CHAPTER II

Clinical influence of epilepsy and antiepileptic treatment on metabolic disorders

Zaburzenia metaboliczne związane z padaczką oraz stosowaniem leków przeciwpadaczkowych

Key words: epilepsy, antiepileptics, stress, thyroid hormones, weight, bone disorders, lipid abnormalities

Epilepsy is a complicated condition that may affect different areas of human life. Epileptic seizures change the endocrine environment mainly through the action on the hypothalamic-pituitary axis. Many hormones, including gonadal and adrenal steroids as well as thyroid hormones affect the excitability of neurons of the cerebral cortex and consequently they alter the threshold for seizures. Epilepsy and seizures have effects on thyroid and adrenal hormones which mainly exert potent metabolic activity, but they also affect the central nervous system, in turn altering seizures and epilepsy. Treatment of epilepsy with antiepileptic drugs alters metabolism of steroid hormones and in this way it may influence on the balance of water and electrolytes and on bone mineralization processes or it may change the body mass.
THYROID DISORDERS

Thyroid hormones can lower seizure threshold. Primary hypothyroidism is characterized by the combination of low levels of thyroid hormone and high levels of thyroid-stimulating hormone (TSH). Decreased TSH, in the course of organic disease or dysregulation of the pituitary gland, causes secondary hypothyroidism. The therapeutic administration of thyroxine in patients with hypothyroidism might constitute the risk for thyrotoxicosis. As a consequence this might induce generalized epileptic fits, both discrete non-convulsive (absence) and heavy generalized tonic-clonic seizures even in non-epileptic individuals. In epileptic patients this supplementary treatment with thyroxine may exacerbate preexisting partial and generalized epilepsy. The incidence of seizures in hypothyroidism is as high as 20% of patients (1). Hyperthyroidism or excess thyroxine can also trigger seizures in non-epileptics and may exacerbate the course of preexisting epilepsy. Seizures associated with thyrotoxicosis have been considered in 9% of patients. Though epilepsy associated with thyrotoxicosis must be considered among the causes of adult-onset epileptic disorders. Patients with hyperthyroidism complain from both partial and generalized epileptic fits (2). Antiepileptic therapy for these seizures is only interventional in the acute state. Chronic antiepileptic treatment is not necessary and helpful because this kind of seizures is not successfully controlled with antiepileptic drugs. The basic therapy consists of the proper correction of thyrotoxicosis to the euthyroid state. Additionally, antiepileptic drugs may decrease the levels of thyroid hormones. Enzyme-inducing older antiepileptics such as cabamazepine, phenytoin and phenobarbital affect thyroid function secondary, by decreasing concentrations of thyroid hormones in blood. These drugs are responsible for increasing the glucuronide metabolism of the thyroid hormones (3). It has been demonstrated in patients with epilepsy treated with carbamazepine, oxcarbazepine or valproic acid, that just valproate not affected thyroid function (55). Lowered thyroid function has been normalized after discontinuation of therapy with carbamazepine or oxcarbazepine (54). Among newer AEDs also oxcarbazepine and lamotrigine are inducers of glucuronidation of thyroxine although both drugs may induce metabolism to a lesser degree than the older ones. The other new AEDs seems to be similar to valproates in their lack of affect on thyroid functions (4). Stress related hormones. Seizures are stressful events which may initiate the release of several hormones. It has been shown that levels of stress hormones also are increased with seizures. Adrenal hormones possess neuroactive potential and can influence neuronal excitability in the brain. Stress produces an increase in circulating and brain concentration of corticosteroids, mostly cortisol and deoxycorticosterone. Although cortisol increases brain excitability, deoxycorticosterone and its tetrahydro-derivative (THDOC) are agonists in type-A receptors for gamma-aminobutyric acid (GABA), that is the main inhibitory neurotransmitter in the brain. Glucocorticoids bind with intracellular steroid receptors and activate them leading to protein synthesis. Many neuroactive effects of steroids are mediated by other mechanisms, at the level of neuronal membrane. Direct interaction of the steroid hormones with their receptors on the plasma membrane may account for their rapid effects. Diverse effects of steroid hormones family are exerted at the
GABA-A and glutamate receptors. Also adrenal deoxycorticosterone exerts its immediate effects on neuronal excitability. It influences gamma-aminobutyric acid-mediated neuronal inhibition by activation of gamma aminobutyric acid receptors-type A and probably has opposing effect on glutamate-mediated excitation at the cell membrane (5). Response to stress is mediated by the hypothalamic-pituitary-adrenal (HPA) axis. Corticotropin-releasing hormone (CRH) neurons in hypothalamus release CRH which further stimulates the pituitary gland to release corticotrophin hormone (ACTH). In humans ACTH triggers the release of cortisol from the adrenal cortex, which binds and activates the steroid hormone receptors. The negative feedback of glucocorticoids is a mechanism regulating the HPA axis. It is also regulated by input from numerous brain regions (mainly cortex and limbic system) and neurotransmitter systems which influence CRH neurons, either directly and indirectly. Ultimately, the control of CRH neurons and HPA axis is regulated by gabaergic inhibition (5). Epilepsy is associated with a dysregulation in the control of the HPA axis. Stress and the HPA axis play a critical role in the pathophysiology of epilepsy. Basic researches have demonstrated that acute stress can be anticonvulsant, whereas chronic stress trigger proconvulsant mechanisms in brain (6). The first effect is thought to be mediated by the neurosteroid allotetrahydrodeoxyorticosterone (THDOC)-an agonist on GABA-A receptors, which potentiate gabaergic inhibition. During chronic stress not only alterations in gabaergic synaptic inhibition have been stated but also decrease in brain production and concentrations of neurosteroids (6). Deficits in neurosteroids following chronic stress may contribute to decreased gabaergic inhibition, which finally results in an increased seizure susceptibility. Patients with epilepsy identify many factors precipitating seizures; the most common factors reported are stressful life events as well as feeling stressed prior to seizure, which is noted in 30-60% of them (7). Individuals with epilepsy also report that stress exacerbates their seizures. Stressful events were found to increase seizures frequency in about 60% patients as well as they were responsible for de novo incidence of seizures in the general population (7). Characteristic pathological EEG changes were observed in 70-90 % patients with epilepsy subjected to the stressful stimuli, while no changes were noted in healthy individuals. Basal levels of stress hormones are elevated in patients with epilepsy; plasma cortisol levels are higher as compared to patients without epilepsy. Cortisol content in blood is further significantly increased after generalized tonic-clonic seizures in patients during the postictal period. Periods of greater seizure frequency are also associated with increased cortisol levels in patients with epilepsy (8). These changes may respond to stress reaction associated with epileptic fit. Simultaneously, in chronic epileptic patients, treated with AEDs cortisol levels were lower in comparison with non-treated and healthy individuals, suggesting influence of treatment on adrenal function. Patients with epilepsy also exhibit increased circulating levels of ACTH and corticosterone, both with the anticonvulsant potential (5). ACTH levels may be lowered in patients with epilepsy treated with AEDs, specially in severe and long lasting disease, suggesting dysfunction of the adrenocortical axis. Synthetic neurosteroid ganaxolone, a modulator of GABA-A receptors has been clinically tested in the treatment of partial seizures and in an infantile spasm (9). It is hypothesized that this well-known
epilepsy of early childhood, the West syndrome (infantile spasm) is related to the presence of abundant receptors for corticotrophin releasing hormone (CRH) in the brain. Abnormal brain’s response to elevation of CRH during stress triggers epileptic fits. Suppression of CRH release by administration of adrenocorticotropic hormone (ACTH) exerts therapeutic effects in infants with West syndrome (10).

**EFFECTS ON LIPIDS AND OTHER METABOLIC RISK FACTORS FOR CARDIOVASCULAR DISEASE**

Elevated total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels, and reduced high density lipoprotein cholesterol (HDL-C) levels are linked to the development of coronary artery disease. C-reactive protein (CRP) also has been found to be correlated with risk of vascular disease. Lipoprotein A is another independent risk factor for cardiovascular disease. The amino acid homocysteine possesses prothrombotic activity and is mainly considered as a risk factor for cardiovascular mortality and stroke but also it is linked with dementia and seizures. The microsomal CYP450 system is involved in the synthesis and metabolism of cholesterol and enzyme-inducing AEDs would be expected to increase cholesterol production. The modest increase in HDL-C levels were measured in patients with epilepsy in the course of treatment with older AEDs: phenytoin, phenobarbital or carbamazepine, which might suggest their positive, protective cardiovascular effect. However therapy with the mentioned drugs was also connected with an increase in TC and LDL-C levels, which in turn might suggest an increased risk for atherosclerosis-related disease (11). The hepatic enzyme-inducing properties of these drugs might be responsible, as elevated HDL-C levels have been correlated with hepatic microsomal CYP450 content and activity in the course of treatment (11). Inducing AEDs also may increase the levels of lipoprotein A and homocysteine. Of the first generation AEDs only non-inducing valproate did not increase HDL-C, and furthermore decreased TC and LDL-C levels. Apolipoprotein A-1 levels in patients treated with valproate were lowered (12). Clinical studies indicate that the effect of enzyme inducing AEDs on lipid fractions may promote atheromatic process and risk for vascular diseases, while valproate with its enzyme inhibiting properties exerts the opposite effects. Epidemiological studies have also demonstrated that morbidity and mortality due to atherosclerosis-related heart disease is higher among patients with epilepsy who are treated with AEDs (13). Contemporary imaging studies also confirm increased risk of cardiovascular diseases in epileptic patients treated with older AEDs. It was demonstrated that intima-media thickness of the carotid artery (a marker of vascular disease) was greater in patients with epilepsy, especially if they were treated with inducing AEDs (14). This confirms the thesis that atherosclerosis is more common in treated individuals with epilepsy. It is supposed that the effects of newer AEDs with non or decreased induction of hepatic enzymes could be more advantageous. In patients with epilepsy in whose treatment was changed from old to new drugs, such as lamotrygine or levetiracetam, a decline in total cholesterol, LDL as well as CRP and lipoprotein A was demonstrated (15). Newer AEDs seem to be better choice for treatment epilepsy in elderly.
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INFLUENCE ON BODY WEIGHT

Proportionally to general population, people with epilepsy also have an increased rate of obesity. This may be related to a high prevalence of depression, physical inactivity, unhealthy diet, buy also antiepileptic pharmacotherapy. Numerous clinical data quantified the risk of weight changes with chronic use of AEDs, not only increase but also decrease. These observations allow to divide AEDs into three groups. Drugs that increase body weight are: valproate, carbamazepine, vigabatrin, gabapentin and pregabalin. Weight loss in connected with topiramate, felbamate and zonisamide and is also dose related for the first two drugs. The group of weight neutral AEDs includes: phenytoin, oxcarbazepine, lamotrigine, levetiracetam and tiagabin (16). Weight gain was reported in up to 71% individuals with valproates and ranged between 4-49 kg within 3-24 months of use. It was also reported in up to 25% patients treated with carbamazepine, in 15-20% treated with gabapentin and in 14% individuals receiving pregabalin (with 7% increase of initial body weight). Weight gain has been found to be dose related for these drugs. Weight loss was observed in 10-20% patients treated with topiramate and ranged between 4-11 kg within 3-12 months of use, with further continuation (17). The mechanisms for weight changes associated with some AEDs is not fully elucidated. The metabolic and endocrinologic influence of AEDS on peripheral and central processes which regulate glucose metabolism, food intake and energy utilization are taken into account. The processes of glucose metabolism and energy balance are regulated peripherally in liver, pancreas and adipose tissue and centrally with the involvement of the hypothalamic-pituitary-adrenal cortex with the complex engagement of multiple neuropeptides and hormones. The main hormones which act on adiposity signals are insulin and leptin. Leptin is secreted from adipose tissue and increased fatty acid metabolism. Insulin is critical for glucose metabolism but also participates in lipid metabolism and stimulates synthesis of cholesterol, fatty acid triglyceride. Insulin and leptin interact with their receptors located both peripherally and in many brain areas, which initiates the reaction of glucose metabolism and energy storage. Among the causes effects of AEDs on appetite and their pharmacokinetic properties can have significance (18). Clinically the most important is valproate-induced body gain as the most frequent and cumulative over the course of many years treatment. It is also a risk factor for fatty liver disease, which occurs in 61% of patients and for polycystic ovary syndrome (17). Weight gain may occur both in adolescent and adult patients and regardless of gender, and may be seen relatively early within 1-2 months. The mechanisms are multiple and uncertain, however reduced energy expenditure and hyperinsulinemia can play a significant role. Valproate did not directly act on adipocytes but competes with free fatty acids for albumin binding, as a fatty acid derivative. It may be also involved in insulin secretion from pancreas, resulting in hyperinsulinemia with insulin-resistance. This effect is connected with its activity as gabaergic agonist (19). In obese patients treated with valproate elevated levels or cortisol and leptin (as well as normal content) were observed. The frequency and levels of carbamazepine-associated weight gain appears to be less, as it was observed in one fifth to one third of patients, with a gain greater than 5 kg
only in 8% of individuals. Among the AEDs that affect the weight loss, widely used drug is topiramate. It was estimated that as much as 86% of patients treated with topiramate had distinct loss weight after 12 months of therapy. The degree of reduction was related to the initial body mass. In obese patients, a mean weight loss between from 4 kg to 11 kg was seen at three months and one year, respectively. It meant 12% reduction of their body weight in comparison to 5% in non-obese. Reduction of body mass was connected with an improvement in blood lipid profile and glucose tolerance test, reduced glucose and leptin levels in blood. Reduction in body weight has been sustained over time (20).

**BONE EFFECTS OF ANTIËPLEPTIC DRUG THERAPY**

AEDs have been implicated as a cause of bone disease for many years. This problem has a growing importance because today AEDs are also widely used in psychiatry, in treatment of pain or prophylaxis of headaches. Long term use of AEDs is associated with disturbed bone metabolism, finally resulting in decreased bone mineral density (BMD) and an increased risk of fractures. Prevalence rates of 50% have been reported for AED-induced skeletal disorders (21). These disorder range from subclinical disease to the full blown clinical syndromes such as abnormal statural growth and dentation, rickets or osteomalacia in young patients as well as osteopenia, osteoporosis and fractures, which is the most severe skeletal consequence in adults. As much as 75% of epilepsy patients treated with AEDs have been found to be osteopenic and 25% osteoporotic, while reduced BMD is the most clinically relevant predictor of fractures (22). Twofold increased risk of fractures (mainly vertebral compression and femoral and hip fractures) in patients with epilepsy is not only secondary to seizure activity (risk for falls and traumas with seizures), and coexisting neurological deficits (e.g. cerebral palsy) but also to AEDs side-effects (dizziness, ataxia) with the most essential influence of these drugs on bone health (23). Several mechanisms have been proposed for the skeletal effects of AEDs therapy. As the drugs most consistently associated with skeletal abnormalities are those that affect the cytochrome P450 system, the main mechanism was that enzyme-inducing AEDs (and particularly phenytoin) influenced negatively on vitamin D homeostasis. Vitamin D deficiency has been attributed to accelerated active vitamin D catabolism to inactive hydroxylated metabolites, thereby resulting in relative hypocalcemia, secondary hyperparathyroidism, increased bone turnover to restore calcium concentrations, and higher rates of bone loss. Decreased bone mineral density was observed mainly in patients with epilepsy receiving enzyme-inducing AEDs phenytoin, phenobarbital and carbamazepine, in whose markers relevant to bone health were also distinctly disturbed (hypocalcemia, hypophosphatemia, decreased active vitamin D in serum and increased alkaline phosphate and parathyroid hormone were found)(24).

This is not the only mechanisms because bone loss in treated with AEDs might occur despite normal serum levels of vitamin D. Direct drugs-effect on bone osteoblast cell function, reduced intestinal absorption of calcium, resistance to parathyroid and other mechanisms were considered (25). Valproate, which is not an enzyme
inducer, but a CY 450 inhibitor has also been shown to have an adverse effect on bone health, resulting in decreased BMD (24). There is limited clinical information whether newer AEDs influence bone metabolism. Neither lamotrigine in woman nor oxcarbamazepine have been found to interfere with bone metabolism. However the latest observation suggested that oxcarbazepine, which is a weak CYP450 inducer, might decrease 25-hydroxy-vitamin D levels simultaneously with and increased bone turnover but without influence on the bone mineral density (26). Topiramate, a drug influencing metabolic processes have been suspected to affect bone health; however preliminary study with topiramate did not indicate changes in bone turnover (27). Subclinical bone disease is characterized by such biochemical abnormalities as decreased serum calcium, and 25-hydroxyvitamin D levels and elevated serum parathyroid hormone levels as well as reduced bone density. Subtle effects of AEDs can occur early in therapy. Clinically evident skeletal disorders are associated with long-term use of AEDs as well as probable coexistence of such risk factors as inadequate physical activity, infrequent sunlight exposure and poor intake of calcium and vitamin D (25). Much of the bone pathology caused by AED therapy can be treated or prevented by administration of calcium and vitamin D. A daily supplement of calcium and vitamin D was found to reverse biochemical abnormalities and restore bone mass in individuals treated with AEDs. Vitamin D supplementation should be advised for all patients with epilepsy, and in particular women, older patients or treated chronically with inducing AEDs. The recommended daily allowance of these supplements depends on age, sex and reproductive status. Because the dose 400 IU of vitamin D was found to increase BMD in epileptic patients this dose is recommended for all patients as a starting dose. Although higher amounts of vitamin D (4000 IU per day) were found to be more effective to restore bone density so they should be recommended to patients with high-risk groups (25). Patients should be periodically tested biochemically and instrumentally. In persons with an evidence of bone disorders, changing of AED treatment to more safe one should be applied.

REFERENCES

11. Nikolaos T, et al. The effect of long-term antiepileptic treatment on serum cholesterol (TC,HDL, LDL) and triglyceride levels in adult epileptic patients on monotherapy. Medical Sci Monitor 2004,10,50-52
17. Greenwood RS. Adverse effects of antiepileptic drugs. Epilepsia 2000,41,S42-52
ABSTRACT

Epilepsy is associated with a range of unfavorable consequences, among which metabolic disorders do not receive appropriate importance. The relationship between epilepsy and metabolic disorders is multi-factorial. Active epilepsy may lead to a variety of metabolic abnormalities, and metabolic disorders are important cause of seizures. Furthermore, adverse metabolic effects of antiepileptic drugs may have a negative impact on general health. Stress exacerbates seizures, and stress related hormones are elevated in patients with epilepsy. The modulation of the hypothalamic-pituitary-adrenal axis may have important clinical implication for seizure control which represent a novel therapeutic target of anticonvulsant therapy. Older and some new antiepileptics affect thyroid function, primarily by decreasing thyroid concentrations. Long-term use of antiepileptic drugs results in disturbed bone metabolism and increased risk of fractures, which requires chronic supplementation of patients. The effects of enzyme-inducing antiepileptic drugs on specific lipid fractions favor an atherogenic profile and increase risk for atherosclerosis-related vascular disease. Antiepileptic drugs may be associated with either increases or reductions in body weight. Most of metabolic disorders result from interactions of antiepileptic drugs with cytochrome CYP450 and UGT enzymes. Mainly old generation drugs are responsible for the health consequences, which might indicate the use of new drugs in sensitized patients.

STRESZCZENIE

Padaczka skutkuje licznymi niekorzystnych następstwami, w tym zaburzeniami metabolicznymi, które nie są powszechnie znane i doceniane. Zależności pomiędzy napadami padaczkowymi i zaburzeniami metabolicznymi są złożone. Aktywna padaczka może wyzwalać choroby metaboliczne, z kolei zaburzenia metaboliczne stanowią istotną przyczynę występowania napadów drgawkowych. Ponadto niekorzystne skutki metaboliczne leków przeciwpadaczkowych mogą mieć negatywny wpływ na ogólny stan zdrowia. Stres nasila napady padaczki, a stężenia hormonów
Związanych ze stresem są podwyższone u pacjentów z padaczką. Modulacja osi podwzgórze-przysadka-nadnercza może mieć istotny wpływ na kliniczną kontrolę napadów, co obecnie stanowi nowy terapeutyczny cel leczenia przeciwpadaczko wego. Starsze i niektóre nowe leki przeciwpadaczkowe wpływają na funkcję tarczy cy, głównie poprzez zmniejszenie stężeń jej hormonów. Długotrwale stosowanie leków przeciwpadaczkowych powoduje zaburzenia metabolizmu kości i zwiększa ryzyko złamań, co wymaga przewlekłego suplementowania leczonych witaminą D i wapniem. Wpływ indukujących enzymy leków przeciwpadaczkowych na zawartość frakcji lipidowych w kierunku zwiększenia profilu miażdżyco-rodnego zwiększa ryzyko chorób naczyniowych powiązanych z miażdżycą u osób leczonych tymi lekami. Leki przeciwpadaczkowe mogą powodować zwiększenie lub rzadziej ubytek masy ciała. Większość zaburzeń i chorób metabolicznych towarzyszy leczeniu lekami przeciwpadaczkowymi, z powinowactwem do mikrosomalnych enzymów CYP450 oraz UGT. Głównie leki starszej generacji są odpowiedzialne za zaburzenia zdrowotne metaboliczne, co może przemawiać za wyborem nowych leków, zwłaszcza u pacjentów ze zwiększonym ryzykiem komplikacji.

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