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CASE REPORT

Severe early onset osteopenia and osteoporosis caused by antiepileptic drugs

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ABSTRACT

We describe two adult patients with epilepsy who received long-term antiepileptic drug therapy, a woman aged 39 years and a man aged 38 years, in whom severe osteopenia and osteoporosis, respectively, were diagnosed. Both had had epilepsy since childhood, both were seizure free and off medication for several years before the epilepsy started again. The female patient first sustained a complicated pelvis fracture after minor trauma. Next, both patients had infractions of several thoracic vertebrae after a generalised tonic-clonic seizure. Dual-energy X-ray absorptiometry for measurement of the bone mineral density revealed osteopenia in both. Bone biopsy was only performed in the male patient and showed moderate osteoporosis. Taking into consideration the young age for osteopenia and osteoporosis and the absence of other underlying causes, the long-term anticonvulsant therapy is the most likely cause of the development of osteopenia and osteoporosis in these patients.

Reviewing recent literature data, advice from healthcare organisations and medical guidelines, the authors were surprised by the lack of protocols and preventive measures for patients with epilepsy who have been on antiepileptic drug therapy for many years. With this article we stress the urgent need to develop protocols and guidelines for preventive interventions.

KEYWORDS

Antiepileptic drugs, epilepsy, osteopenia, osteoporosis

INTRODUCTION

Epilepsy is a chronic neurological disease with an estimated prevalence of five to seven patients per 1000 inhabitants in the Netherlands.[1] Seizures are successfully treated with antiepileptic drugs (AEDs) in about 70% of the patients. Usage of AEDs for 15 years is not uncommon, despite the fact that long-term AED therapy is a known risk factor for bone loss and fractures[2] and is associated with abnormalities in calcium metabolism, including hypocalcaemia, elevated levels of serum alkaline phosphatase and serum parathyroid hormone, reduced serum levels of biologically active vitamin D metabolites, radiological evidence of rickets and histological evidence of osteomalacia.[3-8] Patients aged >50 years and treated for ≥5 years with AED are estimated to have a doubled risk of osteoporotic fractures.[9] Of the female patients, 50% had a hip fracture unrelated to seizure activity.[10]

AEDs such as carbamazepine (CBZ), phenobarbital, and phenytoin accelerate hepatic microsomal metabolism of vitamin D to polar metabolites other than (25-OH) vitamin D (25-OHD) and increase the metabolism of 25-OHD into biologically inactive products.[11] Vitamin D and calcium play an essential role in diseases affecting bone metabolism. Hypovitaminosis D or hypocalcaemia can cause skeletal abnormalities, varying from osteopenia and osteoporosis to manifest osteomalacia.[12] Vitamin D deficiency is frequently cited as the cause of bone loss in patients with epilepsy.[2] Inadequate mineralisation of newly formed bone matrix as a consequence of this vitamin D deficiency can result in osteomalacia and rickets in adults and children, respectively.[10,13,14] Moreover, valproic acid (VPA) may have a direct effect on osteoblasts and osteoclasts resulting in an increased bone turnover and degradation.[15]

The first reports about negative effects of AEDs on bone metabolism were published in the 1960s to 1970s. In these reports particularly the first-generation AEDs, phenobarbital and phenytoin (both enzyme-inducing AEDs), were studied.[3,6,16] However, recent investigations show that the second-generation AEDs, CBZ and VPA, also have negative effects on bone metabolism.[2,8,10,15,17-19] Less is known about the latest or third-generation AEDs because they have not been on the market so long.
To illustrate these negative effects of long-term AED therapy on bone metabolism we describe two cases of adult patients with epilepsy since childhood and with an unexpected early onset osteopenia and osteoporosis after long-term (first- and second-generation) AED therapy. AED therapy was even interrupted for several years in both cases.

CASE REPORT 1

A 39-year-old Caucasian woman had suffered from epilepsy since childhood. The first generalised tonic-clonic seizure occurred at the age of 10 years. Several single- and multi-antiepileptic drug formulas were initiated with adequate consecutive serum drug levels. First-generation AEDs were replaced by second-generation AEDs because of increasing seizure frequency and/or side effects. Overall, the patient had been taking phenobarbital for nine years including six months in combination with ethosuximide, one year with VPA and two years with CBZ, VPA monotherapy for almost three years, oxcarbazepine monotherapy for eight years and lamotrigine monotherapy for three years. She had never taken phenytoin. For six years (from the age of 12 until 15 and from 25 to 28 years) she was seizure free without AEDs.
At the age of 5 and 7 years, the patient sustained a cruris fracture after trauma. She had never had any restriction in her mobility and was on a normal and varied diet with an average intake of dairy products. At the age of 35 years, she sustained a complicated pelvis fracture after a fall from a low chair. Physical and neurological examination revealed no other abnormalities. The patient weighed 72 kg with a length of 1.70 m (body mass index [BMI] 24.9 kg/m^2). She smoked ten cigarettes a day and had a moderate intake of alcohol. Her menstrual cycle was regular without any sign of premature ovarian failure. For several years she had lived in a country with a tropical climate and had had extensive sun exposure.
Laboratory examinations revealed normal values for serum calcium of 2.32 mmol/l, (25-OH) vitamin D 62 nmol/l and (1,25-(OH)$_2$) vitamin D$_3$ 48 pmol/l, thyroid-stimulating hormone (TSH) 2.38 mU/l, parathyroid hormone (PTH) 2.0 pmol/l and a 24-hour urine calcium excretion of 6.1 mmol. Kidney and liver function were normal.

Bone mineral density (BMD) measured with dual X-ray absorptiometry (DEXA) scanning is expressed in standard deviations from the average peak BMD in healthy young persons of the same gender (T-score) and from the mean BMD for persons of the same age and gender (Z-score).[10] Both scores represent fracture risk (*table 1*).

Table 1 *WHO criteria for defining bone density*[28]

Condition	Description
Normal	BMD value within 1.0 SD of the young adult reference mean (T ≥-1.0)
Ostepenia	BMD value of >1 SD below the young adult mean but <2.5 SD below this value (-1.0 >T >-2.5)
Osteoporosis	BMD value of ≥2.5 SD below the adult mean value (T ≤-2.5)
Established osteoporosis	BMD value of ≥2.5 SD below the adult mean value (T ≤-2.5) in the presence of one or more fragility fractures

WHO = World Health Organization; BMD = bone mineral density; SD = standard deviation.

DEXA scanning of the lumbar spine and of the femoral neck in the patient showed T-scores and Z-scores of -1.6 and -1.6 SD measured at the lumbar spine and -2.1 and -1.9 SD measured at the femoral neck, compatible with osteopenia.
After initial surgical treatment the patient was subsequently treated with both alendronine acid and calcitriol for one year, during which bone mass increased according to the altered T- and Z-scores which were -1.5 and -1.4 SD at the lumbar spine and -2.1 and -1.8 SD at the femoral neck. Since the patient wanted to become pregnant after recovery from the pelvic fractures, only the calcitriol was continued. After an uncomplicated pregnancy and delivery of a healthy girl, breast feeding was started and only calcitriol treatment has been continued until the present day.
At the age of 36 years the patient had a generalised tonic-clonic seizure. Postictally she complained of severe back pain. An X-ray of the spine revealed an infraction of two thoracic vertebrae in a still osteopenic skeleton.

CASE REPORT 2

A 38-year-old Caucasian male had suffered from epilepsy since childhood. The patient's history revealed no other diseases, nor bone fractures. He was on a varied diet and both body weight and body development have been normal. He had always refrained from smoking and alcoholic beverages and had practiced sports all his life.

He had his first seizure at the age of 7 years, several weeks after a paramyxovirus infection (measles). An EEG showed generalised epileptic paroxysms and AED treatment was started. Overall, the patient had been on phenobarbital for two years, phenytoin for nine years, CBZ for 12 years and VPA for seven years, in single or combined therapies. Standard doses of AEDs were used and drug levels had always been within therapeutic ranges. He was seizure free for a period of 24 years. During the last ten years of this period, he was not on any AEDs.

At the age of 31 years, the patient experienced severe back pain after a generalised tonic-clonic seizure. At physical examination, his body weight was 85 kg and length 1.90 m (BMI 23.5 kg/m^2). Except for pain over the thoracic and lumbar vertebrae no other abnormalities were found on physical and neurological examination.

Laboratory investigations revealed normal serum values for calcium of 2.33 mmol/l, phosphate 1.18 mmol/l, alkaline phosphatase 93 U/l, testosterone 21 nmol/l, TSH 0.43 mU/l, osteocalcine 3.2 μmol/l, (25-OH) and vitamin D 37 nmol/l. No Bence-Jones paraproteins were detectable in the urine. Urinary excretion of calcium and hydroxyproline were slightly elevated: 7 to 9 mmol/24 h (normal <5 mmol/24 h) and 0.31-0.33 mmol/24 h (normal 0.25 mmol/24 h), respectively. Hepatic and renal function were normal.

An EEG showed epileptic activity over the left temporal side. A CT scan of the brain was normal. X-rays of the thoracic and lumbar spine showed severe osteopenia and traumatic anterior flattening of vertebrae Th7 to Th10 with traumatic infractions.

BMD was measured with a DEXA scan: T-score -1.6 SD at the lumbar spine, T-score -1.3 SD at the femur neck, compatible with osteopenia. Bone biopsy showed moderate osteoporosis with slightly elevated bone turnover activity in the trabecular area.

Treatment with alendronine acid, a bisphosphonate, was started in addition to VPA. Two years after continuous alendronine acid treatment, a control DEXA scan showed an increase in the BMD of the lumbar spine with a T-score of -1.1 SD and at the femoral neck a T-score of -1.2 SD.

DISCUSSION

Both cases illustrate the negative effects of long-term AED therapy during childhood and adolescence on bone structure in adulthood. In both cases AED therapy was started in childhood. Both patients also had several years of seizure freedom in which they were off AED medication. The female subject was treated for nine years with first-generation AEDs during childhood and adolescence and for six years with second-generation AEDs. The male subject was treated for nine years with first-generation AEDs during childhood and adolescence and for 19.5 years with second-generation AEDs.

Other causes of osteopenia and osteoporosis could reasonably be excluded by the normal serum concentrations of calcium, vitamin D, presence of normal renal and hepatic function, absence of malabsorption or endocrine diseases and the otherwise normal physical development of the subjects.

The first cases of the association between bone disorders and AED therapy were reported around the 1960s to 1970s.[3,6,16] Prevalence varies between 4 to 70%, depending on the population studied.[3] The long-term negative effects of phenobarbital and phenytoin on bone structure are well known. Both AEDs are enzyme-inducing AEDs. They were used by our patients for several years during childhood. These enzyme-inducing AEDs accelerate hepatic microsomal metabolism of vitamin D to polar metabolites other than (25-OH) vitamin D (25-OHD) and increase the metabolism of 25-OHD into biologically inactive products resulting in decreased active ($1,25(OH)_2$) vitamin D_3 concentrations.[7,11,20] In contrast to other steroid hormones, vitamin D is not produced by an endocrine organ with a hormonal feedback mechanism. PTH can stimulate hydroxylation of vitamin D3, but it cannot stimulate the production of vitamin D3 by the skin. A ($1,25(OH)_2$) vitamin D_3 deficiency results in an increased bone turnover activity in the presence of a secondary hyperparathyroidism. Longstanding vitamin D deficiency causes a progressive defective mineralisation in the newly formed bone matrix eventually ending in rickets in children and osteomalacia in adults.[10,12-14]

Similar negative effects of the second-generation AEDs (CBZ and VPA) on bone metabolism have been reported.[8,10,15,18] CBZ is also an enzyme-inducing AED. In contrast, VPA is a nonenzyme-inducing AED and thus its negative effects on bone metabolism cannot be explained by the mixed function oxidase induction. Several mechanisms for the negative effects of VPA on bone metabolism have been proposed. First, both the nonenzyme-inducing and the enzyme-inducing AEDs may have direct effects on the balance of osteoblast and osteoclast activity.[15] Second, VPA could induce hormonal changes, as suggested from the association of VPA treatment and the development of a polycystic ovary syndrome.[21] However, a definite explanation for the association between VPA use and the decreased BMD remains undefined.[15] To date there are several new nonenzyme-inducing AEDs on the market, but long-term follow-up of possible side effects on bone mass is still lacking.[10]

It is possible that in our patients a combination of the above-mentioned mechanisms eventually caused a lower BMD, leading to osteopenia and osteoporosis. They had both been on multiple AEDs for many years. The normal

vitamin D level in both patients, who had a normal feeding pattern, is less compatible with the enzyme-induction mechanism. However, one cannot exclude this mechanism as a cause of the bone metabolism abnormalities because both patients took the enzyme-inducing AEDs during their childhood. At that age, laboratory investigations for vitamin D were not carried out. It is known that the BMD continues to increase until about the age of 30 years. After this age, BMD slowly decreases. It is not unlikely that long-term AED use by our patients during their childhood and adolescence caused a lower peak BMD during their 20s to 30s. Consequently, this could impose a greater risk of sustaining fractures throughout their lives and not only during the period in which they were taking AEDs. Moreover, they were still on AEDs with known negative effects on bone metabolism during young adulthood.

In a recent study in the USA, 62% of the children/ adolescent patients and 77% of the adult patients had low vitamin D levels and one third of the children and adults with epilepsy treated with various forms of AEDs had serum concentration of <10 ng/ml. Furthermore, the BMD of the lumbar spine, femur head, femoral neck and trochanter was significantly decreased in these adults for both the T- and Z-score, and 59% had osteopenia at either the spine or the hip.[8] No correlation was observed between the type of AED (enzyme-inducing vs nonenzyme-inducing) and 25-OHD levels. However, no data are available about the (1,25-$(OH)_2$) vitamin D_3 levels, the most potent natural hormone analogue.

Several DEXA studies confirm the observed decrease in BMD during AED therapy.[2,10,15,22] DEXA facilities are widely available, generate a minimal radiation load, and are suitable for follow-up studies. Unfortunately, with DEXA one cannot differentiate between a decrease in the amount of bone (osteoporosis) and improper mineralisation of bone matrix (osteomalacia). Both conditions can only be differentiated by histomorphometric analysis of a bone biopsy.[12]

In the Netherlands no data are available about the prevalence of osteopenia, osteoporosis and osteomalacia nor of the vitamin D status in patients with epilepsy. Probably more relevant are data on the AED effects on the clinical end parameters BMD and fractures. Although the relation between long-term AED therapy and negative effects on bone metabolism has been known for many years, it has neither led to the development of national guidelines for prevention nor to the development of protocols for surveillance and treatment in the Netherlands. Despite the presence of around 120,000 patients with epilepsy in the Netherlands, neither its Council of General Practitioners (NHG), nor the Dutch Health Council[23] seem to be aware of this particular group at risk for the development of skeletal abnormalities/ bone diseases. Moreover, to date the Dutch Osteoporosis Foundation and the Dutch League against Epilepsy have not yet focused their attention on the prevention of metabolic bone abnormalities as a result of long-term AED therapy.

Extrapolating from an informal poll at a recent meeting of the Dutch League against Epilepsy it is estimated that only less than 5% of the neurologists perform active screening for bone disorders/osteoporosis in patients on long-term AED therapy. In the USA one third of the neurologists screen their patients for bone disorders.[24]

In the Netherlands, the estimated fracture incidence is about 5 pro mille, which means that in one year at least 500 to 600 patients with epilepsy have a bone fracture of any kind. It is not unlikely that, in agreement with the Farhat data,[8] the incidence is outnumbered in patients using AEDs chronically. It is not known how many patients on long-term AEDs will eventually develop either osteopenia or osteoporosis and how long they should take this medication. No data are available about the long-term effects of vitamin D treatment in these patients. However, recent studies show that even one month of treatment with 150,000 IE (25-OH) vitamin D_3 results in a significant increase in bone mass.[25,26]

The annual costs of treatment with 1 dd 800 IE cholecalciferol and 1 dd gram calcium[4] are estimated at around € 200 and just around € 30 for vitamin D alone. The direct costs of a spontaneous fracture of a vertebrae or forearm fracture are estimated at around € 1000 per year, for a hip fracture the direct costs are around € 12,000,[27] not counting the secondary costs due to loss of working capacity. Therefore, development of guidelines for screening and treatment for metabolic bone disease in epileptic patients at high risk seems reasonable and cost effective. We conclude that osteopenia and later on osteoporosis as a result of long-term AED use is an underestimated problem in patients taking AEDs, which theoretically can be quite easily prevented or treated.

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