The effect of antiepileptic drugs in monotherapy on bone mineral density in children

Wpływ leków przeciwpadaczkowych stosowanych w monoterapii na mineralizację tkanki kostnej u dzieci

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ABSTRACT

Among many factors causing reduced bone mineralization, the chronic use of antiepileptic drugs (AEDs). May be one of them. **Aim.** The aim of the study was to asses the effect of carbmaazepine (CBZ), its derivative oxcarbazepine(OXC) and valproic acid (VPA) on bone mineral density (BMD) in children with epilepsy. **Materials and Methods.** The study comprised of 70 children (girls and boys) over five years of age who receivedlong-term AEDs therapy (longer than 2 years). Control group consisted of children without any pharmacologic treatment. Densitometry of the osseous system and the lumbar section of spine were done. **Results.** The group treated with carbamazepine and oxcarbazepine comprised 34 patients, treated with valproic acid 36 and the control group 42 patients. Reduction in BMD was found in 41.2% of CBZ/OXC-treated patients, 38.9% of patients who were receiving VPA, and in the control group 23.8% of respondents. Moreover, the reduced BMD was not significantly different in groups of treated children, but it is statistically higher compared with the control group. Analysis of the determinants of osteopenia and osteoporosis showed that statistically the reduced bone mineral density was often observed in children treated with long-term therapy and with a lower BMI. In addition, no relation to age, gender, developmental period and type of epilepsy has been established. **Conclusion.** 1. Carbamazepine, oxcarbazepine and valproic acid decrease at a comparable level the bone mineral density (BMD). 2. Reduction of bone mineral density occurs more frequently in children who received long-term AEDs therapy. 3. Densytometry examination is helpful in assessing adverse effects on long-term treatment of AEDs.

Key words: children, antiepileptic drugs, bone mineral density

STRESZCZENIE

Spośród wielu czynników przyczyną obniżonej mineralizacji kości może być przewlekłe stosowanie leków przeciwpadaczkowych (LPP). **Cel.** Badano wpływ karbamazepiny(CBZ) i jej pochodnej okskarbazepiny (OXC) oraz kwasu walproinowego (VPA) na mineralizację kości u dzieci z padaczką. **Materiał i metody**. Badaniem objęto 70 dzieci obojga płci, powyżej 5 r.ż., leczonych w monoterapii ponad 2 lata. Wykluczono dzieci niesprawne ruchowo, przewlekle chore, leczone dietetycznie, przyjmujące leki i suplementy wpływające na układ kostny. Grupę kontrolną stanowiły dzieci z wadami postawy oraz obserwowane w kierunku astmy przed włączeniem sterydów.Wykonywano densytometrię całego układu kostnego i dodatkowo odcinka lędźwiowego kręgosłupa. **Wyniki.** Grupa leczonych CBZ/0XC liczyła 34, VPA – 36, grupa kontrolna – 42. Grupy leczonych i kontrolna były porównywalne pod względem płci, wieku, aktywności fizycznej, BMI; u dzieci z padaczką nie stwierdzono istotnej statystycznie różnicy w odniesieniu do czasu trwania padaczki i jej rodzaju. Obniżenie mineralizacji kości stwierdzono u 41,2% leczonych CBZ, u 38,9% leczonych VPA, w grupie kontrolnej u 23,8% badanych. Częstość występowania obniżenia mineralizacji kości nie różniła się istotnie w grupach dzieci leczonych, ale była statystycznie wyższa w porównaniu z grupą kontrolną. Analiza czynników warunkujących osteopenię i osteoporozę wykazała,że statystycznie częściej obniżoną mineralizację tkanki kostnej wykazywały u dzieci dłużej leczone i z niższym wskaźnikiem BMI. Nie stwierdzono zależności od wieku, płci, okresu rozwojowego, rodzaju padaczki. **Wnioski**. 1. Karbamazepina oraz kwas walproinowy w porównywalnym stopniu obniżają mineralizację kości. 2. Obniżenie mineralizacji kości występuje częściej u dzieci leczonych dłużej LPP. 3. Densytometria jest badaniem pomocnym w ocenie objawów niepożądanych przy długotrwałym leczeniu LPP.

Słowa kluczowe: dzieci, leki przeciwpadaczkowe, mineralizacja kości

Osteoporosis is a disease of bone that leads to an increased risk of fracture. In osteoporosis the bone mineral density is reduced and bone micro architecture is disrupted. One of risk factors is antiepileptic drug treatment. Many studies in recent 40 years have shown a significant reduction in bone mineral density in patients treated with antiepileptic drugs.

The fracture risk in epileptic patients is 2-6 times greater than in others. It is caused both by the injuries during the epileptic attack and the treatment which deteriorates motor coordination and directly the bone mineral density. The aim of screening for osteopenia and osteoporosis is to identify the responsible antiepileptic drug and to identify the population in need of intervention i.e. diet modification, lifestyle change or a drug treatment to decline the risk of fracture and improve the quality of life.

AIM

The aim of the study was to asses the effect of carbamazepine (CBZ), its derivative oxcarbazepine(OXC) and valproic acid (VPA) on bone mineral density(BMD) in children with epilepsy.

PATIENTS AND METHODS

The study comprised 70 children (girls and boys) over five years of age who received long-term antiepileptic drug monotherapy (longer than 2 years) without any additional chronic disease and with moderate physical activity. The group treated with carbamazepine and oxcarbazepine comprised 34 children: 14 girls and 20 boys (age range 5,5-19 years, mean11,7). The group treated with VPA comprised 36 children: 18 girls and 18 boys (age range 6,2-19,8 years, mean 13,5). Control group consisted of 42 children with posture defects or asthma before the steroid treatment: 18 girls and 24 boys (age range 5–17,8 years, mean 11,8 years).

Densitometry of the osseous system and the lumbar section of spine was done using GE Lunar Prodigy USA densitometer.

Photo 1. Densitometer Ge Healthcare Lunar Prodigy Advance USA *Densytometr Ge Healthcare Lunar Prodigy Advance USA*

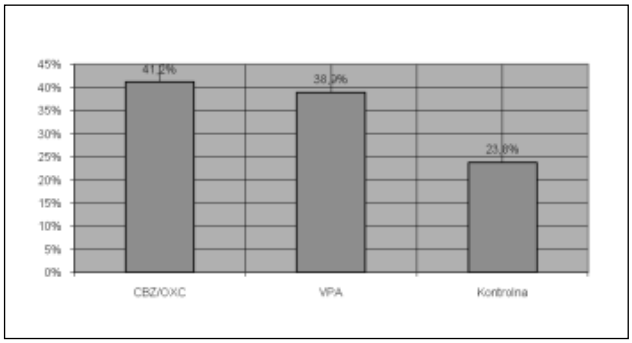
According to guidelines of International Society for Clinical Densitometry(ISCD) osteopenia was defined with z-score ≤ -1, osteoporosis (in children is recommended to use term "low age specific bone mass") with z-score≤2,0 in at least one from measured z-scores.

Statistical analysis was done with parametric tests t Student, Cochran-Cox, F Snedecor and nonparametric tests Shapiro-Wilk, Mann-Whitney.

RESULTS

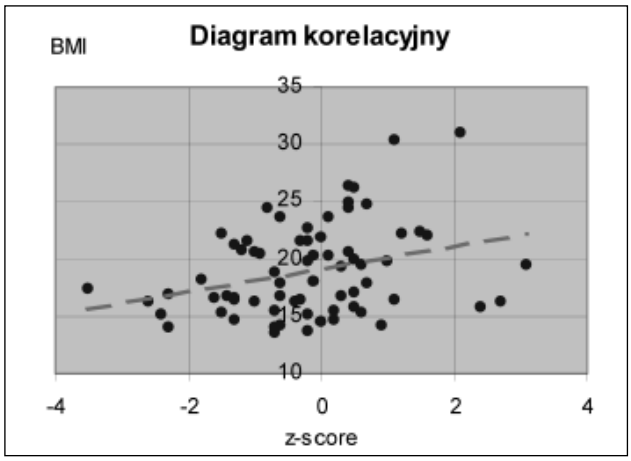
The study and control groups were comparable in terms of gender, developmental period, physical activity and BMI. In the epileptic children group the time of treatment and the type of epilepsy were comparable. Children treated with VPA were a little older than those treated with CBZ/OXC (13,5 vs 11,7). In the CBZ/OXC group osteopenia (z-score ≤ -1) was defined in 35,3%, osteoporosis (with z-score≤2,0) in 5,9% children. In VPA ostopenia was diagnosed in 30,6%, osteoporosis in 8,3% children. In control group osteopenia occurred in 19%, osteoporosis in 4,8% children. The statistical analysis has proved that bone mineralization disorders occur more frequently in children treated with antiepileptic drug. We did not find any significant differences between the VPA and CBZ/OXC groups.

Tab. I. *Częstość występowania osteopenii i osteoporozy w badanych grupach.* The incidence of osteopenia and osteoporosis in the treated groups



The incidence of the bone mineral deterioration is similar in both treated groups and is statistically lower comparing to control. We analyzed risk factors for osteopenia and osteoporosis in the treated groups. We divided treated population into 2 groups: with decreased and normal bone mineral density (BMD). We did not find any correlation between age, gender, developmental period and osteopenia or osteoporosis occurrence. All cases of osteoporosis were observed in children with cryptogenic and symptomatic epilepsy (Dandy-Walker syndrome, chromosomopathy, arachnoid cyst). Children with osteoporosis demonstrated normal motor activity, although not always directed (hyperactive children and with movement stereotypies). In the control group osteoporosis was diagnosed in 18-year old boy with a posture defect and back pain and 5-year old boy with asthma (not treated with steroids). Children with decreased BMD were treated longer with antiepileptic drug (4,5 vs 3,9 p=0.07) and had lower BMI (17,5 vs 19,5 in Cochrane-Cox test p=0.006).

Tab. II. Relationship between BMI and bone mineral density (z-score) in children with epilepsy *Diagram korelacyjny*



DISCUSSION

Epilepsy is a frequent, chronic neurological illness. It occurs especially often in children and older people, 1% of them takes drugs for many years. Antiepileptic drugs (AED) are used to treat also migraine, idiopathic tremor, psychiatric disorders and neuropathic pain [3]. Childhood and adolescence are a critical periods for bone mineralization [4]. In healthy people the mineralization process progressed gradually up to end in the third decade of life. Chronic diseases (urinary tract, gastroenterological, endocrinological and metabolic disorders i.e. homocystynuria) restrictive diet (i.e. ketogenic) may disturb vitamin D, calcium and phosphates homeostasis and influence on osteoclasts and osteoblasts balance in bone matrix, decrease bone mineralization, consequently increasing the fracture risk [5].

The fracture risk in epileptic patients is 2-6 times higher than in general population [6,7]. 25% of epileptic children older than 10 years is suffering from bone fractures, which is caused by injuries frequently occurring during epileptic seizures and the treatment which decreases the movement coordination and could directly influence the osseous system decreasing bone mineralization [2]. Spine fractures in non treated osteoporosis cause spine deformation, posture defects and short-stature.

The adverse effects of antiepileptic drugs (AEDS) on bone health were first reported nearly forty years ago. In the old handbooks osteopathy was described only "in institutionalized handicapped children and adolescents with drug resistant epilepsy treated with high doses of antiepileptic drugs". In 2007 we could read about etiology and clinical implications of "epileptic osteopathy" [1]. Main factors influencing the bone mineralization in epileptic children are: unbalanced diet, vitamin D deficiency, low physical activity, geographic factors and antiepileptic drug therapy [6,8]. The impact AEDs on bone system is not sufficiently investigated [1,2,4,9].

AEDs inducing function CYP 450 (CBZ, PHT) decrease 25(OH)D and increase bone turnover [3,10]. Consecutive studies have proved that VPA, an enzyme inhibitor, increases the risk of osteopenia, osteoporosis and bone fractures [5,7,11,12,13].

Some authors undermine these results [3,14-18]. In our opinion the controversies could result from differences in densitometry methodology. In the first studies only distant parts of bone system were evaluated, z-score was not analyzed and the patient groups were small. Current recommendation is the whole body and lumbar spine densitometry [5].

In our study we analyzed the impact of CBZ/OXC or VPA treatment on bone mineral density. Because of the identical effect of carbamazepine and oxcarbazepine on calcium-phosphate balance, the children treated with this drugs were included in one group. The study and control groups were comparable in terms of gender, age, developmental period and BMI. In AED treatment group we found more osteopenia and osteoporosis (CBZ/OXC 41,2%, VPA 38,9%, control group 23,8%).

Similar results were reported by other authors. Kumandas et al [19] analyzed 33 children in pre pubertal period treated with CBZ in monotherapy for at least 2 years. They found the decrease in L1-L4 bone mineral density and 25(OH)D in blood. Babaygit et al [14] observed decrease in bone mineral density in 68 children treated with valproic acid, carbamazepine and oxcarbazepine in relation to control group.

Cansu et al [20] did not found any significant change in bone mineral density in new diagnosed idiopathic epilepsy in children after 18-month oxcarbazepine treatment. Three cases of osteoporosis after the 18-month treatment were related to osteopenia before treatment.

Studies analyzing the influence of antiepileptic drugs on bone mineral density after shorter duration of treatment (6-12 month) reported small or no effect of AEDs on the bone mineral density. Vurucu et al [21] did not find any effect of oxcarbazepine on bone mineralization patients treated for six months. Bostancioglou et al. [8] studied bone mineralization in 61 epileptic children before and after one year of treatment with VPA. They found 2 cases of osteoporosis (z-score<2). In authors opinion the biochemical markers: 25(OH)D, calcium, phosphates, alkali phosphatase, calcitonin, parathormon are not sufficient indicators of bone health as the densitometry should be done.

Ecevit et al. [23] proved the decrease in bone mineralization in proximal part of femur in one-third of children treated with VPA for at least 6 months.

Oner et al. [24] found in 33 idiopahtic epilepsy children treated with VPA over 6 months the decrease in z-score BMD in lumbar spine (-0.36 vs 0.21 in control p=0.04). In this study 7 children with osteopenia were treated longer and took higher doses than other children.

Similar observations were made by Verrotti [25] after analyzing 20 boys with idiopathic epilepsy treated with VPA in the pubertal period.

Ecevit et al.[23] did not find any influence of CBZ treatment on bone mineralization (the distal parts of the osseous system were evaluated, z-score was not calculated) in 17 children with idiopathic epilepsy treated longer than 6 months.

Tegkul et al. [16] found osteopenia (z-score<1.5) after the 2 -year antiepileptic drugs treatment only in 6,7% chil-

dren (the study group comprised 30 children: 15 treated with valproic acid, 11 with carbamazepine, 4 with barbiturates). The decrease in bone mineralization occurred in 1 child treated with carbamazepine and in 1 child treated with barbiturates. Limitation of this study is the lack of control group and the small number of the studied population.

Rieger-Wettengl et al. did not find any influence of the valproic acid or carbamazepine treatment on children's bone mineral density. Thirty nine children with idiopathic epilepsy treated over 1 year undergone radius bone densitometry. In comparison to control, the bone turnover was more intensive, but no important changes in BMD were found.

In our study we compared children treated with AEDs with osteopenia and osteoporosis to those treated with AEDs with normal bone mineral density. In adults receiving AEDs therapy BMD decline was associated with age and gender. In women, increasing age was significantly associated with an abnormal BMD[26].In our study children with epilepsy have lower BMD for both females and males compared to controls. Similar observations were made by Sheth after analyzing 82 children receiving AEDs therapy [27].

It has been established that the time of the treatment decreases BMD. This conclusion corresponds with other reports [4,15,26,27]. Although Fuleihan et al.[28] observed only in adults a positive correlation between the treatment time and the decrease of bone mineral density. In our study children without bone mineralization disorders had higher BMI. The children with osteopenia or osteoporosis had significantly lower BMI. Sayo et al. reports that the body mass increase could protect bone mineralization [29]. According to studies conducted on adults, the obesity does not protect from osteoporosis. Low body mass predestinates to osteoporosis [30]. Similar result were obtained by Coppola et al. [4] after analysing 96 children with idiopathic and symptomatic epilepsy. The positive correlation between the BMI increase and the BMD decrease was found in the group of 92 Chinese epileptic children [31]. Sheth et al. [27] did not find any correlation between BMI and BMD.

Considering many controversies regarding the influence of AEDs on BMD we need more multicenter studies on lager groups of children to find correlations between antiepileptic drugs and bone mineralization.

CONCLUSIONS

1. Carbamazepine,oxcarbazepine and valproic acid decrease at a comparable level the bone mineral density.
2. Reduction of bone mineral density occurs more frequently in children who received
3. long-term AEDs therapy.
4. Densytometry examination is helpful in assessing the adverse effects on long-term treatment of AEDs.

Reference books for epileptic patients should contain diet indications [diet rich in dairy products, magnesium – cacao, chocolate, with limited supply of phosphates and natrium – coca-cola, table salt] and life style indications. It is necessary to provide prophylaxis and information to prevent osteopenia and osteoporosis, to decline fracture-risk and improve the quality of life long-term treated epileptic children.

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