Osteomalacia should be sought and treated before withdrawal of anticonvulsant therapy in UK Asians

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Summary: Individuals from the Asian sub-continent in the United Kingdom are at particular risk of developing osteomalacia. We report a Gujarati woman who developed osteomalacia whilst taking anticonvulsant drugs; withdrawal of anticonvulsant therapy was followed by a seizure complicated by femoral neck fracture.

In patients with other risk factors for osteomalacia, as is the case for Asians living in Britain, anticonvulsant drugs should not be reduced or withdrawn until osteomalacia, which puts the skeleton at increased risk of fracture, and its associated hypocalcaemia, which reduces seizure threshold, have been sought and adequately treated.

Introduction

Osteomalacia is one of a number of complications that may develop during the long-term use of anticonvulsant drugs. The majority of such adverse effects, including osteomalacia, are benefitted by discontinuing the drugs. If, however, a seizure occurs shortly after anticonvulsant drugs are withdrawn in an individual with osteomalacia the skeleton is likely to be at considerable risk.

We describe a patient on anticonvulsant drugs in whom the diagnosis of osteomalacia was made and appropriate treatment given. Unfortunately, cessation of the anticonvulsant drugs was followed by a seizure which, because insufficient time had been allowed for the bones to heal, was associated with a fracture.

This case has implications for patients with major epilepsy in whom withdrawal of anticonvulsant therapy is being considered, particularly if there are other risk factors for the development of osteomalacia.

Case report

A 26 year old woman presented with a 2 year history of pain in the hips and lower back. Her symptoms seemed worse in the winter and she had started to limp. She had a past medical history of a single grand mal convolution at the age of 16 years and had been taking phenobarbitone 200 mg and phenytoin 100 mg (Garoin®) once a day ever since without further seizures.

She was born in Gujarat of Asian parents and came to England from Bombay at the age of 21 years. She ate a traditional Gujarati vegetarian diet except that she consumed dairy products, margarine and eggs.

Pelvic X-rays demonstrated Looser's zones in both femoral necks. Biochemical assessment revealed a serum calcium of 1.85 mmol/l and phosphate of 0.93 mmol/l with a normal albumin and mildly raised alkaline phosphatase (142 iU/l; normal <100). Plasma 25-OH vitamin D was 12 nmol/l (normal 25–100). Investigation of the gastrointestinal tract showed no evidence of malabsorption.

A diagnosis of anticonvulsant-related osteomalacia compounded by dietary and cultural factors was made. She was started on oral vitamin D₂ and at the same time the anticonvulsant drugs were discontinued. Four days later she suffered a grand mal convolution resulting in sub-capital fracture of the right femoral neck. Treatment by internal fixation resulted in healing of the fracture but the patient subsequently developed avascular necrosis of the femoral head (Figure 1).

Eleven years later, she presented with back and thigh pain and was found to have radiological and biochemical evidence of osteomalacia once again.

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It became apparent that despite continuing anticonvulsant drugs, she had discontinued prescribed oral vitamin D₂. On recommencing oral vitamin D₂ therapy her symptoms and biochemical abnormalities resolved. She is however left with shortening of the right leg and a limp.

Discussion

Epileptic individuals receiving anticonvulsant drugs have an increased risk of developing osteomalacia. For a given intake of vitamin D such individuals have lower plasma 25-OH vitamin D levels than normal controls. Hepatic metabolism of vitamin D appears to be disturbed by the induction of microsomal enzyme systems but other mechanisms, such as a direct effect of some anticonvulsant drugs on bone, may also be important. Nevertheless, rapid clinical, radiographic and histological healing usually occurs when vitamin D is given.

Osteomalacia in epileptics is multifactorial; the three major risk factors are multi-drug therapy, institutionalization and cultural factors which affect vitamin D intake and sunlight exposure. When several risk factors coexist the risk is presumably greater. In Great Britain there are around 1.27 million individuals (2.3% of the population) originating from the Indian subcontinent and epileptics from this group are at particular risk of developing anticonvulsant related osteomalacia.

In our patient, the fact that she took a traditional Gujarati diet and kept her arms and legs fully covered throughout the year undoubtedly contributed to her metabolic bone disease.

As she had been seizure-free for 10 years and a major complication of drug therapy had arisen it was considered appropriate both to discontinue anticonvulsant treatment and at the same time to start vitamin D therapy. In the light of subsequent events, however, it would have been advisable to have ensured adequate treatment of her metabolic bone disease before withdrawing the anticonvulsant drugs.

In individuals in whom a reduction or withdrawal of anticonvulsant therapy is being considered, especially in those originating from the Indian sub-continent, it is particularly important to consider and rule out this form, and indeed any other form, of metabolic bone disease. In practice this may not be easy since many patients on phenytoin, for example, have raised serum alkaline phosphatase levels. In such a patient the absence of a raised bone component in combination with a normal plasma calcium and phosphate would normally be sufficient to rule out significant osteomalacia.

It should be remembered that hypocalcaemia increases neuromuscular excitability so that individuals with unsuspected osteomalacia may actually be more likely than those with normal bones to have a seizure when anticonvulsant drugs are withdrawn.

Femoral neck fracture has been reported as a complication of hypocalcaemic seizures in an Asian woman, in whom hypocalcaemia was induced by lactation and earlier, in patients following parathyroidectomy. In our patient too, hypocalcaemia may have contributed to the seizure. Clearly, if the osteomalacia had been treated well before the drugs were discontinued there might not have been a seizure and fracture risk would have been negligible.

Where deficiency of vitamin D is suspected, repletion should be ensured before anticonvulsant drugs are stopped. Higher doses than usual of vitamin D may be required in these patients because of increased hepatic enzyme activity. A recent study showed healing of the bone, measured by return to normal of alkaline phosphatase activity, in 42% of children on anticonvulsant drugs after 6 months vitamin D treatment. Hence, it would seem reasonable to give therapeutic doses of vitamin D for at least 6 months to ensure adequate healing of bone. In individuals, such as our patient, with continuing risk factors, long-term vitamin D prophylaxis is indicated.

Because of the increased risk of seizure associated with anticonvulsant withdrawal, underlying metabolic bone disease should first be sought and

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Figure 1 Antero-posterior radiograph of pelvis 11 years after fracture showing necrosis of the right femoral head. New Looser's zones seen below the right lesser trochanter and in the pubic rami (arrowed) developed later when anticonvulsants were continued but prescribed vitamin D was not being taken.
identified in patients, especially those from the Indian sub-continent with additional risk factors for metabolic bone disease. Only when adequate treatment has been given should anticonvulsant drugs be withdrawn.

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References

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