Phenytoin Induced Severe Disabling Osteomalacia in A Young Male with Seizure Disorder

Ambar Khaira*, Ankur Gupta**, SV Madhu***, Deepa Dash Khaira+

Abstract
While the use of anti epileptic drugs (AEDs) 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. It is now believed that the patients who have fractures due to long term treatment with anticonvulsants have osteomalacia as the predominant lesion. This has been attributed to the alterations in the levels of circulating calcium and calcitropic hormones. Here we report a case of a young male who had been on anticonvulsants for 11 years and was admitted with us with severe bone pains, multiple pathological pseudo fractures and a severe degree of disability secondary to phenytoin induced osteomalacia.

INTRODUCTION
While the use of anti epileptic drugs (AEDs) 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. It is now believed that the patients who have fractures due to long term treatment with anticonvulsants have osteomalacia as the predominant lesion. This has been attributed to the alterations in the levels of circulating calcium and calcitropic hormones. Here we report a case of a young male who had been on anticonvulsants for 11 years and was admitted with us with severe bone pains, multiple pathological pseudo fractures and a severe degree of disability secondary to phenytoin induced osteomalacia.

CASE REPORT
A 17-year-old male presented to the endocrinology and metabolic clinic of our hospital with complaints of severe bone pains and bony deformities for 2-3 years. The patient had history of an encephalitic illness at 5 years of age. Since then the patient was diagnosed to have some degree of mental retardation. He had few episodes of generalized tonic clonic seizures for which he was put on tab phenytoin sodium at the age of seven years. The patient had been on phenytoin sodium 200 mg/ day for about 4 years and on 300mg/ day since then. The patient started experiencing bone pains after about 4 years of initiation of treatment with anticonvulsants. Thereafter he developed a downhill course with repeated fractures particularly following seizures. He eventually became immobilized and bed ridden over next 2-3 years. Before finally coming to us he had been to several physicians and hospitals where the underlying bone problem was either not spotted or the contribution of phenytoin was completely overlooked. He continued to have pains and progression of disability. There was a history of poor sun exposure and the patient was a non-vegetarian. There was no history of antacid abuse. On examination the patient was found to have multiple flexion contractures at various joints (Fig. 1). Examination of the upper limb revealed complete range of motion at all joints except at wrist extension. There was a fixed flexion contracture of 100° and 110° at the right and left knee joint respectively. The hip joints of both sides also had restricted range of motion however the ankle joints were normal. The patient was completely bed ridden and could only sit in the bed with the help of the attendants. Investigations showed a Hb-13 g/dl, TLC - 8500 with a normal platelet count and differential count. The blood urea was 22 mg% and serum creatinine was 0.6 mg%. Patient had a Serum bilirubin of 0.8 mg% with an alkaline phosphate - 2494 IU and SGOT/SGPT - normal. The serum albumin was 4.5 g%. The patient had a serum Ca –6.5 mg%, serum phosphate-1.1 mg% and serum uric acid –4.5 mg%. The patient had a 24 hour urinary calcium- 24mg/day, urinary phosphate –15 mg/day and urinary creatinine –65mg/day. The X-ray chest revealed scoliotic deformity of the spine with marked concavity to the right side, which could be appreciated clinically as well (Fig. 2). The X-ray of the pelvis had multiple looser’s zones and other features of frank osteomalacia.
A diagnosis of drug-induced osteomalacia was made and the patient was started on calcium carbonate-1500 mg/day and alpha D3-0.25 µg/day supplemented with a calcium rich diet and active and passive physiotherapy. The patient was taken off tab phenytoin and started on tab sodium valproate. Over the next few weeks the patient started to show improvement.

**DISCUSSION**

Here we are presenting a case of severe osteomalacia with serious disabilities leading to the confinement of the patient to the bed, multiple pseudo fractures and contractures secondary to long term use of the antiepileptic drug Phenytoin. Long term use of anticonvulsants is associated with an increased risk of fractures. Other secondary factors in our case which could have compounded the problem are prolonged immobilization secondary to severe bone pains and history of a poor exposure of sunlight due to the confinement of the patient to the bed. Of note is that patients of seizure disorder are more prone to fractures compared to the general population anyway. The fact that this patient had been to several physicians who apparently ignored his complaints and attributed his disability only to possible post encephalitic sequelae and mental retardation reflects a widely prevalent lack of sensitization amongst treating physicians to the possibility of anticonvulsant related osteomalacia. Phenytoin induced osteomalacia may occur in upto one third of the patients receiving this drug and in one series changes in the bone mineral density were noticed in upto 47% of the patients.

Osteomalacia with hypocalcemia and elevated alkaline phosphatase levels occurs frequently in patients on long term phenytoin therapy. This has been attributed to both altered metabolism of vitamin D and the inhibition of intestinal absorption of calcium. It also increases the metabolism of vitamin K and reduces the concentration of vitamin K–dependant proteins that are important for normal calcium metabolism. A recent in vitro study has also shown that AEDs directly stimulate the osteoblastic activity and lead to osteomalacia. 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. 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 fact that the anticonvulsants directly stimulate the bone turnover was suggested by (Valemaki et al), when young men receiving phenytoin or carbamazepine were found to have higher parameters for bone formation and resorption than age matched controls. The relentless progress of osteomalacia associated with continued phenytoin use on the one hand and the greater fracture risk from recurrent seizures on the other have combined to result in multiple fractures, severe disability and complete immobilization in this case. A large part of this disability was preventable had timely diagnosis and treatment of osteomalacia been instituted. Other risk factors associated in our case were a poor exposure to sunlight. 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. 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.

**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 normal bone turnover. 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.

**REFERENCES**