually and was discharged.

She was advised to get a brain MRI scan done within 3 months to assess the regression of PRES.

However, the patient returned to the hospital within a month, with complaints of severe vomiting and dehydration. The labs showed a creatinine of 1.4mg/dl from a baseline of 1.1mg/dl, with concomitant hypercalcemia and hyperparathyroidism (PTH: 800pg/ml).

Once again, our patient was managed symptomatically but was not rendered stable for a bilateral surgical exploration of the neck to evaluate the cause of a consistent hyperparathyroidism. Soon, the condition of the patient worsened rapidly and she could not survive as she suffered from a sudden aspiration pneumonia which advanced to a cardiopulmonary arrest. Informed and written consent was obtained from the patient's next of kin before accessing the medical record and images for this publication.

Discussion

PRES is described as a diverse clinico-radiologic syndrome with a wide array of clinical symptoms and characteristic MRI features. The pathophysiology of PRES remains poorly understood. However, two essential conditions have been proposed - hypertension related loss of cerebral auto-regulation and resultant hypoperfusion due to vasoconstriction; and toxin induced endothelial damage leading to cerebral edema.[4] Nonetheless, PRES can also occur in a subset of normotensive patients, suggesting that endothelial dysfunction may play an important and superior role in the development of this syndrome.

This is further shown in a study done by Bartynski and Boardman, [5] who found no association between absolute blood pressure and clinical and radiographic presentations of PRES.

A wide variety of clinical settings are known to cause PRES, including hypertension, sepsis, renal failure, various immunosuppressants such as cyclosporine and shock.[6] A retrospective review of PRES cases in German hospitals found similar associated comorbidities.[7] However, hypercalcemia coupled with hypertension, as seen in our patient, is an extremely rare association of PRES- a literature search only reveled three cases[8-10] with a similar presentation. About 40% of patients with hypercalcemia report neurological symptoms, such as fatigue, weakness and confusion.[11] Interestingly, our patient presented with an acute onset of seizures, which independently is a relatively rare alteration of hypercalcemia and could be recognized as a separate manifestation of PRES instead. The etiology of hypercalcemia can be divided into those governed by PTH and those which are not- the latter attributable to genetic or neoplastic factors. By far, a complete workup in our patient revealed no underlying condition that could have otherwise resulted in an elevated PTH level, thus leading to a probable spontaneous origin of the hormone.

The mechanism of isolated hypercalcemia induced PRES is thought to be mediated by cerebral arterial vasospasm, [8-10] possibly due to unchecked interactions between actin and myosin within the arteriolar bed. On the contrary, patients with PTH-dominant hypercalcemia have impaired vascular endothelial cells with diminished vasodilatory mechanisms of the arterial media.[12] Even so, the aforementioned mechanisms of hypercalcemia related PRES do seem to come in line with the proposed pathophysiology of this syndrome and physicians should consider it as a suitable sequalae in this setting.

Clinically, PRES is characterized by headache, visual disturbances, altered mental status and seizures- the

latter being the most common manifestation with an occurrence rate of 74%.[13] On radiographic MRI imaging, the lesions of PRES are typically seen as reversible hyperintense signals on T2 and FLAIR with a predominance of the parieto-occiptal and temporal lobes. The relatively poor sympathetic innervation of the posterior fossa of the brain makes this area particularly susceptible to hyperperfusion and vasogenic edema.[13] However this is not strictly confined to these areas, as a study at Mayo Clinic showed that 53% of reported cases had cerebellar involvement while 34% had basal ganglia involvement.[13] A study done by Lee et al.[14] indicated that hypertensive patients tend to have larger vasogenic edematous lesions that could potentially lead to the development of PRES. Contrary to this, a similar study did not establish a correlation between the severity of brain edema on MRI with the degree of hypertension.[13]

The treatment of PRES is challenging and is targeted at removing the triggering agent. A generalized consensus on the importance of blood pressure control exists, however no studies have been conducted to establish causation or to associate blood pressure management with resolution of PRES.[13] Our patient presented with hypercalcemia and so we opted for a symptomatic management in order to resolve the episode of acute pancreatitis and PRES. Volume resuscitation is crucial in the early treatment of malignant hypercalcemia in order to preserve renal function.[1]

As such, bisphosphonates are the treatment of choice and are effective within 24-48 hours after administration.[15] We followed a similar approach and our patient improved significantly on her first admission. Unfortunately, she relapsed with a similar presentation of illness and could not survive. Therefore it is essential to recognize the cause of a consistent hypercalcemia due to hyperparathyroidism when all standard investigations including ultrasound, a ^{99m}Tc-sestamibi scan and MRI reveal no abnormality.

A bilateral surgical exploration is recommended in this setting and has been successful in identifying the source of PTH at relatively superior locations within the neck. In a series of 288 patients with persistent hyperparathyroidism, lesions in the wall of the nasopharynx and vagus nerve were seen among two patients.[16] Chan et al. also reported cases with ectopic adenomas within the pharyngeal area.[17] A similar study described an ectopic production of PTH from a sub-mucosal tissue in the soft palate after three exhaustive surgical parathyroid explorations.

Intraoperative parathyroid hormone monitoring and frozen section were useful at the time of re-exploration. Selective venous sampling for parathyroid hormone levels can also be considered while evaluating the cause of a persistent hyperparathyroidism.[18]

Conclusion

Although quite rare, PRES can occur in a setting of hypercalcemia and must be considered in patients who present with neurological signs and symptoms. Immediate correction of the underlying cause yields speedy recovery without any major sequelae. Nonetheless, our patient could not survive, essentially due to rapid deterioration of her health owing to persistently elevated calcium levels.

A prompt bilateral surgical neck exploration would have primarily helped to identify the source of the ectopic production of PTH, eliminate the cause of hypercalcemia and potentially alleviate our patient's symptoms. This highlights the need to improve surgical expertise and resources in a low socio economic setting as ours, in order to achieve the best possible standards of effective patient care.

References

1. Carlos R. Camara-Lemarroy, Emmanuel I. Gonzalez-Moreno, Jose de Jesus Ortiz-Corona, et al. Posterior Reversible Encephalopathy Syndrome Due to Malignant Hypercalcemia: Physiopathological Considerations, *The Journal of Clinical Endocrinology & Metabolism*, Volume 99, Issue 4, 1 April 2014, Pages 1112–1116.
2. Feske SK. Posterior reversible encephalopathy syndrome: a review. *Semin Neurol*. 2011; 31:202–215.
3. Okuda I, Nakajima Y, Miura D, Maruno H, Kohno T, Hirata K. Diagnostic localization of ectopic parathyroid lesions: developmental consideration. Jpn J Radiol. 2010;28(10):707–13
4. Pula JH, Eggenberger E. Posterior reversible encephalopathy syndrome. *Curr Opin Ophthalmol*. 2008; 19:479–484.
5. Bartynski WS, Boardman JF: Distinct imaging patterns and lesion distribution in posterior reversible encephalopathy syndrome. AJNR Am J Neuroradiol. 2007, 28 (7): 1320-1327.
6. Bartynski WS, Boardman JF, Zeigler ZR, Shadduck RK, Lister J. Posterior reversible encephalopathy syndrome in infection, sepsis, and shock. AJNR Am J Neuroradiol 2006; 27: 2179-90
7. Liman TG, Bohner G, Heuschmann PU, Endres M, Siebert E: The clinical and radiological spectrum of posterior reversible encephalopathy syndrome: the retrospective Berlin PRES study. J Neurol. 2012, 259 (1): 155-164. 10.1007/s00415-011-6152-4.
8. Frank Y, Pavlakis S, Black K, Bakshi S. Reversible occipital-parietal encephalopathy syndrome in an HIV-infected child. *Neurology*. 1998; 51:915–916.
9. Au, S., Dunham, M., & Godinez, T. (2012). Treatment of Medically Refractory Hypercalcemic Crisis. *The International Journal of Artificial Organs*, *35*(7), 538–541
10. Kaplan, P. W. (1998). Reversible Hypercalcemic Cerebral Vasoconstriction with Seizures and Blindness: A Paradigm for Eclampsia? *Clinical Electroencephalography*, *29*(3), 120–123.
11. Jack E Riggs, Neurologic Manifestations of Electrolyte Disturbances,Neurologic Clinics. 2002; Volume 20(1), 227-239.
12. Thomas Neunteufl, Reinhold Katzenschlager, Claudette Abela, Karam Kostner, Bruno Niederle, Franz Weidinger, Thomas Stefenelli, Impairment of endothelium-independent vasodilation in patients with hypercalcemia, *Cardiovascular Research*, Volume 40, Issue 2, November 1998, Pages 396–401.
13. Fugate JE, Claassen DO, Cloft HJ, Kallmes DF, Kozak OS, Rabinstein AA: Posterior reversible encephalopathy syndrome: associated clinical and radiologic findings. Mayo Clin Proc. 2010, 85 (5): 427-432.
14. Lee MK, Cho YJ, Lee SK, Jung SK, Heo K. 2018. The effect of presymptomatic hypertension in posterior reversible encephalopathy syndrome. Brain Behav 8(8): e01061
15. Santarpia L, Koch CA, Sarlis NJ. Hypercalcemia in cancer patients: pathobiology and management. *Horm Metab Res*. 2010; 42:153–164.
16. Jaskowiak N, Norton JA, Alexander HR, et al. A prospective trial evaluating a standard approach to reoperation for missed parathyroid adenoma. Ann Surg. 1996;224(3):308–20.
17. Chan TJ, Libutti SK, McCart JA, et al. Persistent primary hyperparathyroidism caused by adenomas identified in pharyngeal or adjacent structures. World J Surg. 2003;27(6):675–9.

18. Chang, B.A., Sharma, A. & Anderson, D.W. Ectopic parathyroid adenoma in the soft palate: a case report. *J of Otolaryngol - Head & Neck Surg* 45, 53 (2016)

Legend Figure

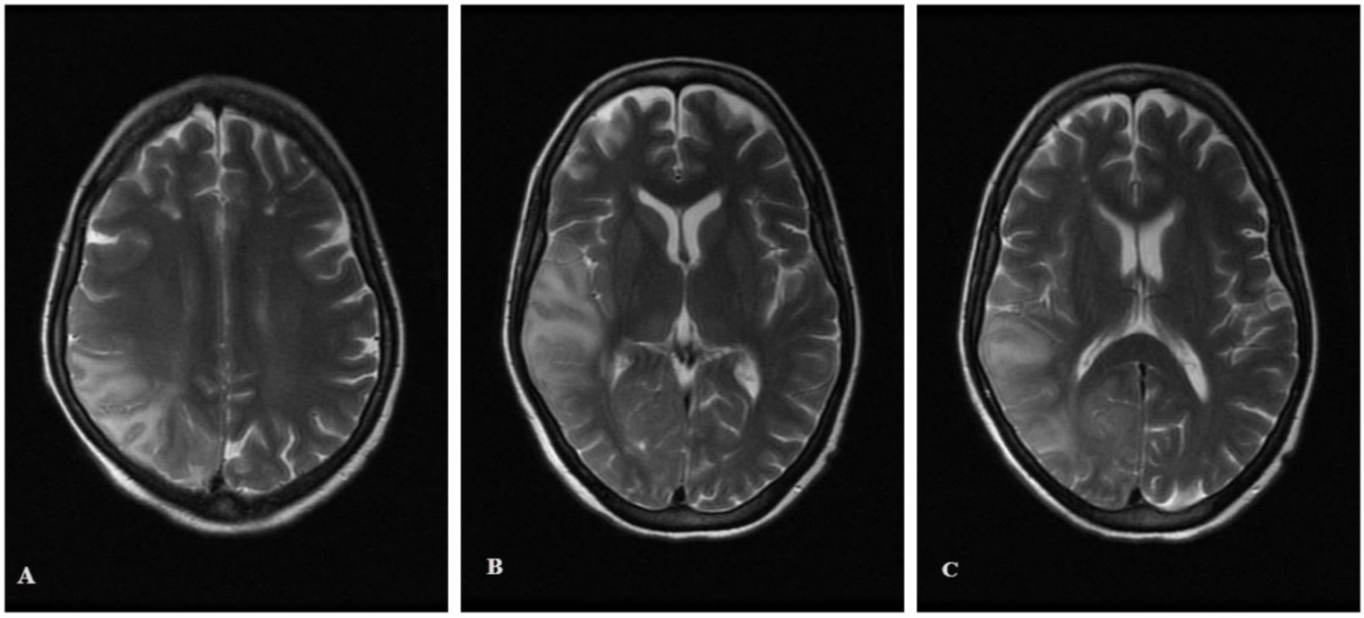

Figure 1: T2: weighted axial image of the brain showing diffuse hyperintense signals in deep white matter of bilateral frontal and parietal lobes (A,B,C) and occipital lobes (C).