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Carbamazepine Induced Pathological Fracture In Young Female

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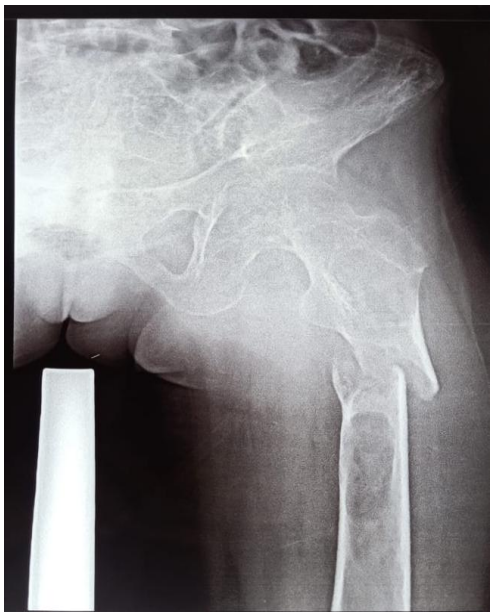
I. Introduction

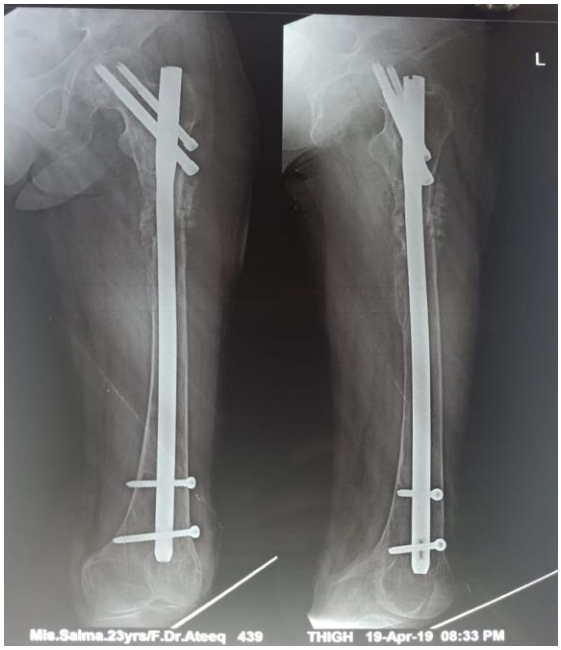
Anti-epileptic drugs (AED) encompass a wide range of medications which may lead to catabolism of vitamin D and hypocalcemia that may significantly effect the risk for low bone mass and fractures. Carbamazepine is an anticonvulsant used primarily in the treatment of epilepsy and neuropathic pain. It acts by blocking sodium channel and prevents repetitive and sustained firing of action potential. With the current estimates of 50 million people worldwide with epilepsy together with the rapid increase in utilization of these medications for other indications, bone disease associated with the use of anti-epileptic medications is emerging as a serious health threat for millions of people. Nevertheless, it usually goes unrecognized and untreated. While the use of anti epileptic drugs for a long period is a known risk factor for bone loss and pathological fractures, yet the physicians are not yet sensitized to this possibility. Here we report a case of a young female who had been on anticonvulsants for 8 years and was admitted with us with fracture of femur.

II. Case Report

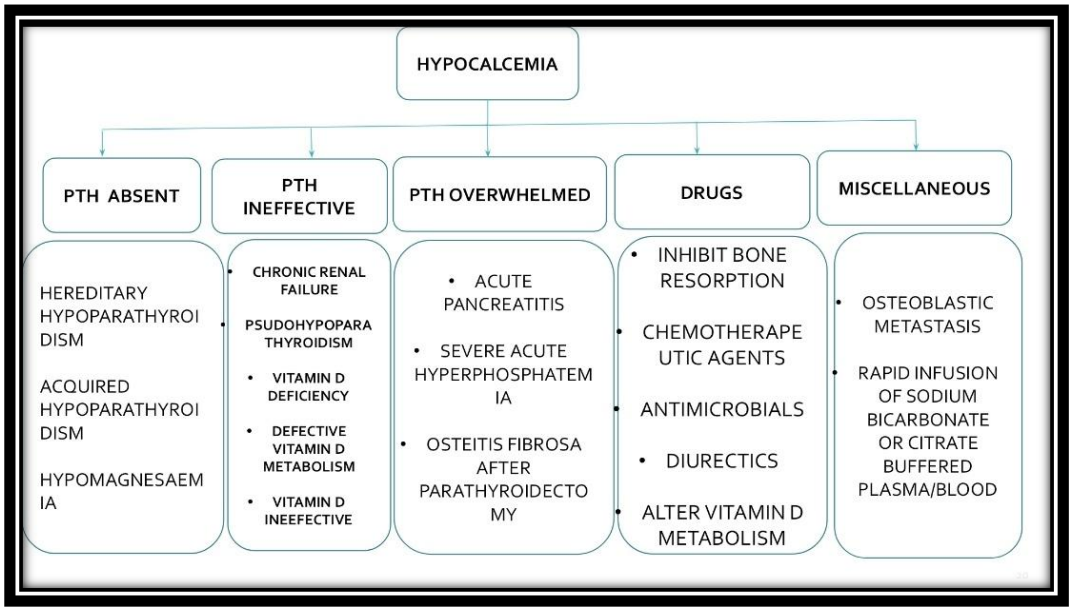
A 22-year-old female presented to emergency room of our hospital with complaints of severe pain in left thigh since 4hrs. The patient had history of slip and fall in the bathroom following which she developed severe pain in the left thigh which was acute in onset, severe in intensity, non radiating, aggravated on moving the limb. She also complained of generalised body pain and tiredness since 6 months. Patient is a known case of epilepsy for which she was started on tab carbamazepine 200mg twice daily at the age of fourteen and she was taking it regularly. Her seizure episodes were under control and her last episode was 3years back when she missed her antiepileptic tablets for a week. She is also a known case of pulmonary TB on ATT since 2months.Her bladder and bowel habits were normal. She was a non-vegetarian and her menstrual cycle was normal. Her body mass index was 17.1kg/m^2. On examination her vitals were stable. Examination of left lower limb revealed severe tenderness with deformity over left proximal thigh. There was shortening of the limb, movement at the left hip was restricted and crepitus was present which was suggestive of fracture femur. Examination of all the systems was within normal limits. Investigations revealed Hb-9.7 g/dl, TLC- 10400 with a normal platelet count and differential count. Renal parameters were normal. Patient had a serum bilirubin of 0.39 mg% with an alkaline phosphatase – 539 IU and SGOT/SGPT- normal. Serum albumin was 2.99 g%. Patient had a serum Ca – 4.52 mg/dL. X –ray of the pelvis showed fracture of proximal shaft of femur with reduced density of bone. Further evaluation revealed Serum phosphate-1.84 mg%, serum PTH – 129.28pg/mL and vitamin D3 – 12.85ng/mL.Her serum carbamazepine levels were estimated and was found to be elevated (Sr.CBZ – 12.6ug/mL).



A diagnosis of carbamazepine induced hypocalcemia with fracture femur was made and the patient was started on calcium and vitamin D supplements. The patient was taken off tab carbamazepine and started on tab levitracetam 500mg twice daily.



Over the next few weeks the patient started to show improvement and she was operated after 3 months when her general condition improved.



III. Discussion

Long term use of anticonvulsants is associated with an increased risk of fractures.[1] Of note is that patients of seizure disorder are more prone to fractures compared to the general population anyway. Osteomalacia with hypocalcemia and elevated alkaline phosphatase levels occurs frequently in patients on long term carbamazepine therapy. This has been attributed to both altered metabolism of vitamin D and the inhibition of intestinal absorption of calcium. Vitamin D is an important modulator of osteoblastic function and also facilitates differentiation along the osteoclastic lines[4]. Vitamin D deficiency associated with use of AEDs is likely mediated through the orphan nuclear receptor, pregnane X receptor (PXR)[5]. The PXR shares 60% homology in their DNA binding domains with the vitamin D receptor (VDRs) and is expressed in intestine, kidney and liver. PXR has been shown to mediate induction of cytochrome P450 enzymes involved in the drug metabolism. Furthermore, PXR can be activated by a variety of pharmaceutical agents including phenytoin, phenobarbital, carbamazepine and rifampicin[5]. Emerging evidence shows that these PXR activators can increase the expression of the CYP24, a VDR target gene in cultured cells and *in vivo* in mice. CYP24 is an enzyme that directs the side chain oxidation and cleavage of 25 $(OH)_2$ D_3 and 1, 25 $(OH)_2$ D_3 to carboxylic acid end products (calcitroic acid), resulting in lower cellular concentration of active vitamin D. This induces a state of vitamin D deficiency and results in hypocalcemia, secondary hyperparathyroidism and increased bone turnover predisposing to low bone density and bone loss[5,6]. Decreased vitamin D_3 levels may affect osteoblast activity through the aromatase pathway. Physiological concentrations of vitamin D_3 are necessary for maintenance of aromatase activity in osteoblasts. Further certain AEDs have a direct effect on bone turnover and it is said that anticonvulsants can cause bone loss without inducing Vitamin D deficiency-related osteomalacia.[2] Many studies have shown AEDs increase bone turnover and this may contribute to bone loss[7,8]. In a study by Andress *et al* it was noticed that younger patients had the highest rate of bone loss suggesting that the bone cell activity in the young male skeleton is more susceptible to the direct effects of AEDs. The relentless use of carbamazepine has lead to progress of osteomalacia and hypocalcemia to result in fractures and complete immobilization in this case. A large part of this disability was preventable had timely diagnosis and treatment of osteomalacia and hypocalcemia been instituted. Various other risk factors have previously been associated with bone loss in patients who have seizures include Vitamin D deficiency, decrease in levels of serum calcium and secondary hyperparathyroidism.[3] Therefore it is imperative that the younger skeleton with enhanced bone turnover due to direct effects of anticonvulsants may require substantially higher calcium intake to adequately suppress bone resorption and to optimize bone mineralization.

IV. Conclusion

Patients who have seizures are more susceptible to fractures when on long term anticonvulsant therapy. This may be related to several other factors but is most importantly due to a direct effect of AEDs on the

The current evidence also suggests that young adults may be at particularly increased risk of bone loss. Despite the evidence suggesting adverse effects of AEDs on bone, there appears to be a general lack of

awareness among physicians about these effects. It is important to get periodic DEXA scans and assess the bone mineral density to identify the patients who are at an increased risk of fractures. These patients should receive a higher calcium supplementation. The case also emphasizes the need for a much higher index of suspicion of this entity so that timely withdrawal of the drug and appropriate therapy can avoid major disabilities.

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