A modern perspective of antiepileptic drugs effect on Vitamin D rate (reference data and clinical case)

Abstract. This article presents a clinical case of the antiepileptic drug effect on the Vitamin D rate (namely, the patient has been taking Sodium Valproate for a long time) and new data from the foreign publications on this problem. It is known that there is a list of drugs that adversely affect the Vitamin D metabolism. In particular, the drugs reducing the Vitamin D absorption include drugs for the treatment of epilepsy. Antiepileptic drugs are drugs of various origins that are used to prevent or reduce seizures, their corresponding conditions (loss or impairment of consciousness, behavioral and autonomic disorders, etc.), which are observed with recurrent seizures of various forms of epilepsy. The widespread use of these drugs in medical practice requires a detailed study of possible side effects of these drugs and their timely correction, as foreign sources indicate that antiepileptic drugs increase Vitamin D deficiency and worsen the symptoms of proximal myopathy, requiring mandatory medical correction; patients with epilepsy are deficient in vitamin D; chronic Valproate therapy is associated with lower bone mineral density in young patients with epilepsy. This clinical case showed how a long-term use of Sodium Valproate led to the development of secondary systemic osteoporosis and Vitamin D deficiency, as evidenced by the results of laboratory and instrumental studies, and the discontinued antiepileptic drugs along with Vitamin D supplementation improved the general health of the patient and Vitamin D blood rates. Based on the systemic review and our own observations, it has been concluded that epilepsy patients taking antiepileptic drugs should be given Vitamin D supplements to prevent the development of osteoporosis and Vitamin D deficiency.

Keywords: vitamin D deficiency; antiepileptic drugs; systemic osteoporosis

Introduction

Since ancient times, the physicians have been noting the importance of control over various medications being prescribed. According to the famous Hippocrates and Socrates: 

As to diseases, make a habit of two things — to help, or at least, to do no harm (Hippocrates); Some drugs are more dangerous than the diseases they cure (Socrates).

At present, the problem of increasing Vitamin D deficiency frequency takes up an increasingly urgent topicality at a global scale. This fact is proved by a lot of national and international publications on various aspects of this problem.

Beginning with the previous century, the physicians were actively prescribing Vitamin D to children in order to prevent rickets. However, the researchers were observing a significant increase of pathological conditions associated with this Vitamin’s deficiency in the human body. They were also actively trying to explore the reasons for such a rapid increase in the Vitamin D deficiency’s frequency among the world population.

It is worthy of note that the progress of pharmacological technologies and release of numerous modern medications in various fields of medicine promote the frequency of their use in the healthcare practice. It is well-known that there is a number of drugs negatively affecting the Vitamin D turnover; namely, the anticonvulsants reducing the Vitamin D absorption.

At present, the valproates (VPA) belong to one of the anticonvulsant groups which are in a great demand and used as a basic medication for the monotherapy of seizure patients. Thus, the anticonvulsants are medications of various origins, used for prevention or reduction of seizures, as well as other similar conditions (fainting, behavioral and autonomic conditions etc.) attending regularly-occurring attacks of various seizure forms. A wide use of various medications...
in the healthcare practice requires a thorough study of possible side effects and a timely correction of their use.

The study of anticonvulsant medication influence on Vitamin D rate is extremely important, this fact being confirmed by a large number of foreign publications devoted to this issue [1-5]. For instance, Sharma A. et al. in their article “A complication of valproate therapy and a thought beyond Vitamin D deficiency” suggested that a long-term use of vitamin D supplements for 6 months in combination with carnitine and discontinuation of sodium valproate promoted the recovery of patients with proximal myopathy [6]. In 2019, the Department of Orthopaedics at the Medical College of New Delhi (India) admitted a 13-year-old patient complaining of walking abnormalities. The patient was gradually affected by a growing weakness and reduced physical activity. The impaired mobility progressed up to a complete incapacity of walking the usual distances. The patient’s medical history did not show any traces of infections or chronic conditions. There were no congenital disorders. At the time of examination, there was an augmented lumbar lordosis, the strength of hip abductors and deltoids was 4/5, the strength of all other muscles amounted to 5/5. The tendon reflexes were preserved. The Trendelenburg’s sign is positive on both sides. She could squat; however, standing up caused great difficulties. The weakness of neck muscles, thoracic spine and abdominal muscles was not registered. The electromyography (EMG) and X-ray study provided normal data. The patient was taking a combined therapy of sodium valproate (200 mg twice a day), risperidone (2 mg once a day), trihexyphenidyl (2 mg once a day) for 3 years to treat absence seizures and mood disorders. The lab examination revealed that alkaline phosphatase rate grew up to 897 IU/l (the normal rate being 53-128 IU/l), creatine phosphokinase (CPK) to 35.9 IU/l (the normal rate being 0-25 IU/l). The vitamin D rate was 40.60 ng/ml (the normal rate being 30-50 ng/ml); the patient’s medication history revealed that the patient was not taking vitamin D supplements for a long time. The diagnosis “proximal myopathy” was made; the healthcare providers suspected that this condition might have been provoked by the low rates of vitamin D and valproate use. That’s why they made a decision to discontinue the anticonvulsants and to prescribe a long-term vitamin D treatment. They also added carnitine to the treatment regimen. After 3 months of such treatment, the patient’s general condition improved: the walking capacity was recovered and weakness disappeared. The strength of all muscles was registered as 5/5. That way, the researchers made their conclusion that anticonvulsants increase the vitamin D deficiency and aggravate the symptoms of proximal myopathy, requiring a mandatory pharmaceutical correction by vitamin D supplements.

In 2016, the European Journal of Clinical Nutrition published the paper “Vitamin D in epilepsy: Vitamin D levels in epilepsy patients, patients on antiepileptic drug polytherapy and drug-resistant epilepsy sufferers”. This paper presented the findings of studies into the vitamin D rates of epilepsy patients on antiepileptic drug mono- and polytherapy. For that purpose, 98 patients were recruited (43 subjects with epilepsy and 55 subjects - practically healthy). The researchers also considered such factors as being in the sun, taking physical exercises and consuming vitamin D with food in order to assay the vitamin D blood rate. The study findings revealed that 41 % patients had the vitamin D deficiency, 49% patients - the vitamin D insufficiency, 9 % patients - the normal vitamin D rates. The elderly people and patients working at the offices or at schools had lower blood rates of vitamin D. That way, the researchers made their conclusion that the epilepsy patients had the vitamin D deficiency requiring a mandatory correction [7].

The authors Fernandez H., Mohammed H., Patel T. focused their attention on the study into the negative anticonvulsant effect on the bone state and the reduced vitamin D rates [8]. In 2018, they made a search for reference sources and published their findings in the Epilepsia journal, using the following sources: PubMed, Medline, Embase, Scopus, Cochrane Clinical Trials, International Pharmaceutical Abstracts, Health Canada Clinical Trials Database. In particular, they reported a negative anticonvulsant effect on the bone tissue, a high risk of the vitamin D deficiency in the epilepsy patients, an importance of mandatory vitamin D supplementation for this group of patients and a further study into this issue in order to obtain findings on the duration of use and correction of the vitamin D supplement doses among the epilepsy patients on anticonvulsants.

The article “Bone health and vitamin D status in young epilepsy patients on valproate monotherapy” published by the Clinical Neurology and Neurosurgery journal in 2016 presented the findings of studies on valproate use association with bone mineral density (BMD) reduction among the epilepsy patients. The researchers were evaluating the vitamin D blood rate and BMD, recruiting 50 epilepsy patients taking sodium valproate and 50 practically healthy subjects aged 26±7.2 years. They found that the frequency of reduced BMD values (Z-score < -2.0) was 26 % at the lumbar spine level and 10 % at the femoral neck level among the epilepsy patients and 10 % and 4 % among the practically healthy subjects, respectively. The correlation of valproate duration or dosage and BMD was not detected. The vitamin D deficiency was reported in both groups. The findings of this study revealed the following: chronic valproate therapy was associated with the lower BMD values in the young epilepsy patients. That was why, the researchers recommended preventive osteoporosis treatment of those patients [9].

Clinical case

In this publication, we present a clinical case of anticonvulsant (sodium valproate) effect on vitamin D rate. It was observed at the Clinical Physiology and Pathology of Locomotor Apparatus Department, State Institution “D. F. Chebotaryov Institute of Gerontology” by the National Academy of Medical Sciences of Ukraine.

The patient T., 59 years of age, consulted the Ukrainian Scientific-Medical Center of Osteoporosis, complaining of left and right forearm pain, augmented general weakness, anxiety, regular epileptic seizures.
**Medical anamnesis.** The medical anamnesis reveals that in the winter of 2018 the patient started having the mobility “freezing” attacks of about one minute during which the patient did not respond to calls or any irritants (touch, shaking, and water ablutions). Those attacks occurred on the background of a satisfactory health and frequent stressful events. According to the patient, she did not remember what happened during those attacks. During the following two-three minutes, the patient gradually recovered, making various automatic movements. She did not consult any medical institutions, considering those episodes to be of no importance. Due to the ever-increasing frequency of those attacks, in January 2019 she presented herself at the neurologist office of one Kyiv clinic. Based on the objective examination, neurologic examination and prolonged video electroencephalography (EEG) performed in January 2019, the healthcare providers revealed an epileptiform peak-wave activity involving generalized simultaneous discharges. The focal changes or interhemispheric asymmetry were not detected. The response to afferent irritation is adequate. The focal symptoms were not revealed by the neurologic examination. The diagnosis of “Idiopathic generalized absence epilepsy” was made.

According to the attending physician’s recommendations, the patient took 600 mg of Sodium Valproate per day and 500 mg of Bifren per day for 1 month. During the following 21 days, the attending physician recommended to reduce the Sodium Valproate dose to 150 mg per day and to add a long-term use of Ethosuximide at a dose of 20 ml per day and Magnesium lactate dehydrate at a dose of 940 mg per day during 1 month. Since mid-September 2019, the Sodium Valproate dose had been reduced by titration.

The medical history reveals that in June 2019 there were radius fractures after a fall on the patient’s extended arms from her own height’s level. The history of allergies is not aggravated. The patient denies any harmful professional life factors. The periods started at 14 years, the menopause at 54 years, the patient was not taking any hormone replacement therapy. The pregnancy and labors: 1, no complications. The medical history: Hepatitis A (childhood), appendectomy in 1975. There were no other infectious diseases, namely TB and venereal diseases (according to the patient). Comorbidities: calculus cholecystitis due to which she took a course of Ursodeoxycholic acid (UDCA) in the spring of 2019.

**Objective status**

The body composition is regular, normostenic, a spine with no pathological curvatures, a height of 164 cm, a body mass of 55 kg, body mass index – 20.4 kg/m². The skin, visible mucous membranes are pale pink. The peripheral lymph nodes are accessible for palpation, not enlarged. The thyroid gland is not enlarged at palpation, not tender, elastic. The palpation of left mammary gland’s upper lateral quadrant revealed an infiltration of 10x15 mm, right mammary gland with no visual or palpatory changes (one recommends a mammography and mammologist’s referral). The pulmonary breathing is vesicular, no wheezing, the breathing rate is 16 breaths per minute. The cardiac tones are weakened, the cardiac activity – rhythmic, pulse – 78 strokes per min., symmetric on both hands, arterial blood pressure - 110/70 mmHg. The stomach is soft at palpation, not tender. The lower border of the liver is located at the edge of costal curve; the edge is smooth. The spleen is not accessible to palpation. The costovertebral angle (CVA) tenderness is absent bilaterally, no peripheral edema. The diuresis is adequate; the bladder emptying is normal. The neurological status does not reveal any pathological changes.

**Laboratory examinations.** Complete blood count (CBC, 24.07.2019): Alanine transaminase (ALT) – 10.6 IU/l (the normal rate being up to 40 IU/l), Aspartate aminotransferase (AST) – 15.6 IU/l (the normal rate being up to 40 IU/l), direct bilirubin (BR) – 6.6 umol/l (0-5.1 IU/l), alkaline phosphatase (ALP) – 212.2 IU/l (64-306 IU/l), Carcinoembryonic antigen (CEA) – 2.23 μg/l (0-5.0 μg/l); (05.02.2019): ALT – 7.3 IU/l (up to 40 IU/l), AST – 13.7 IU/l (up to 40 IU/l), total bilirubin (BR) – 19.7 umol/l (up to 21 umol/l), direct bilirubin (BR) – 5.6 umol/l (0-5.1 IU/l), γ-glutamyltransferase (GGT) – 18.9 IU/l (5-32 IU/l).

Bone turnover parameters: Calcium (Ca) total – 2.3 umol/l (norm: 2.15-2.5 umol/l), Phosphorus - 1.22 umol/l (norm: 0.81-1.45 umol/l), Parathormon – 30.3 μg/mL (15.0-65.0 μg/mL), Vitamin D total (25(OH)D) – 12 μg/ml (optimal rate – 30.0-50.0 μg/ml). Bone remodeling markers: Osteocalcin – 5.2 ng/ml (2.0-22.0 ng/ml), β-isomerized C-terminal telopeptides (β-CtX) – 0.73 ng/ml (<1.008 ng/ml).

**Instrumental examinations.** EKG (04.04.2014) - sinus tachycardia, heart rate – 85 strokes/min., electrical heart axis – horizontal, incomplete bundle branch block (right bundle branch), signs of left ventricle hypertrophy.

Dual-energy X-ray absorptiometry (DXA) of proximal femoral and forearm bone (22.08.2019), total skeleton and lumbar spine (02.09.2019): BMD corresponds to osteoporosis according to the WHO criteria (at the lumbar spine (T-score – 2.9), proximal femur (T-score – 2.6), total skeleton (T-score – 2.9), forearm (T-score – 2.5), Trabecular Bone Score (TBS) characterizing the trabecular bone quality – 1.209.

Based on the clinical picture, medical history, laboratory and instrumental examinations, the diagnosis of “Second- ary systemic osteoporosis on the background of Sodium Valproate use” Vitamin D deficiency” was made. By the physician’s recommendations, the patient discontinued anticonvulsants. Vitamin D supplement in a dose of 4, 000 IU once a day was prescribed.

After 1 month, during the follow-up consultation, there were no complaints of bone-muscular and nervous nature registered. The objective examination did not reveal any pathological changes. The following results were obtained: bone turnover markers (21.10.2019): Ca total – 2.24 umol/l (norm: 2.15-2.58 umol/l), Ca ionized – 1.25 umol/l (norm: 1.13-1.32 umol/l), Vitamin D total – 44.77 μg/ml (optimal rate – 30.0-50.0 μg/ml). Thus, we may see that Vitamin D values have changed from 12.0 μg/ml to 44.77 μg/ml on the background of Vitamin D supplementation and Sodium Valproate discontinuing.
Conclusions
The foreign reference sources demonstrate the fact that anticonvulsants aggravate Vitamin D deficiency and symptoms of proximal myopathy, requiring a mandatory Vitamin D supplementation. The epilepsy patients have Vitamin D deficiency; chronic Sodium Valproate therapy is associated with lower BMD in the young epilepsy patients. That’s why the physicians are recommending the preventive osteoporosis treatment for such patients.

Based on the data of systematic review and our individual observations, namely clinical case, we may conclude that the epilepsy patients taking anticonvulsants should also use Vitamin D supplements in order to prevent osteoporosis and Vitamin D deficiency. The patients should be tested for Vitamin D rates at the beginning of anticonvulsant therapy and during the epilepsy treatment. Depending on the Vitamin D blood rates at the beginning of treatment, the physician decides which supplement dose to prescribe (therapeutic or preventive).

Conflicts of interests. Authors declare the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

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Сучасний погляд на проблему впливу протиепілептичних препаратів на статус вітаміну D (клінічний випадок з оглядом літературних джерел)

Резюме. У даній статті наведені клінічний випадок впливу протиепілептичних препаратів (ПП) на рівень вітаміну D (зокрема, на тлі тривалого прийому антиепілептичного препарату валпроату на рівень вітаміну D та середніх структурних показників) та сучасні дані зарубіжних публікацій щодо цієї проблеми. Як відомо, анамнез лікарських препаратів, що негативно впливають на метаболізм вітаміну D. Зокрема, до такої групи відносяться антиепілептичні препарати (АДП), діуретики та інші антигіпертензивні препарати. Дана праця присвячена клінічному випадку, що демонструє для запобігання чи зменшення судом, відповідно до вітаміну D (клінічний випадок з оглядом літературних джерел).
них їм еквівалентів (отримання або порушення свідомості, поведінкових змін) при періодичному виникненні відповідних реакцій на епілепсію. Широке застосування в медиціні цих лікарських препаратів потребує детального вивчення можливих їх побічних реакцій та проведення своєчасної їх корекції, оскільки їх використання може призвести до розвитку вторинного системного остеопорозу та дефіциту вітаміну D, що супроводжується ураженням нервових та нервових клітин. На основі даних літературного огляду та власнимої споживання, зокрема, клінічного випадку, можна зробити висновок, що пацієнти, які використовують ПП, повинні приймати препарати вітаміну D3 у цілях запобігання розвитку остеопорозу та дефіциту цього вітаміну.

Ключові слова: дефіцит вітаміну D; противезепіліптичні препарати; системний остеопороз