Posterior encephalopathy: An uncommon manifestation of calcium toxicity

Sir,

Hypercalcemia is a common metabolic abnormality encountered in clinical practice, with primary hyperparathyroidism and malignancy being the commonest causes.[1] We present a case of iatrogenic hypercalcemia, which presented with features of posterior encephalopathy, illustrates an uncommon neurotoxic manifestation of hypercalcemia.

A 63-year-old woman, with Grave’s disease, complicated active thyroid eye disease, underwent a total thyroidectomy 5 months after diagnosis. This operation was complicated by severe hypocalcemia (calcium 0.9 mmol/l) and hypoparathyroidism (parathyroid hormone or PTH < 0.3 pmol/l). It was thought to be secondary to ischemic injury to parathyroid glands as they had been visualized and left intact intraoperatively. Stability was attained on oral calcium and high dose of alfacalcidol.

Six weeks later, her family admitted her with symptoms of confusion. She had a high serum calcium level of 4.45 mmol/l. Other bone parameters, i.e. phosphate (1.34 mmol/l) and alkaline phosphatase (70 IU/l), were normal. Liver, renal, and thyroid profiles were normal. A concurrent parathyroid level (<0.3 pmol/l) was low. She then developed seizures, limb weakness, hyperreflexia, and severe visual impairment. An urgent computed tomography (CT) scan of the head showed ill-defined changes in the occipital lobes. An MRI scan that followed showed symmetrical white matter edema in both the posterior parietal and occipital lobes [Figure 1], consistent with features of a posterior encephalopathy syndrome (PES). Cerebrospinal fluid (CSF) analysis showed normal glucose and protein content, with no organisms. An electroencephalogram (EEG) showed generalized slow wave activity suggestive of encephalopathy.

After aggressive hydration and intravenous bisphosphonate therapy, she became hypocalcemic (1.92 mmol/l), and therefore IV calcium supplements together with alfacalcidol were needed to stabilize calcium. Magnesium level (0.50 mmol/l), which was slightly low, was corrected.

During the initial phase of stabilization, focal seizure activity in the limbs was noticed with fluctuations in the calcium level, which resolved promptly with its correction. Later on, calcium levels were steady on a fixed dose of oral calcium citrate (2.5 g TDS) and alfacalcidol (2 mcg TDS). PTH level remained low (<0.3 pmol/l). Initially, there was clinical improvement: the limb weakness, attention span, and cognition improved. At that point, a repeat MRI scan of the brain showed a significant improvement in the white matter changes [Figure 2], confirming a diagnosis of posterior reversible encephalopathy syndrome (PRES). Gradually, prolonged periods of mental lucidity were punctuated by intermittent episodes of confusion, which then became persistent and progressive. She became progressively apathetic despite having stable calcium levels.

Figure 1: A T2-weighted FLAIR image of the brain showing extensive high signal changes involving the cortex of the right temporal/parietal lobes and the occipital lobes bilaterally (white arrows)

Figure 2: On a repeat scan, a T2-weighted FLAIR image of the brain shows resolved high signal changes in the right temporal/parietal lobes and the occipital lobes bilaterally (white arrows)
The severe visual impairment that was noted at the onset of encephalopathy never improved.

We feel that our patient may have developed irreversible cytotoxic brain injury from prolonged hypercalcemia which may have gone undetected at its onset, as the patient lived alone and was only found by her daughter to be in a confused state, on a weekly visit.

A review of literature on posterior encephalopathy from hypercalcemia revealed a condition called PRES which is a rare, recently described neurologic condition identifiable by clinical presentation typical of posterior encephalopathy correlating with MRI appearance of white matter changes in the posterior cerebrum.

Hypertension,[5,6] use of immunosuppressive agents,[2-4] eclampsia,[7,8] etc. can predispose to this syndrome. The condition is reversible by definition, but irreversable cases have been described. The pathogenesis of this condition is not clear, but it appears to be related to disordered cerebral autoregulation and endothelial dysfunction.[5] It is postulated that as the posterior circulation supplied by vertebrobasilar system has poor sympathetic innervation, it is frequently involved. Some patients have presented with weakness and incoordination of the limbs and hyporeflexia.[1-3] Visual perception abnormalities are invariably observed. Imaging studies show predominantly transient, posterior cerebral hyperintensities on T2-weighted images, and diffusion weighted imaging (DWI)[7,8] shows high computed apparent diffusion coefficient (ADC) values.

Treatment is essentially supportive and symptom directed. The offending agent should be dealt with. Where hypercalcemia is the cause, general principles of management apply. Intravenous bisphosphonate may not be of much use, considering the mechanism of action. A stable calcium level should be the goal of therapy with an emphasis on regular monitoring.

We suspect our patient may have sustained gradually progressive neurological injury from prolonged exposure to high calcium levels. This case may not entirely conform to the diagnosis of PRES, which was initially suggestive, when the patient showed signs of improved cognition, in tandem with the improvement of radiological signs on repeat imaging [Figures 1 and 2].

We felt, in hindsight, that the 3-week in-patient postoperative period may have been too short a period to titrate vitamin D and calcium to a safe maintenance dose. During hospital stay, calcium levels were checked on alternate days, if not daily. It is advisable that patients have daily or alternate day serum calcium levels checked for 10 days postoperatively in the outpatient setting, if discharged within 24–48 hours. If hypoparathyroidism is established and treatment is commenced, we recommend, weekly monitoring of serum calcium for 2 months at least or till the levels are stable and then every 2 months for at least the next 6 months.

This case emphasizes the importance of biochemical and clinical vigilance in patients who are on replacement therapy for hypoparathyroidism, especially if it is iatrogenic, as the body has insufficient time to adapt to a disturbed calcium homeostasis. Unfortunately, calcitonin, which has a counterregulatory action in animals,[9] has no role in calcium homeostasis in humans, and therefore cannot protect against dangerous hypercalcemia.

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References
1. Hinchen J, Chaves C, Appignani B, Breen J, Pao L, Wang A, et al. A reversible posterior leukoencephalopathy syndrome. N Engl J Med 1996;334:494-500.
2. Drummond AD, Williamson RM, Silverdale MA, Rothwell MP. Postoperative muscle weakness in a patient recently treated with infliximab. Anaesthesia 2008;63:548-50.
3. Tanno M, Nakamura I, Kobayashi S, Kurihara K, Ito K. New-onset demyelination induced by infliximab therapy in two rheumatoid arthritis patients. Clin Rheumatol 2006;25:929-33.
4. Heiss S, Krampla W, Hauser-Braun R. A patient recently transplanted with a living donor kidney develops severe neurological symptoms. Nephrol Dial Transplant 2006;21:2017-9.
5. Schwartz RB, Feske SK, Polak JF, DeGirolami U, Iaia A, Beckner KM, et al. Preeclampsia-eclampsia: Clinical and neuroradiographic correlates and insights into the pathogenesis of hypertensive encephalopathy. Radiology 2000;217:371-6.
6. Easton JD. Severe preeclampsia-eclampsia: Hypertensive encephalopathy of pregnancy? Cerebrovasc Dis 1998;8:53-8.
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7. Covarrubias DJ, Luetmer PH, Campeau NG. Posterior reversible encephalopathy syndrome: Prognostic utility of quantitative diffusion-weighted MR images. Am J Neuroradiol 2002;23:1038-48.

8. Lamy C, Oppenheim C, Méder JF, Mas JL. Neuroimaging in posterior reversible encephalopathy syndrome. J Neuroimaging 2004;14:89-96.

9. Lamy C, Oppenheim C, Méder JF, Mas JL. Evidence for calcitonin- A new hormone from the parathyroid that lowers blood calcium. Endocrinology 1962;70:638-49.

References