CASE STUDY

ARRHYTHMIA IN THE COURSE OF GENERALISED EPILEPSY OF UNKNOWN ETIOLOGY – A CASE STUDY

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ABSTRACT
The aim: To draw attention to the need for careful analysis of patients with epilepsy in terms of the possibility of co-occurring arrhythmia.
Material and methods: Analysis of video-EEG registration in the inter-seizure period in a patient with diagnosed epilepsy.
Case study: The authors present a 33-year-old patient with generalised epilepsy of unknown etiology diagnosed in childhood. In this subject, generalised seizure discharges without clinical manifestation of epileptic seizure and with concomitant cardiac arrhythmias in the form of atrial fibrillation were recorded during video-EEG registration. This was carried out during the patient's of hospitalisation at the neurology ward.
Conclusions: The case study presented is as an example of existing complex and not fully understood interactions between epilepsy and arrhythmia. A mutation within the SCN1B encoding genes, which is responsible for channelopathy within the voltage-dependent Na_v sodium channels, may be considered as a potential cause for this state. However, further analysis and research is needed that would eventually allow to find out the reason for these relationships.

KEY WORDS: epilepsy, arrhythmia, video-EEG registration

INTRODUCTION

Arrhythmia is a common and overlooked problem in patients with epilepsy. Often, the diagnosis of epilepsy ends with cardiological diagnostics and vice versa. It is common knowledge that a relationship exists between epileptic seizures and the autonomic function of the heart, however, in clinical practice, it is frequently forgotten that these dysfunctions may coexist [1, 2]. Miakotnykh and Antiuf'ev showed that 64.44% of patients with epileptic seizures have different pathologies in the cardiac stimulus system [3].

Nonetheless, the impact of seizure or status epilepticus on the heart muscle still remains a mystery. These relationships are complex and not fully understood. On the other hand, it is known that epileptic seizures can cause arrhythmias which may be mild, severe or life-threatening. The incidence of sudden death in patients with epilepsy is estimated at 1/1,000. The most frequently reported type of cardiac arrhythmia during an epileptic seizure is sinus tachycardia, which is accompanied by 80% of seizures and is asymptomatic in just over 80% of patients. The analogous parameter in a group of healthy individuals does not exceed 10% [4]. A different but clinically significant arrhythmia found in EEG recordings is asystole. It occurs in 0.318% of people with refractory focal epilepsy [5]. It is often preceded by sinus bradycardia registered in about 6% of cases with focal epilepsy [6, 7, 8]. This problem was noted by Reeves et al. in the journal *Epilepsy.* In 1996, these authors demonstrated that the occurrence of bradycardia should

be considered in both the group of patients with syncope as well as epilepsy [9]. Supraventricular tachycardia, atrioventricular block or atrial fibrillation are other potentially dangerous arrhythmias [8, 10, 11].

Arrhythmia often coincides with or may precede epileptic seizures [12]. Inverse situations, i.e. – the occurrence of epileptic seizures preceding the incidence of cardiac arrhythmia such as sinus tachycardia, ventricular fibrillation, bradycardia, asystole, are also frequently reported [13].

To date, the pathophysiology of cardiac arrhythmia in epilepsy has not yet been established. There are a number of hypotheses explaining this dysfunction. Activation or inhibition of cortical autonomic centres, inflammation (IL-6), activation or inhibition of cortical autonomic centres, increase in vagus nerve tension by activation of brainstem reflex centres, respiratory failure, altered ion channel in drug-resistant epilepsy are considered [14]. In the pathogenesis of epilepsy and ventricular arrhythmia, inflammatory processes play a significant role. IL-6 is considered a key mediator of inflammation in the pathogenesis of both disturbances [15]. Increased levels of circulating IL-6 in patients with heart failure as well as in those with epilepsy contributes to the generation of seizures and is positively correlated with the presence of cardiac arrhythmias. Another potentially dangerous cause of death of a patient is the dysfunction of cortical autonomous centres. This is greatly important within the aspect of temporal lobe focal epilepsy most commonly described in adults.

Epilepsy in this area is associated with autonomic instability, which significantly increases the risk of postpartum arrhythmia [16]. Focal stimulation of parts of the limbic system – amygdala, cigulate gyrus may lead to asystole [17-21]. The altered ion channel, especially in the case of drug-resistant epilepsy, may also explain the co-occurrence of cardiac arrhythmias and epilepsy.

Ion channel mutations found in the heart and brain may indicate more susceptibility to both epilepsy and arrhythmia. Some ion channel mutations that have been found in both organs may indicate increased susceptibility to both epilepsy and arrhythmia [22-25].

Therefore, cardiac arrhythmia in epilepsy may result not only from seizure activity, but also from a common genetic susceptibility [4].

The genetic relationship between epilepsy and cardiac arrhythmia has been documented when the cardiac sodium channel gene SCN5A, SCN1B has been found in the brain, and pathogenic variants in the long gene family QT (LQT) (i.e. *KCNQ1, KCNH2* and *SCN5A*) encoding cardiac potassium channels [25-30].

Auerbach DS. et al., in the journal *Neurology* in 2016, analysed mutations in the LQTS 1, LQTS 2, LQTS 3 genes, showing that mutations in the LQTS 2 gene have a predilection both for epileptic seizures and arrhythmia [31].

A mutation within KCNA1, a gene encoding voltage dependent $K_v1.1$ potassium channels, resulting in epileptic seizures, can also predispose to bradyarrhythmia, making the KCNA1 gene a potential risk factor for sudden unexpected death among patients with epilepsy [32, 33]. Those especially at risk of SUDEP (Sudden Unexpected Death in Epileptic Patients) are patients with wrongly-controlled or drug-resistant epilepsy.

Of the various phenotypes of voltage-dependent sodium channels responsible for the generation and spreading of action potential in the CNS, especially mutations within encoding genes SCN3A ($Na_v1.3$), SCN8A ($Na_v1.6$) and SCN1B ($Na_v1.1$) are associated with seizure-related disorders, whereby the mutation within SCN1B ($Na_v1.1$) may simultaneously imply cardiac channelopathy [26].

Drug therapy among patients with epilepsy is not without influence on heart rhythm. The negative effects on cardiac rhythm in epilepsy have been documented for drugs such as carbamazepine, levetiracetam and lacosamide [34-36].

Adverse reactions to carbamazepine, although rare, may be: conduction disturbances, hypertension or hypotension, as well as bradycardia, arrhythmia or atrioventricular block. In the case of lacosamide, atrial fibrillation and flutter were observed during high dose therapy, around 600 mg/day in patients with epilepsy without significant risk of cardiovascular disease. Phenytoin and phenobarbital are two other drugs, the use of which is associated with a high risk of arrhythmogenic effects in predisposed patients [37]. Phenytoin has a narrow range of therapeutic concentrations (from 10 to 20 µg/mL), and already a slight increase (above 25 µg/mL) may cause signs of toxicity. During therapy with this anti-epileptic drug, it is necessary to monitor ECG recordings, blood pressure, as well as to regularly measure the concentration of the drug in the blood. In the aspect of valproic acid, its potential effect on heart rate cannot be clearly excluded. The drug has a complex mechanism. The most likely action of valproic acid is the selective increase of gamma-aminobutyric acid (GABA) among synapses in the CNS and reduction of GABA consumption by glial cells by activating glutamic acid decarboxylase and inhibition of GABA-transaminase. The drug also affects excitatory neurotransmitters and may affect the sodium and potassium channels in neuronal cell membranes. Similar to valproic acid, there is no clear understanding of lamotrigine's effect on heart rate. Pharmacological results indicate that the drug is a voltage-gated sodium channel blocker. It stabilizes neuronal membranes by inhibiting potential-dependent sodium channels while also blocking the release of excitatory amino acids (glutamic acid).

THE AIM
To draw attention to the need for careful analysis of patients with epilepsy in terms of the possibility of co-occurring arrhythmia.

CASE STUDY
The authors describe the case of a 33-year-old patient diagnosed with generalised epilepsy of unknown etiology in childhood, hospitalised at the Neurology ward to optimize anti-epileptic treatment. Generalised tonic-clonic seizures occurred in the patient at a frequency of 1x/3 months. In the patient's opinion, the number of epileptic seizures had recently increased, they were recorded at a frequency of 1x/month. Before the seizures, the patient felt irritable and experienced weakened concentration preventing from functioning both at work and in everyday activities. The patient complained of impaired concentration and attention accompanied by drowsiness, assuming this was related to the adverse effects of valproic acid. So far, apart from generalised tonic-clonic seizures, no other types were observed in the case of this patient.

The patient took lamotrigine at a dose of 150 mg/day (the level of the drug during hospitalisation was 2.6 L µg/mL) (range of 3-15 µg/mL) and valproic acid at a dose of 2,000 mg/day (the level of valproic acid was 29.3 L µg/mL) (range of 40-100 µg/mL). Pregnancy and perinatal history as well as in the direction of childhood febrile seizures was not burdensome. Family history of sudden cardiac deaths before age 40 was also not applicable. In addition, the patient had not been treated chronically, and had not used any other pharmacotherapy besides anti-epileptic drugs.

In the physical examination, the patient was cardiovascularly and respiratorily stable. No other deviations from the norms were noted. Laboratory diagnostics of thyroid function with assessment of THS concentation, fT_3 and fT_4 were also within the norm. In neurological examination, it was found that: the patient was fully conscious, fully auto- and

allopsychically aware, the pupils were even with a direct and indirect response to light, in the area of other cranial nerves, there were no abnormalities, meningeal and focal symptoms were negative. In MRI of the brain with contrast (with 3 T camera sensitivity in sagittal, frontal, transverse cross-section and thickness layers of 0.9 mm) a single zone of non-specific demyelination in the deep structures of the left island was visualised, and no pathology was shown in the radiological image of the brain.

In the video-EEG, generalised seizure discharges were recorded in the form of spike complexes, slow wave with an amplitude higher than the background of the record compared to normal basal rhythm, without clinical manifestation of epileptic seizure (no occurrence of a seizure), both during and before cardiac arrhythmias were recorded in the ECG record. These disorders persisted throughout the 80-minute video-EEG recording period, independent of the inter-seizure discharges recorded during video-EEG examination. In the video-EEG performed after testing, with a 12-channel ECG, atrial fibrillation and flutter were recorded with a ventricular rate up to 150-160/min, without any other recorded pathologies. No attempts at emergency anti-epileptic or anti-arrhythmic pharmacotherapy were made at the ward.

Both during the current and previous hospitalisations, the patient underwent repeated ECG tests, Holter-ECG monitoring cardiac function – in none of the above were any significant pathologies found.

After cardiological consultation, the patient was directed to a cardiology clinic where detailed diagnostics was performed.

In extensive non-invasive tests: echocardiography, cardiac monitoring by Holter-ECG, stress test, incorrect results were not noted.

The patient, apart from the beta- blocker- bisoprolol at a dose of 1.25 mg/day, did not undergo any special cardiological treatment.

Based on the neuropsychological testing, no impairment of cognitive function was found, the MMPI-2 test was normal.

During hospitalisation, anti-epileptic treatment was modified, and the dose of valproic acid was reduced to a total daily dose of 500 mg. A dose increase of lamotrigine to a total of 200 mg daily was planned. The decision to modify anti-epileptic pharmacotherapy in the manner described above was the result of the patient reporting adverse effects of valproic acid on cognitive functions and pathological drowsiness. The authors of the work also wanted to maintain monotherapy with anti-epileptic drugs acting, among others, via sodium channels. In the 6-month follow-up period after modification of the anti-epileptic treatment, the patient did not experience any epileptic seizures or cardiac events. In the video recording-EEG, paroxysmal changes were not clinically or electroencephalographically observed. Due to the clinical effect of anti-epileptic drugs manifested by the absence of epileptic seizures, blood anti-epileptic drug levels were not measured at that time.

DISCUSSION

The case study described by the authors is another example of existing complex and not fully understood interactions between epilepsy and arrhythmia. Our patient experienced only generalised tonic-clonic seizures, no other types of epileptic seizures were observed. The single zone of non-specific demyelination in the deep insular cortex structure of the left insulae, found in MRI of the head, may have been clinically silent pathological area concerning the aspect of seizure activity, while the arrhythmias resulted from stimulation of the cortex in this location [38]. Nonetheless, the patient remains under clinical observation and in the future, it is possible that we will be able to enrich our knowledge on this subject.

The issue of low blood levels of both AEDs is also under discussion. Based on the medical history (the patient declaring the use of both anti-epileptic drugs as prescribed by the physician), improper intake of medication seems unlikely. Perhaps the low levels of the anti-epileptic drug were due to existing pharmacokinetic variability in particular for valproic acid. The consequence of this in clinical practice should be an increase in the frequency of blood tests for anti-epileptic drugs. However in our patient, during the 6-month follow-up no blood tests for anti-epileptic drugs were made. Therefore, a toxic effect of lamotrigine resulting from the inhibitory metabolism of valproic acid cannot be excluded, neither may it be assumed that increasing the dose of lamotrigine and reducing the dose of valproic acid could have had a neutral effect on the concentration of the first of the listed anti-epileptic drugs.

Our patient, similarly as in the case of the patient described in the work published in the journal Epilepsia in May 2000, Nei M et al. also confirmed ECG abnormalities after and during seizure activity in electroencephalographic recording [6]. In addition, similar as in the work by Herskovitz M et al., published in the journal Arch Neurol. in 2012, our patient arrhythmia in the form of atrial fibrillation appeared as the first symptom of heart disease [39]. Arrhythmias, regardless of seizure activity in electroencephalographic recording, may also have occurred earlier

The fact is that atrial fibrillation is asymptomatic in about 1/3 of cases. It should also be considered whether there is a need for special pharmacotherapy treatment in patients with such a diagnosis.

It seems likely that in the case described by us, we encounter a mutation within the SCN1B encoding genes, which are responsible for channelopathy within the Na_v 1.1 voltage-dependent sodium channels both in the CNS and the heart [26]. Already in 2002, Maier et al. proved that individual sodium channel isoforms physiologically present in the CNS play an important role in both the initiation and conduction of cardiac action potential (Na_v 1.5) as well as in coupling the depolarisation of cardiomyocytes with their contraction (Na_v 1.1, Na_v 1.3 and Na_v 1.6) [40].

Considering the main mechanism of action, in the case of epileptic seizures, the most effective of the sodium channel blockers are phenytoin, carbamazepine and lamotrigine.

Research results prove that lamotrigine is a blocker of voltage-dependent sodium channels, simultaneously

inhibiting discharges and reducing the excitability of the neuronal membrane [41].

Confirmation of our assumption is the 6-month observation period of our patient on modified lamotrigine therapy (as a well-known non-selective Na_v inhibitor), which provided a satisfactory clinical effect, i.e. lack of observed epileptic seizures. This indicates the rightness decision regarding modification of anti-antiepileptic pharmacotherapy.

In the article, there is no unambiguous answer to the question regarding the reason for the documented relationship between arrhythmias and epilepsy. Epilepsy, as a disease entity, should therefore be seen as a complex of symptoms, and all co-morbidities, even the most inconspicuous ones, should be considered as part of stratification and phenotyping in people with such a diagnosis. There is a need for further clinical trials that would allow to ultimately develop optimal strategies. In addition, predictors/markers initiating the onset of epileptic seizures may be established in the future [6]. In this manner, the authors wanted to highlight the problem concerning the co-occurrence of cardiac arrhythmias discussed for many years in patients with epilepsy in the aspect of the growing interest in diagnosing ion channel subunit functions in this group of patients.

CONCLUSION

The diagnosis of epilepsy with concomitant cardiac arrhythmias provides the basis for a more rational diagnosis and therapy of epilepsy taking into account ion channel defects.

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Conflict of interest
Authors declare no conflict of interest

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