Carbamazepine induced secondary hyperparathyroidism: A rare clinical entity

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Abstract

Antiepileptic drugs (AEDs) are associated with altered bone metabolism and decreased bone density thereby increasing the risk of fractures several folds. This is a unique case report of a young 34 year old female diagnosed as a case of partial epilepsy two years back, was on carbamazepine (CBZ) therapy (300 mg SR twice a day). The seizures were fully controlled but she presented with gradual pure motor weakness involving proximal muscles over the duration of one year. There was a pentad of weakness, raised alkaline phosphatase (ALP), hypocalcaemia, hypophosphatemia and raised parathyroid hormone PTH. On dechallenge by tapering the doses of carbamazepine and starting newer antiepileptic there was marked improvement in the weakness. It has been found that epilepsy itself increases the risk of seizures and also anti-epileptics alter the bone metabolism by various mechanisms. Therefore while starting the antiepileptic in young patients for long term, high levels of suspicion should be kept in mind in view of altered calcium metabolism and even the first sign should not be missed. This patient presented with inability to walk and on evaluation was found to have secondary hyperparathyroidism. The pentad of weakness, raised ALP, hypocalcaemia and increased PTH in a patient on carbemazapine can easily lead to diagnosis.

Keywords: Carbamazepine; Adverse drug reaction; Hyperparathyroidism

Introduction

Adverse drug effects of an anticonvulsant therapy on calcium metabolism is a known entity. We present a rare case report of a patient on chronic carbamazepine therapy, presented with inability to walk and on evaluation were found to have secondary hyperparathyroidism which was easily treated with change of antiepileptic drug and Vit D supplementation. The pentad of weakness, raised ALP, hypocalcaemia and increased PTH in a patient on CBZ can easily lead to diagnosis.

Case Summary

This 34 year old house wife a resident of nearby village of Kullu in state of Himachal Pradesh India presented in Medicine OPD with complaints of inability to walk for last 2 months and inability to do routine house work for last 8 months. Patient was brought in a wheel chair by her husband. The patient had been married for last10 years and had two kids of age 8 and 5 yrs which were born of a full term normal vaginal delivery at Regional Hospital Kullu. Her post partum period had been un-eventful. Patient had been a known case of partial seizures with cognitive loss for the last 4 years. Patient got evaluated for the complaints of seizures from Kullu and was diagnosed to have neurocystiscercosis which were calcified. Patient was started on carbamazapine 300 mg twice daily and was taking regularly. Her seizure episodes were under control and her last episode of seizure was 1 yr back. Patient started complaining of generalized weakness for last 8 months. She usually got fatigued after doing minimal house hold work and would need someone's help. She always complained of low back ache and pain in legs. She could not climb stairs in one go and had to rest after 5 to 6 steps and then again walk. She could not get up from squatting position and had to be helped by someone. She had problem in rolling chapattis and picking up utensils from upper shelves. She also had problem in combing her hair or lifting objects above her head. For these complaints she had been showing at various places but no improvement was been seen. She also received multivitamin injections at various places and calcium tablets and injections but after minimal improvement she again complained same. She had been bed bound for last 1 month and only could go for toilet with someone's help. During last one month she also started having twitches in right side of face and also complained that fingers of her hands would contract and adduct. This episode would remain for 1-2 minutes and then improve on its own. Considering it to be seizure her family doctor had increased dose of CBZ to 400 BD. During all this time her compliance for CBZ was good and she was seizure free. Otherwise she had no sensory complaints and her bladder and bowel habits were normal except for constipation. Her social relations were good and she had no complaints in relation to other organ systems. She was a vegetarian and her menstrual cycle was normal. Her body mass index was 20.3kg/m2which was normal for her age. On examination patient was conscious oriented to time place and person. She was not cheerful but maintained good eye to eye contact during whole conversation. Her pulse was 78/min, regular; her blood pressure in sitting position was 126/78 mm hg in right arm with no postural drop. Her respiratory rate was normal. She did not have pallor, jaundice lymphadenopathy, pedal edema or jugular venous pressure raised. Her skin and

thyroid gland were unremarkable. Her bones were tender to touch. Her joints were normal. She felt pain when her spine was examined and pelvis compressed. Her trousseau's sign was ellicitable and chvosteck sign was positive. On nervous system examination her higher mental functions were normal; she had no cranial nerve palsies. Her motor system examination showed a power of 4/5 in all proximal muscles with decreased deep tendon reflexes with sparing of distal muscles. Her sensory system was normal. Her gait could not be assessed. Examination of all other systems was within normal limits. Her hemoglobin was 12.2gm/dl with normal other hematological parameters. Her biochemistry showed normal renal function tests, liver function tests and lipids. Her alkaline phosphatase levels were raised to three times upper limit normal. Her serum calcium was 7.2 with ionic ca of 3.7. Her phosphorus was reduced (2.1). 24 hr urinary ca was 10.25 mol/l (12.5-75 mmol/l). Urinary phosphate levels were raised. Her vitamin d levels were low (<6). Her intact parathyroid levels were raised to (226ng/L). Her creatinine kinase total level was normal. Her ultrasound neck was normal. Pre treatment X rays of hip and long bone showed looser zone with osteoporosis. Bone mineral density showed a z score of – 3.5. Keeping in view the possibility of altered calcium homeostasis due to CBZ the dose of CBZ was tapered and pt was put on levetirecetam 500 mg BD along with therapeutic doses of Vit d3 and calcium supplementation. Over a period of one month her weakness improved and the patient came to OPD walking herself. Her proximal muscle power had improved to 4+/5 in lower limbs and 5/5 in upper limb. There were no episodes of twitching and both the hypocalcaemia signs were absent. At 3 month f/u the pt was perfectly alright with normal power in all four limbs. Her calcium was 9.2 and parathyroid levels came down to normal. A provisional diagnosis of carbamazapine induced hypocalcaemia with secondary hyperparathyroidism was made. The naranjo adverse drug reaction probability score of 6 was suggestive of this diagnosis.

Discussion

Altered calcium metabolism is a known side effect of antiepileptic medicines mainly CBZ and phenytoin.[1] Multiple mechanisms have been postulated for the pathogenesis. Decreased absorption of calcium and acquired Vit d deficiency state causing secondary hyperparathyroidism are the main proposed mechanisms.[2,3] Chronic AED use induces hepatic cytochrome P450 enzymes that may cause increased conversion of vitamin D to polar inactive metabolites in the liver microsomes, reducing bioavailable vitamin D.[4,5] This causes insufficient parathyroid action because of defective PTH1R – signaling protein complex. The bone loss with enzyme-inducing AEDs is because they increase CYP450-mediated catabolism of 25-OHD to less biologically active metabolites, producing a decrease in vitamin D–mediated bone mineralization and intestinal calcium absorption.[6] This in turn causes a compensatory increase in PTH, which stimulates the production of P450C1, the enzyme responsible for the conversion of 25-OHD to 1, 25-dihydroxyvitamin D (1, 25-OHD), which is the biologically active form of the molecule.[7] This leads to a form of high bone turnover disease with hypocalcaemia and hyperparathyroidism. The mechanism of osteomalacia in our patient may depend on CBZ induced reduction of Vit d. The combination of muscle weakness, with hypocalcaemia, increased alkaline phosphatase; increased parathyroid hormone with antecedent CBZ therapy may guide the diagnosis to this rare clinical entity. Our patient improved with change of anticonvulsant and Vit d3 supplementation. This side effect may appear with even short course of therapy and the patient needs to be followed for symptoms.

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