



WHEN SHOULD CLINICIANS WORRY ABOUT BONE DENSITY FOR PATIENTS WITH EPILEPSY?

Progressive Bone Deficit in Epilepsy. Sheth RD, Binkley N, Hermann BP. *Neurology* 2008;70(3):170–176. **OBJECTIVE:** Chronic treatment with antiepileptic medication is associated with reduced bone mineral density (BMD), which may underlie the two- to sixfold increase in fracture rates observed in patients with epilepsy. The objective was to determine the timing of the BMD deficit in ambulatory children with epilepsy. **METHODS:** A cross-sectional evaluation was conducted in 82 ambulatory children aged 6 to 18 years (12.4 ± 3.3 years) with epilepsy for <1 year ($n = 18$), 1 to 5 years ($n = 37$), and 6 or more years ($n = 27$). Controls were 32 healthy children aged 12.8 ± 2.6 years. Age- and sex-corrected total body BMD Z-score was measured. **RESULTS:** Total BMD Z-score was lower in children with epilepsy (0.10 ± 0.96 ; CI = $-0.08, 0.34$) compared to controls (0.57 ± 0.74 ; CI = $0.3, 0.84$; $p = 0.03$). Increasing duration of epilepsy was associated with a progressive reduction in BMD compared to controls (Spearman $r = -0.197$; $p = 0.03$). Compared to controls, those with epilepsy for 1 to 5 years had a mean BMD Z-score of 0.13 ± 0.78 (CI = $-0.13, 0.39$; $p = 0.04$) and in those treated for 6 or more years BMD was 0.06 ± 1.11 (CI = $-0.38, 0.5$; $p = 0.04$). For those with epilepsy for <1 year BMD was 0.23 ± 1.1 (CI = $-0.31, 0.77$; $p = 0.21$). **CONCLUSIONS:** Children treated for epilepsy sustain significant bone mineral density (BMD) deficit compared to controls during the initial 1 to 5 years of treatment which progressively worsens thereafter. This progressive BMD deficit may be a contributing factor to the increased fracture risk observed in patients with epilepsy and may accelerate aging-related osteoporosis.

COMMENTARY

Epilepsy is associated with an increased risk of fractures. These fractures can be a direct result of injury sustained during a seizure or falls due to impaired coordination from antiepileptic drugs. However, individuals with epilepsy also have an increased risk of unexpected pathological fractures that occur during normal activity (1) and an increased incidence of osteopenia or osteoporosis that predispose them to pathologic as well as traumatic fractures (2). There is evidence that chronic treatment with enzyme-inducing antiepileptic drugs may reduce bone density through increased metabolism of vitamin D; however, at least one nonenzyme inducing antiepileptic drug, valproate, also may reduce bone density (3). It is clear that drug-induced reduction in bone density may have several mechanisms (4). One study suggested that reduction in bone mineral density may be observed within 1 year of treatment with phenytoin (5), but the temporal pattern of reduced bone density generally is not known.

In their cross-sectional study of bone mineral density among children with epilepsy, Sheth and colleagues found only a trend toward reduced bone mineral density in children treated for less than 1 year, but a statistically signifi-

cant reduction was seen after 1 year of treatment. The group of children treated for 6 or more years had the greatest reduction in bone mineral density and included two girls who had experienced pathological fractures. The authors investigated possible other contributing factors in reduced bone density. For instance, they calculated calcium intake, using a 3-day questionnaire, and found no effect on bone density. Similarly, growth metrics did not distinguish patients from controls. Based on activity logs, physical activity also was not different between the controls and children who had had epilepsy for less than 6 years but was reduced in children with epilepsy ≥ 6 years.

The study of Sheth and colleagues was not designed to assess the effect of specific antiepileptic medications on bone density, because the patients with the greatest reduction in bone density often were treated with more than one antiepileptic drug. Earlier studies implicated several of the old antiepileptic drugs in bone density reduction, but only limited information is available for the new antiepileptic drugs, which theoretically are expected to have less effect on bone density because they are less likely to induce liver enzymes. However, while preliminary data are favorable for lamotrigine (5,6), they do not suggest an advantage for oxcarbazepine over carbamazepine (7,8). Importantly, all of this emphasizes the need for studies to identify antiepileptic drugs that are not associated with reduction in bone density.

Sheth et al. point out that puberty and adolescence are periods of rapid growth and bone mineral density accrual, emphasizing that reduction in bone mineral density during this period of life could be particularly deleterious to bone health. Their hypothesis could be investigated by measuring bone density in patients with seizure onset before puberty and then comparing it with patients who have seizure onset after puberty. A recent study involving ambulatory patients with epilepsy showed greater reduction in bone density in adults than in children as well as different independent predictors of bone mineral density reduction between children and adults: polytherapy in the pediatric group and both duration of treatment and use of enzyme-inducing drugs in the adult group were the key factors (9).

As a result of the findings of Sheth and colleagues, patients with epilepsy treated for 1 year or longer should be considered for bone density assessment. Prophylactic supplementation with calcium and vitamin D is often recommended for individuals considered at risk of reduced bone density from antiepileptic drugs, without data to indicate that this supplementation will prevent osteopenia. One study demonstrated that vitamin D supplementation increased bone density after 1 year of treatment for ambulatory patients taking antiepileptic drugs (10). Children derived equal benefit from 400 IU and 2,000 IU per day, while adults only benefited from high-dose vitamin D (4,000 IU per day). Although calcium supplementation also is recommended, the recommendation is not evidence-based for individuals with epilepsy. A large multicenter study is urgently needed to guide the clinician in the prevention and treatment of osteopenia for patients with epilepsy.

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