Neurology Asia 2011; 16 (Supplement 1) : 63 – 64

Epilepsy and bone health

Sandra Petty

Department of Medicine, Royal Melbourne Hospital, The University of Melbourne, Victoria, Australia

Abstract

Patients with epilepsy have in increased risk of fractures. The morbidity and mortality associated particularly with hip fractures make this an important clinical issue for patients with epilepsy. The mechanisms for fracture risk in epilepsy are likely multi-factorial, and are under investigation. There are some limitations of available data, which have likely resulted in uncertainties for clinicians managing bone health in patients with epilepsy, and a lack of formal guideline availability for clinicians to follow.

Patients with epilepsy have at least twice the fracture risk of the general population.[1] The reasons for the association of fractures with epilepsy and anti-epileptic medication (AED) usage are likely multi-factorial.[2] Potential reasons for this association remain to be fully established, but may include factors such as epilepsy itself, direct and indirect side effects of AED use including direct effects on bone, calcium absorption and metabolism, induction of vitamin D metabolism and hormonal changes seen in some patients with epilepsy taking AED.[3] There are a number of confounding lifestyle factors in epilepsy which may predispose to reduced bone density including lower exercise levels, low vitamin D levels due to reduced sun exposure, smoking and dietary factors.[4,5] There is limited data available to examine whether the type and severity of epilepsy itself may be associated with differing fracture risk.[6,7] Fractures may begin to occur at a younger age, although this is not always a consistent finding in the research.[8,9] Fractures may occur during seizures as a result of falls or mechanical forces generated during seizures; the relative incidence of fractures during seizures or at other times varies across studies[1,6,10,11], therefore it is likely both mechanisms are of importance. Falls risk may be increased at other times due to balance impairment[12] either as a result of neurological lesions or possibly as a side effect of AED use or toxicity. Early studies implicated osteomalacia, possibly due to inducer-AEDs causing metabolism of vitamin D and altered calcium balance, although diet and lifestyle were often also potential confounders in the early studies of patients with epilepsy residing in institutionalised settings.[13] Later studies also identified bone health issues in patients taking the non-inducer sodium valproate, with both reduced bone mineral density (BMD) and serum markers demonstrating increased bone resorption.[14] Reduced bone mineral density has been demonstrated in some, but not all patients[15,16], whether this is related to specific AEDs and/or other factors including type of epilepsy[7] requires further study. Longitudinal data is now emerging: in a study of older women, continuous users of AED had a 1.7-fold annualised loss in hip BMD compared to controls[17]; in older men, the was a rate of 0.6% per year of bone lost at the hip in users of non-enzyme inducing AED.[18] Some studies in the paediatric age group have also demonstrated an association of epilepsy/AED with reduced bone density[19,20]; any effects of epilepsy/AED on peak bone mass remain to be fully established.

POSSIBLE PREVENTION AND TREATMENT STRATEGIES

Physician awareness[21] and patient education in this setting are important. Seizure prevention with appropriate AED therapy is of very high importance, and should therefore reduce the risk of injury and fracture during seizures. Lifestyle factors to optimise bone health, including weight-bearing exercise (where possible), sensible levels of sun exposure (balanced against skin health risks), avoidance of smoking and alcohol, promotion of good diet including adequate calcium intake, and foods containing vitamin D should be encouraged.[22] Assessing falls risk factors and modifying these, including allied health assessment where required may be beneficial.

Address correspondence to: Dr Sandra Petty, Department of Medicine, RMH/WH, The University of Melbourne, 4th Floor, Clinical Sciences Building, Royal Parade, Parkville VIC 3050 Australia. Tel: + 61 3 8344 3252, Fax: + 61 3 9348 2254, email: pettys@unimelb.edu.au

While no formal management guidelines exist, it would be prudent to intermittently measure serum Vitamin D levels and supplement Vitamin D (and/or calcium) where required. A baseline DXA scan and follow-up 2-3 years later would provide useful additional data (please note, DXA should be avoided during pregnancy (for radiation safety reasons), breastfeeding (due to a temporary physiological reduction in BMD), and other monitoring recommendations may be appropriate in the paediatric age group, as DXA scanning does require a relatively low exposure to radiation). Measurement of bone turnover markers, serum calcium, albumin, and parathyroid hormone (PTH) provide useful information at least in some patients, however neurologists may wish to refer to a specialist in bone health for expert interpretation and management.

Bisphosphonate therapy has been suggested for patients with established osteoporosis who have not responded to Vitamin D replacement[23], however there are no specific guidelines in epilepsy to assist physicians in this area, essentially due to the lack of available interventional data.[24] Further data is required in the paediatric age range, and bone specialist opinion is recommended if neurologists have concerns regarding bone health and/or growth problems in children taking AEDs. Trials of treatment strategies are still required to establish evidence for best practice.

REFERENCES

1. Vestergaard P. Epilepsy, osteoporosis and fracture risk - a meta-analysis. *Acta Neurol Scand* 2005; 112(5):277-86.
2. Petty SJ, O'Brien TJ, Wark JD. Anti-epileptic medication and bone health. *Osteoporos Int* 2007; 18(2):129-42.
3. Morrell MJ. Reproductive and metabolic disorders in women with epilepsy. *Epilepsia* 2003; 44 (Suppl 4):11-20.
4. Elliott JO, Lu B, Moore JL, McAuley JW, Long L. Exercise, diet, health behaviors, and risk factors among persons with epilepsy based on the California Health Interview Survey, 2005. *Epilepsy Behav* 2008; 13(2):307-15.
5. Fitzpatrick LA. Pathophysiology of bone loss in patients receiving anticonvulsant therapy. *Epilepsy Behav* 2004; 5(Suppl 2):S3-15.
6. Persson HB, Alberts KA, Farahmand BY, Tomson T. Risk of extremity fractures in adult outpatients with epilepsy. *Epilepsia* 2002; 43(7):768-72.
7. Sheth RD, Hermann BP. Bone in idiopathic and symptomatic epilepsy. *Epilepsy Res* 2008; 78(1):71-6.
8. Lidgren L, Walloe A. Incidence of fracture in epileptics. *Acta Orthop Scand* 1977; 48(4):356-61.
9. Desai KB, Ribbans WJ, Taylor GJ. Incidence of five common fracture types in an institutional epileptic population. *Injury* 1996; 27(2):97-100.
10. Koppel BS, Harden CL, Nikolov BG, Labar DR. An analysis of lifetime fractures in women with epilepsy. *Acta Neurol Scand* 2005; 111(4):225-8.
11. Sheth RD, Gidal BE, Hermann BP. Pathological fractures in epilepsy. *Epilepsy Behav* 2006; 9(4):601-5.
12. Petty SJ, Hill KD, Haber NE, *et al*. Balance impairment in chronic antiepileptic drug users: A twin and sibling study. *Epilepsia* 2010; 51(2):280-8.
13. Hunter J, Maxwell JS, Stewart DA, Parsons V, Williams R. Altered calcium metabolism in epileptic children on anticonvulsants. *BMJ* 1971; 4(781):202-4.
14. Sato Y, Kondo I, Ishida S, *et al*. Decreased bone mass and increased bone turnover with valproate therapy in adults with epilepsy. *Neurology* 2001; 57(3):445-9.
15. Petty SJ, Paton LM, O'Brien TJ, *et al*. Effect of antiepileptic medication on bone mineral measures. *Neurology* 2005; 65(9):1358-65.
16. Pack AM, Morrell MJ, Randall A, McMahon DJ, Shane E. Bone health in young women with epilepsy after one year of antiepileptic drug monotherapy. *Neurology* 2008; 70(18):1586-93.
17. Ensrud KE, Walczak TS, Blackwell T, Ensrud ER, Bowman PJ, Stone KL.Antiepileptic drug use increases rates of bone loss in older women: a prospective study. *Neurology* 2004; 62(11):2051-7.
18. Ensrud KE, Walczak TS, Blackwell TL, *et al*. Antiepileptic drug use and rates of hip bone loss in older men: a prospective study. *Neurology* 2008; 71(10):723-30.
19. Sheth RD, Binkley N, Hermann BP. Progressive bone deficit in epilepsy. *Neurology* 2008; 70(3):170-6.
20. Chou IJ, Lin KL, Wang HS, Wang CJ. Evaluation of bone mineral density in children receiving carbamazepine or valproate monotherapy. *Acta Paediatr Taiwan* 2007; 48(6):317-22.
21. Valmadrid C, Voorhees C, Litt B, Schneyer CR. Practice patterns of neurologists regarding bone and mineral effects of antiepileptic drug therapy. *Arch Neurol* 2001; 58(9): 1369-74.
22. Nakken KO, Tauboll E, *Bone loss associated with use of antiepileptic drugs*. *Expert Opin Drug Saf* 2010; 9(4):561-71.
23. Drezner MK. Treatment of anticonvulsant drug-induced bone disease. *Epilepsy Behav* 2004; 5 (Suppl 2):S41-7.
24. Pack A. Bone health in people with epilepsy: Is it impaired and what are the risk factors? *Seizure* 2008; 17(2):181-6.