Metabolic bone disorders in children with epilepsy

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Abstract

Epilepsy during childhood is the most frequent neurological disease and it is characterized by recurrent seizures influencing the everyday life of children. As a treatment, antiepileptic drugs (AEDs) affect the bone metabolism resulting in osteoporosis, osteomalacia, rickets, abnormal dentition and increased rate of fractures. Reduced bone mass density (BMD) has been found in the majority of children with epilepsy and a large proportion of these patients has osteoporosis. Furthermore, in many studies the BMD in the epileptic children is significantly lower than in the healthy one. Overall nutritional status affects the manifestation of seizures and the physiology of bone tissue. Especially the levels of vitamin D and calcium play a vital role in the expression of epilepsy related bone disease (ERBD) in children. In parallel, epileptic children should be adequately mobilized as less physical daily activity and inability to walk independently lead to decreased BMD levels which are the major cause of increased number of fractures. Close monitoring of BMD, nutritional status evaluation and prevention of ERBD is as crucial as treatment of epilepsy with antiepileptic drugs, in order to prevent the expression of fractures. Every specialty involved in the treatment of epileptic children must be aware of the consequences of epilepsy in bone tissue.

Introduction

Epilepsy

Epilepsy is a severe chronic disease, characterized by recurrent seizures and affecting the everyday life of many children as it is the most frequent neurological disease during the childhood [1]. In order to manage and treat this condition, children with epilepsy receive antiepileptic drugs (AEDs), which cause a plethora of behavioral and psychiatric problems. Particularly, AEDs affect the bone metabolism causing several bone deformities as short stature, rickets, osteomalacia, osteoporosis and abnormal dentition. AEDs are traditionally divided in two categories: a) AEDs which induce the cytochrome p450 enzyme in the liver (phenytoin, phenobarbitale, carvamazepine, primidone, sulthiame) and b) non inducing AEDs (valproic acid, lamotrigine, gabapentin, clonazepam, topiramate). Non cytochrome p450 inducing AEDs influence the bone metabolism through different ways in relation to traditional AEDs, and their interaction with bone metabolism constitute an interesting research field [2].

Reduced bone mass density (BMD) has been found in the majority of patients with epilepsy and also 25% of epileptic patients suffered from osteoporosis [3]. Furthermore, BMD of the epileptic children has been found to be significantly lower in comparison to the healthy children; consequently the diagnosis and treatment of this progress is of paramount importance. The levels of calcium and vitamin D seem to play a vital role in the pathophysiology of the epilepsy-induced osteoporosis. Moreover, the nutritional status of the epileptic children affects the manifestation of seizures and the bone metabolism, as malnutrition and ketogenic diet adversely affect the BMD. Furthermore, reduced mobility and weight bearing activities are a common problem which leads to decreased bone growth in epileptic children. It is essential that epileptic children are adequately mobilized in order to avoid the manifestation of the epilepsy-associated metabolic bone disorders.

During childhood, the 90% of predicted BMD is achieved so these years are crucial for proper development of the bone tissue [4]. Especially, the levels of essential nutrient factors as calcium, phosphate, and vitamin D are crucial for the normal bone growth. In particular, daily calcium intake during childhood must be at least 1300 mg per day which is achieved by the minority of children and adolescents. In parallel, vitamin D levels must be above 30 ng/ml, which is achieved by receiving about 600IU vitamin D for children and adolescents. Children and adolescent bone physiology differs from that of the adults due to the existence of growth plates which are essential for the development of bone. Bone growth plates can be directly negatively affected by AEDs especially valproate acid [5].

Pathophysiology of Epilepsy-Related Bone Disease (ERBD)

Role of AEDs

Epilepsy alters the bone metabolism especially by the influence of AEDs which react with the bone in many different ways according to which specific drug is prescribed in order to treat the epilepsy. AEDs negatively affect the bone physiology and especially BMD and subsequently calcium levels are reduced in epileptic children.

AEDs and BMD

As it is suggested by a recent meta-analysis, anticonvulsant treatment in children is associated with decreased BMD [6]. Similarly, in a recent study, BMD in pediatric epileptic patients has been found to be decreased by 9%. In particular, 5 patients, all boys, showed...
osteoopenia and especially BMD lower than -1.5 SD [7]. This finding indicates that male children are prone to develop osteopenia; however the exact mechanism is not clear yet. Another study by Coppola et al., which has the limitation that included children, adolescents and young adults, found abnormal BMD in 58% of the patients and furthermore 25% of them had osteoporosis and the rest 75% had osteopenia [3]. The same study indicated that the duration of treatment and the number of AEDs subscribed (monotherapy or polytherapy) were correlated with abnormal BMD to a greater extent. Moreover, other studies have indicated that polytherapy treatment for epilepsy in children is related to decreased BMD levels [8-10]. In parallel, a study by Yaghini et al. indicated that both cytochrome p450 inducing and non-inducing AEDs had caused a reduction of BMD although epileptic children without treatment had no decrease in BMD. In particular, this study suggests that patients under carbamazepine, phenobarbital, or primidone had lower Z-score compared to patients under valproate acid and also had reduced alkaline phosphate (ALP), which is a sign of secondary hyperparathyroidism as the responsible mechanism for ERBD [11]. Furthermore, changes in serum markers indicative of osteomalacia were found in about 50% of the epileptic children treated with the classic AEDs primidone, phenovarvital and phenytoin. Carbamazepine, despite being a cytochrome p450 inducer AED, has not been correlated to bone disease except a reduction of BMD in lumbar spine about 8% which was not statistically important [12].

Phenovarvital has been correlated with reduced BMD [13]. A study by Aggelopoulou et al. indicated that phenobarbital was related to lower levels of BMD in patients with Down syndrome, although these findings were based on adult patients and not in children [14]. Additionally, phenobarbital, carbamazepine, and also newer AEDs, especially valproate acid and lamotrigine, have been related to decreased levels of BMD in the lumbar spine of epileptic children [15]. According to another study by Babayigit et al., oxcarvazepine, carbamazepine and valproate acid have been related to reduced BMD in the lumbar spine of epileptic children which comes along with hypocalcemia, hypophosphatemia and reduced vitamin D levels [16]. Another study by Petty et al. compared the BMD in 21 epileptic children and concluded that carbamazepine, compared to valproate, lessen the BMD in L1-L4 in epileptic children [17].

A Polish study, which examined the BMD of epileptic children, the majority of whom were under valproate acid treatment, found not only reduced BMD in proximal femur and lumbar spine but also increased fracture risk, about 2 times more frequent in epileptic children [18]. Additionally, Sheth et al. mentioned that valproate treatment is associated with reduced BMD in lumbar spine and in distal and mid radius, suggesting that valproate acid may interact with insulin growth factor (IGF) which is a possible mechanism for decrease in BMD in epileptic children under valproate therapy [12]. Valproate acid has been suggested to reduce the bone turnover which leads to reduced BMD. Furthermore, the decrease in BMD was found to be presumably due to direct effects of AEDs on bone cells and not because of hyperparathyroidism, as the levels of PTH were normal. It is suggested that increased bone absorption may be the major cause of decrease on BMD as a patient ages and the duration of anticonvulsant treatment is more prolonged [7].

The combination of valproate acid and lamotrigine as a regime of epileptic treatment may be responsible for reduced BMD, short stature and bone formation as it is mentioned in a study by Guo et al. [19]. Also, Borusiak et al. correlated the valproate acid, oxcarbazepine, sulthiame treatment with reduced calcium, phosphate and PTH levels, although the patients under lamotrigine treatment had normal levels of calcium [20]. Additionally, a study by Lee et al. found that lamotrigine treatment didn’t affect BMD, vitamin D or calcium levels [5]. Treatment with lamotrigine is correlated with reduced BMD in children [13]. Furthermore, Coppola et al. found that the combination of valproate aid and lamotrigine is related to decreased BMD although these patients had decreased physical activity levels [3].

Tosun et al. suggested that phenytoin, carbamazepine and valproate acid are suspicious for altering the synthesis and metabolism of sex steroids which are essential for bone development and maintenance of adequate bone mass [10]. Additionally, phenytoin and phenobarbitale can cause vitamin K deficiency as vitamin K acts as a cofactor for the production of osteocalcin, matrix GI protein and protein S from osteoblasts, which are essential proteins for the bone production. Topiramate, a newer antiepileptic drug, has been associated with decreased levels of BMD [3,13], osteoporosis, hypocalcemia and increased bone turnover [5]. Finally, treatment with sulthiame, a carbonic anhydrase inhibitor, is associated with reduced calcium levels [20].

A meta-analysis from Zhang et al. suggested that the BMD in the lumbar spine of children receiving valproic acid was significantly decreased while there was no difference in the children under carbamazepine. On the other hand, in trochanter and femoral neck, the BMD was significantly decreased in both groups of epileptic children. Moreover, there was no difference in the levels of calcium and PTH between epileptic children and controls which comes partially in contradiction with the proposed mechanism of secondary hyperparathyroidism. Authors have concluded that there are still gaps to be filled with further studies as far as the impact of anitiepileptic treatment on the bone tissue is concerned although AEDs generally are associated with reduced BMD levels [9]. A recent review of 11 articles has come in conclusion that both carbamazepine and valproate acid negatively affect BMD. There are limited research data for oxcarvazepine, levetiracetam, phenytoin, phenovarvital, topiramate, with only one study for each drug, none of which found reduced BMD [21].

**AEDs and Vitamin D**

Vitamin D belongs to a group of fat-soluble secosteroid molecules which act as hormones and are essential for the metabolism of calcium, phosphate, magnesium. Particularly, vitamin D and especially its active form 25(OH)D3 calcitriol is responsible for the regulation of bone metabolism via the absorption of calcium and phosphate from the intestine. Inadequate levels of calcium and vitamin D lead to the softening of the bone and the impairment of bone mineralization. The final result is the manifestation of clinical osteomalacia [22], while vitamin D supplementation can increase the bone mineral content [23]. Vitamin D receptor contains two sites for ligand binding, the genomic pocket which is responsible for gene transcription and the alternative pocket which acts for direct rapid responses. Vitamin D receptor can interact with signal interaction pathways, like PKC or MAP kinase, and as a result the opening of calcium and chloride channels [24].

Vitamin D has been found to be significantly lower in children with newly diagnosed epilepsy rather than in healthy children. A study by Shu-Hao Wei et al. mentioned that 50% of epileptic children have reduced vitamin D levels [13]. A possible etiology for that phenomenon is a direct effect of vitamin D in the brain, especially by reducing the levels of calcium in the brain while increasing its levels in the blood. As a result, neuronal hyperexcitability and rate of seizures are reduced. Vitamin D may affect seizures by regulating the expression of genes which take part in the neurotransmission, like interleukin 6 or...
neurotrophin 3 and glial cell-derived neurotrophic factor. Moreover, vitamin D, as a neurosteroid, can directly interact with GABA-A receptors in the brain [25].

Anticonvulsant treatment has been associated with decreased levels of vitamin D [9]. A Korean study suggested that the children which have received anticonvulsants for at least two years have lower vitamin D levels in comparison with children that had received anticonvulsant treatment for less time. Sixty-five per cent of epileptic patients with vitamin D deficiency were diagnosed with either osteoporosis or osteopenia. So the duration of the anticonvulsant treatment is a major factor of the development of vitamin D deficiency which leads to epilepsy-related bone disease [26]. In children with epilepsy and cerebral palsy under anticonvulsant treatment, 75% of the patients have vitamin D deficiency [4]. Additionally, Weisman et al. found that children receiving either phenobarbitone or phenytoin had lower levels of vitamin D [27].

Children who receive cytochrome p450 inducing AEDs have hypocalcaemia due to the catabolism of vitamin D in the liver. Epileptic children under oxcarvamazepine treatment have decreased vitamin D levels and lower BMD, resulting in increased fracture risk [5]. A Korean study compared 143 epileptic children taking anticonvulsant treatment for at least one year and concluded that children under oxcarvamazepine had significantly lower 25(OH)D3 levels than these treated with valproate, which indicates the difference between an inducer and a non-inducer antiepileptic drug [26]. A study by Borusiak et al. indicated that anticonvulsant treatment, especially more often carvamazepine, is related with vitamin D deficiency [20]. Children under phenytoin or phenobarbitone have decreased 24,25-(OH)2D levels, although 25OH-D3 levels were normal. Reduced 24,25-(OH)2D levels may be a major step in the mechanism of epilepsy related osteomalacia and osteopenia [27]. Polytherapy for the treatment of epilepsy is combined with reduced vitamin D levels [10]. Topiramate can cause osteomalacia, renal calculi and osteoporosis through increased bone turnover and the hypocalcaemia. Additionally, topiramate and oxcarvamazepine may interact with the bone tissue not only through decreasing the vitamin D levels but also by altering the bone microstructure and the bone turnover rate [22].

Administration of valproate acid has been associated with vitamin D deficiency and osteomalacia. Valproate may interfere negatively with the nuclear pregnane X receptor (PXR) which promotes the expression of vitamin D [28]. The previous is supported also by the meta-analysis from Zhang et al. where also is proposed that both inducing the cytochrome p450 and non-inducing antiepileptic drugs are related with decreased vitamin D levels [9]. More specifically, Sonmez et al. mentioned that valproate acid may be responsible for causing hypovitaminosis D in children with epilepsy [25]. Also, a study by Lee et al. found that the epileptic children after one year of valproate treatment had reduced statural growth and lower body height compared to controls which was potentially due to the direct effect of valproate to the cell proliferation as the cell proliferation rate was significantly lower in patients under anticonvulsant treatment and controls, suggesting that calcium levels seem not to be directly affected by anticonvulsant treatment [5,32]. However, the decrease of calcium levels seems to be caused by decreased vitamin D levels due to limited sun exposure or limited prevention through food [5,7]. PTH and phosphate levels are significantly reduced vitamin D levels due to limited sun exposure or limited prevention through food [5,7]. PTH and phosphate levels are significantly reduced [23]. However, the meta-analysis by Zhang et al. has clarified that there was no difference in calcium, phosphate and PTH levels between children under anticonvulsant treatment and controls, except for the ALP elevated levels [9]. In parallel, Burusiak et al. found reduced calcium concentration in epileptic children under oxcarvamazepine therapy [20]. All these come in contradiction with studies that found no difference in calcium levels between epileptic children under anticonvulsant treatment and controls, suggesting that calcium levels seem to be directly affected by anticonvulsant treatment [5,32]. However, the decrease of calcium levels seems to be caused by decreased vitamin D levels due to limited sun exposure or limited prevention through food [5,7]. PTH and phosphate levels are significantly reduced in patients under anticonvulsant treatment [20] and valproate acid usage leads to resistance to PTH and inhibition of calcitonin secretion [33]. Additionally, increased ALP levels are an essential indicator for osteomalacia [16].

**AEDs and calcium, phosphate, PTH and ALP levels**

Traditionally it is believed that cytochrome p450 inducing anticonvulsant drugs can cause hypocalcaemia due to secondary hyperparathyroidism, a finding especially observed in adults [18,31]. A classic study by Christiansen et al. has found that hypocalcaemia and increased serum ALP levels was apparent in 20% of epileptic children [23]. However, the meta-analysis by Zhang et al. has clarified that there was no difference in calcium, phosphate and PTH levels between children under anticonvulsant treatment and controls, except for the ALP elevated levels [9]. In parallel, Burusiak et al. found reduced calcium concentration in epileptic children under oxcarvamazepine therapy [20]. All these come in contradiction with studies that found no difference in calcium levels between epileptic children under anticonvulsant treatment and controls, suggesting that calcium levels seem to be directly affected by anticonvulsant treatment [5,32]. However, the decrease of calcium levels seems to be caused by decreased vitamin D levels due to limited sun exposure or limited prevention through food [5,7]. PTH and phosphate levels are significantly reduced in patients under anticonvulsant treatment [20] and valproate acid usage leads to resistance to PTH and inhibition of calcitonin secretion [33]. Additionally, increased ALP levels are an essential indicator for osteomalacia [16].

**Nutrition and exercise**

Exercise and diet seem to play a vital role in the development and the expression of ERBD in children. Absence of daily calcium requirements can lead to decreased BMD. Daily calcium intake during childhood must be about 700 mg between 1-3 years, 1000 mg between 4-8 years, 1300 mg between 9-18 years of age [10].

**Role of ketogenic diet**

Ketogenic diet is a high fat, low carbohydrate and protein diet which are proven to lower the frequency of seizures in epileptic patients. Although the number of seizures is reduced with ketogenic diet, the bone mineral content (BMC) was decreased while children received...
supplementary vitamin D and calcium too. In particularly, acidosis is a potential mechanism through which the ketogenic diet leads to increased bone loss [34]. Moreover, the ketonic bodies are acidic and the acidic environment may decrease the BMC accumulation. In parallel, ketogenic diet has a negative effect on linear growth through acidosis and impairment of insulin growth factor 1 (IGF-1) which is essential for the regulation of bone size and bone mass density. It is proven that acidosis has anti-anabolic effect due to resistance to growth hormone and IGF-1 [35].

**Role of nutrition in children with refractory epilepsy**

Refractory epilepsy is a subcategory of epilepsy in which the patients do not respond to first and second-line anticonvulsant treatment. Especially, these children tend to suffer from feeding difficulties due to neurological impairment and also prolonged drug use, and the neurological impairment is the best predictor for their nutritional status. A study from Bertoli et al. found that 40% of children with refractory epilepsy were malnourished and in particularly they received less than 60% of daily calcium iron and zinc required [36].

**Role of exercise**

Exercise, mobility and the level of daily activities of epileptic children seem to play a major role in the ERBD pathogenesis. While bone formation is affected in epileptic children, weight bearing exercise is proven to increase BMD in normal children which can be a treatment measure which could diminish the effect of anticonvulsant treatment on BMD [7,37]. Moreover, children with diseases that coexist with epilepsy, as cerebral palsy, spina bifida and muscular dystrophy, tend to have reduced mobility weight bearing activities levels. Thereafter, these children tend to be in high risk for the development of osteoporosis [4].

The trabecular bone of epileptic children has increased resorptive activity and osteoporosis, perhaps due to reduced mobility and also increased levels of osteoid, indicative of osteomalacia [17]. In parallel, less physical daily activity, inability to walk independently and mental retardation lead to diminished levels of BMD, a sign that leads to the statement that decreased daily exercise and worse ambulatory status results to ERBD [3,7,13]. Furthermore, a study from Coppola et al. found that better ambulatory status was related to normal BMD levels and also non ambulatory status was related to abnormal BMD levels in children with epilepsy [3]. Non ambulatory children tend to have lower BMC compared to ambulatory children. Worst ambulatory status and increased bone mass index (BMI) is related with lower levels of vitamin D [31]. In parallel, the inadequate mobilization of many of the epileptic children has been seen to lead to a degree of osteoporosis due to immobilization [17]. As a result, the level of activity has been seen to be the main predictor of BMD [34].

**Comorbidities**

**Cerebral palsy and epilepsy related bone disease**

Cerebral palsy is a common disease of the central neuron which is usually combined with epilepsy and ERBD. According to a study by Tosun et al., all epileptic children with cerebral palsy, transported in a manual wheelchair, have lower BMD levels. Additionally, the same study indicated that inability to walk was related to lower BMD levels in children with epilepsy and cerebral palsy combined [10]. Also, cerebral palsy is accompanied more frequently with patients with decreased BMD rather than with patients with normal BMD. Furthermore, children with combined cerebral palsy and epilepsy are often staying indoors many hours per day, so they receive decreased levels of vitamin D from sun exposure which increase the risk of vitamin D deficiency. Also increased difficulty in feeding children with combined epilepsy and cerebral palsy contributes to reduced BMC levels [3]. Consequently, cerebral palsy is a comorbidity which when combined with epilepsy in children leads to increased frequency of ERBD. Management of these young patients is crucial in order to prevent the major complication of pediatric osteoporosis, such as fractures.

**ERBD and fractures**

Epilepsy is accompanied by raised frequency of falls resulting in increased rate of fractures [38]. Fracture risk is 2-3 times more often in epileptic children than in controls which become a major disability cause for these children [39]. In parallel, the number of seizures leads to increased seizure-induced injuries which frequently are greenstick fractures in children. Vertigo, dizziness and sedation associated with AEDs use may contribute to the increased frequency of fractures [4].

In contradiction with epileptic adults, where the majority of fractures are located in lumbar and thoracic spine, in children and adolescents most fractures are limited to upper and lower extremity and usually appear as greenstick fractures. In a Polish study, 81% of children under valproate acid treatment had a fracture. Epileptic children had significantly lower BMD than controls which is the major cause for the increase of fractures [18].

**Management of ERBD**

Prevention of ERBD is the most crucial step in the management of children with epilepsy. Children must be evaluated clinically and every fracture must be referred as it is essential for further treatment decisions and for the diagnosis of children’s osteoporosis. The lack of consensus between physicians for the treatment approach is dangerous and this gap must be filled with proper guideline instructions not only for the beginning of treatment but also for prevention and general recommendations.

DXA screening is an initial tool for the evaluation of BMD and bone metabolism which must be measured in every child under AED treatment. Especially measurement of spine, femur or even rib BMD can be very useful in the direction of diagnose of ERBD [3,11,17,40]. Annual measure of DXA can be suggested in severe cases and further studies can be organized in order to find which is the appropriate reevaluation time interval for DXA measurement in epileptic children. Moreover, the DXA machine should be equipped with a pediatric analysis software which should assess the age specific z-score for each epileptic child [33]. The specific z-score for the age of each epileptic child under risk of fractures must be evaluated and every child with z-score below -2 and history of undergoing a fracture should begin antiosteoporotic treatment. It is questionable whether children with z-score below -2 should receive antiosteoporotic treatment or not [4]. FRAX score could be potentially useful and especially it could be modified for epilepsy patients. Further studies could investigate its usage for fracture risk assessment and prediction [17].

Levels of nutrients like calcium, phosphorus, vitamin D must be calculated in order to begin early supplementation, especially with vitamin D and calcium. The screening of vitamin D levels is suggested by many authors and low dose vitamin D, 400IU, is currently often subscribed [25,41]. Furthermore, it has been suggested that every epileptic children under anticonvulsant drugs for 24 months or more should receive supplement of vitamin D and calcium [8,18]. Bone ALP isoenzyme can be important as a first screening test in order to distinguish which cases require further bone physiology evaluation.
Adequate sun exposure is also essential especially in countries where the sunlight is apparent many hours per day. Enrichment of milk and other foods with extra calcium and vitamin D can lead to higher levels of these nutrients. In parallel, anthropometric evaluation, especially body weight and body height assessment is essential for the adequate and early monitoring of body and bone metabolism and it should be the first step in the evaluation of every epileptic child. Furthermore, due to the fact that undernutrition has been found to be a major problem in epileptic children, a routine nutritional status evaluation can be useful for every epileptic child in the direction of correcting the levels of every essential nutrient [36]. Additionally, weight bearing exercises are proven to be beneficial for BMD levels and should be prescribed for every epileptic child, especially for those with mobilization difficulties [3]. Control of seizures is an important step for the prevention of falls which is the major cause of fractures. Furthermore, education of parents and physicians regarding fracture risk in epileptic children can lead to better compliance levels with anticonvulsant treatment. The use of bisphosphonates can be a useful measure which can reduce the number of osteoporotic fractures and also prevent the bone loss. In particularly, pamidronate intravenously has been found to be effective in the treatment of osteoporosis in ambulatory epileptic children [21].

Conclusively, every single physician who is involved in the treatment plan of epileptic children should be aware of osteoporosis, osteomalacia, and delayed bone growth related to epilepsy. It has been found that in the past the majority of pediatric neurologists did not consider the bone health issues of epileptic children [33]. ERBD is not a matter of a single specialty as it is a systematic multifactorial disease and many subspecialties as pediatric orthopedics, pediatric endocrinologists and pediatricians should be involved.

Conclusions

The epileptic children suffer from fractures or short stature and it is a real challenge for the physician, pediatrician, neurologist or orthopaedic surgeon, to manage and treat not only the epilepsy itself but the comorbidities like ERBD. Every physician must be sensitized with mobilization difficulties and oral alendronate have been used successfully in epileptic children [4].

Conflict of interest

Authors declare no conflict of interest

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