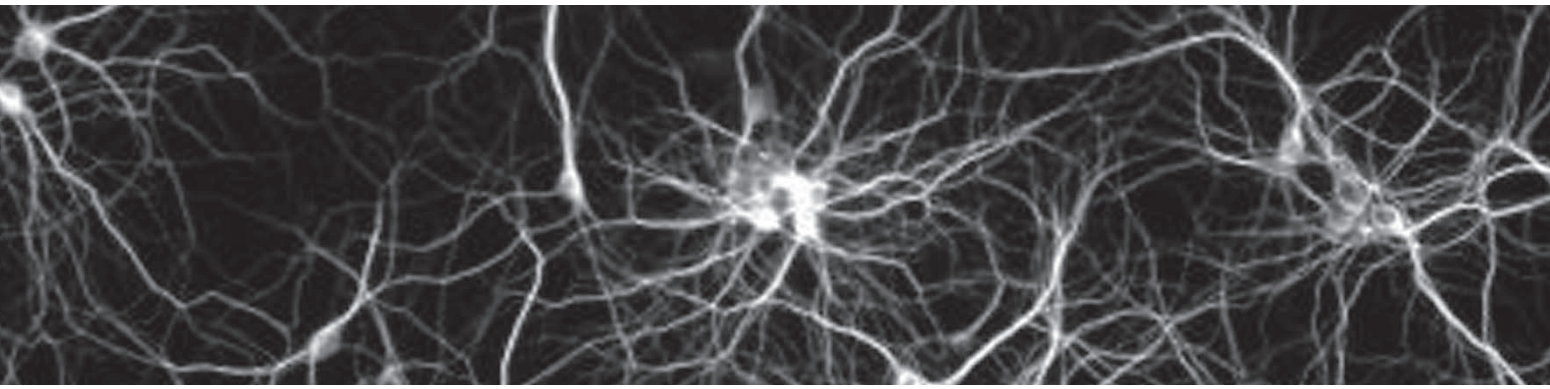

Epilepsy and comorbidities

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INTRODUCTION

Epilepsy is one of the most common neurological diseases (1,2). It is a chronic brain disorder characterized by an enduring predisposition to generate epileptic seizures. Recurring seizures leave neurobiological, cognitive, psychological and social consequences which affect patients' quality of life (2,3). Comprehensive medical term comorbidity refers to distinct conditions, diseases and syndromes that occur alongside the main condition. Comorbidities are defined as medical conditions that simultaneously coexist with a primary diagnosis (4). It is estimated that more than half of young adults suffer from at least one chronic health condition (4) and the number increases with age (6). Numerous somatic, psychiatric and cognitive diseases are more often present in patients with epilepsy than in the general population (7). Approximately 50% of adults with epilepsy have at least one comorbidity (4). Their importance in the clinical approach towards patients is emphasized by the fact that they are an essential part of the current classification according to International League Against Epilepsy (ILAE) (8).

THE SIGNIFICANCE OF COMORBIDITIES IN PATIENTS WITH EPILEPSY

The results have shown that the most common comorbidities in people with epilepsy are anxiety and major depressive disorder. Despite the significant frequency, depression and anxiety are still poorly recognized by physicians. In adults, hypertension (18.2%), stroke (14.5%), heart disease (11%), diabetes (10.2%) and arthritis (9.2%) are among frequent comorbidities as well (9). Comorbidities have a significant impact on selecting appropriate treatment option. Treatment can be more complex because it requires an approach that extends beyond controlling seizures alone (10). However, co-

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morbidities can enable earlier detection of epilepsy. For example, if a patient suffers from neoplastic brain disease, epilepsy may be detected earlier due to regular monitoring and clinical examinations. It is necessary to timely diagnose and properly treat comorbidities because they can be predisposing factors to unfavorable seizure outcomes. Treating comorbidities enables better control of epileptic seizures. It works the other way around, too. Treating epileptic seizures has a beneficial effect on comorbid conditions. Further research of comorbidities will contribute to a better understanding of epilepsy itself (4). Genetic factors can also modify the mutual interaction between epilepsy and comorbidities (4). Charlson and Elixhauser comorbidity indices are well-established for prediction of hospitalization costs, hospital length of stay and impact of comorbidities on hospital mortality. Each comorbidity is weighted and assigned a score, and based on their sum, individual prognosis is predicted. (4,11,12). Epilepsy-specific comorbidity index (ESI) is also used in clinical practice. Prognostic points are assigned to numerous conditions: disorders of the pulmonary circulation, hypertension, arrhythmias, congestive heart failure, peripheral vascular disease, kidney disease, solid tumors without metastases, paraplegia and hemiplegia, aspiration pneumonia, dementia, brain tumors, anoxic brain injury, moderate and severe liver disease and metastatic cancer. A higher number of points achieved is associated with higher mortality (4,13,14). The most common causes of death among patients with epilepsy are comorbidities such as neoplastic, cardiovascular or cerebrovascular disease (4,15).

EPILEPSY AND NEURODEVELOPMENTAL DISORDERS

Among children and young people with epilepsy, there is a higher prevalence of neurodevelopmental disorders which include autistic spectrum related disorders (ASDs), intellectual disabilities and attention deficit hyperactivity disorder (ADHD). Despite the high prevalence and negative effect on the clinical course of epilepsy, patients often don't receive adequate therapy due to delayed diagnosis or misdiagnosis. These patients experience side effects of antiepileptic drugs (AEDs) more frequently and are prone to developing drug-resistant epilepsy (16). The risk of developing epilepsy among patients with autism is 2.7-44.4%, which is seven times higher risk than the rest of the population. The coexistence of these conditions is particularly present among people with intellectual disabilities, and it is more common in women, elderly, people with lower socioeconomic status (17). Two theories explain the higher incidence of ASDs in patients with epilepsy. Epileptic seizures can affect the synaptic plasticity responsible for learning and behavior. The excitatory/inhibitory imbalance noted during seizures can produce permanent physiological and functional damage during neurodevelopment. It can cause abnormal synaptic reorganization and cortical neurons dysfunction. Another theory assumes that an underlying neurological disorder predisposes individuals to the development of both epilepsy and ASDs (17). Genetic disorders in which coexistence of these conditions is more common include Rett syndrome, fragile X syndrome and complex tuberous sclerosis complex (18). Some of the specific epileptic syndromes in which it is more frequent are infantile spasms and Dravet syndrome (17).

EPILEPSY AND VASCULAR DISEASES

Cerebrovascular diseases are the most common underlying cause of epilepsy in elderly (19). They cause 30-50% of new-onset epilepsies (20). There is an expected growth of the epilepsy prevalence due to the increasing percentage of elderly people in the population. Cerebrovascular diseases associated with epilepsy are ischemic stroke, cerebral hemorrhage, post-reperfusion state (after thrombolysis or thrombectomy) and small blood vessel diseases due to arteriolosclerosis (19). Predictors of the epilepsy development after stroke are younger age, cortical involvement, extent and severity of post-stroke lesions and a hemorrhagic component (19). Genetic factors have an important role in the epilepsy pathogenesis. For example, CD40-1C/T polymorphism is associated with an increased tendency of post-stroke seizures (20). Early epileptic seizures occur within the first seven days of a stroke, while seizures that occur after this period are considered late (19). Epilepsy after an ischemic stroke usually occurs in an area with insufficient oxygenation which is not completely necrotic. Hemorrhages due to blood-brain barrier disruption after an ischemic insult are extremely important as well (20). Seizures are more frequent after primary intracerebral or subarachnoid hemorrhage than after cerebral ischemic infarction (21). Epilepsy is usually caused by cortical venous hemorrhage (20). The frontal and temporal lobes are

characteristic sites of epileptogenesis, which explains increased incidence of seizures after complete infarction of the anterior cerebral circulation (21). Epilepsy is usually caused by cortical venous hemorrhage (20). The frontal and temporal lobes are characteristic sites of epileptogenesis, which explains increased incidence of seizures after complete infarction of the anterior cerebral circulation (21). Risk factors for cerebrovascular diseases are also associated with the development of epilepsy. Among them, high blood pressure, high cholesterol, coronary and peripheral arterial disease have the largest effect (22). Epileptic patients have an increased risk of acute myocardial infarction and sudden cardiac death (SCD) (23). In 2020, the clinical entity „epileptic heart" was introduced into the literature. It is described as the damage to the heart and coronary vasculature caused by the cardiotoxic effect of catecholamines and repeated hypoxia (24, 25). Sudden cardiac death constitutes a 4.5-fold greater risk for premature death in patients with epilepsy compared to sudden unexpected death in epilepsy (SUDEP), which by definition excludes all known causes of mortality, including cardiac comorbidities (25). Antiepileptic drugs have adverse effects on the electrophysiology of the cardiac myocytes and circulating lipids (23). Inducers of cytochrome P450 can adversely affect the lipid profile, while sodium channel blockers may be potentially arrhythmogenic. Moreover, there is a possibility of the interaction between the AEDs and anticoagulant/ antiplatelet therapy. Therefore, it is necessary to appropriately prescribe medications and their dosage. This particularly refers to the potent inducers of liver enzymes, such as carbamazepine, phenobarbitone, phenytoin and primidone, which can reduce the levels of concomitantly administered drugs in therapy. Due to the increasing use of new oral anticoagulant drugs, the use of zonisamide, lamotrigine and lacosamide is recommended. They have no clinically relevant interactions with the mentioned group of medications (24,25).

EPILEPSY AND NEURODEGENERATIVE DISEASES

Primary neurodegenerative diseases cause 10-20% of epilepsy in the elderly. The number is assumed to be even higher because clinical manifestations of epilepsy are often unrecognized and misdiagnosed (20). Half of epilepsy cases in the elderly is of unknown cause. It is estimated that neurodegenerative diseases are the second most common cause of epilepsy after a stroke. Some theories presume that certain percentage of epilepsies of unknown cause is actually consequence of presymptomatic neurodegenerative diseases (26).

EPILEPSY AND MIGRAINE

Headache has long been associated with epilepsy. Postictal epileptic headache is more common than preictal and ictal (27,28). The hypothesis of a possible mutual pathogenetic background is based on the neurons hyperexcitability and ion channels abnormalities. Imbalance between excitatory molecules such as glutamate and inhibitory like gamma-aminobutyric acid (GABA) has been proven both in epilepsy and migraine (28). It is assumed that the migraine aura phenomenon is caused by a transient wave of mass neuronal depolarizations, also known as cortical spreading depression. It leads to oligemia (hypoperfusion), after which, during the headache phase, hyperperfusion occurs (29). In the differential diagnosis of migraine aura, especially the visual one, it is necessary to think about epileptic seizure because they have overlapping symptoms (27). In familial hemiplegic migraine (FHM), a rare autosomal dominant form of migraine with aura, these two conditions can coexist (27). Numerous AEDs are effective in the migraine treatment. The ones used for prophylaxis are topiramate and valproate. It has been proven their harmful effect during pregnancy (27).

EPILEPSY AND MULTIPLE SCLEROSIS

The prevalence of epilepsy among patients with multiple sclerosis (MS) is between 0.5% and 10.8%, and epileptic seizures are 3 to 6 times more common than in the general population (30). Epilepsy is usually diagnosed ten years after establishing MS diagnose (31). The cause of epileptic seizures is insufficiently explained. However, it is assumed that cortical and juxtacortical inflammation, demyelination and atrophy play an important role in pathogenesis (32). Status epilepticus is more frequent, but resistance to AEDs is less common (32). Early introduction of immunomodulatory/immunosuppressive therapy decreases prevalence of epilepsy in patients with multiple sclerosis (31). Research on the frequency of certain types of epileptic seizures that occur in multiple sclerosis show different results. Some have indicated that focal to bilateral tonic-clonic seizures are the most common, while others have revealed generalized tonic-clonic seizures being most prevalent. It is difficult to determine the epilepsy prognosis (32). Active

epilepsy carries the risk of MS progression from relapsing-remitting multiple sclerosis into secondary progressive multiple sclerosis (33). Epileptic seizures can be the first clinical presentation of multiple sclerosis because demyelinated plaques in the brain act as epileptic foci (34). Depending on the relationship between epileptic seizures and MS activity, patients are divided into three groups (34):

a) those whose seizures are associated with MS relapse
b) those whose seizures are not associated with MS relapse
c) those with frequent seizures associated with cognitive deterioration.

EPILEPSY AND AUTOIMMUNE DISEASES

ILAE included autoimmunity in the classification of epilepsy based on six etiological factors (35). Since 2017, according to ILAE recommendations, it is considered if the seizures result from an underlying autoimmune disorder (36). Antibodies directed against antigens on neuronal cell surface are the most important in epileptogenesis. There are also antibodies directed against intracellular antigens such as anti-glutamic acid decarboxylase antibodies. These can be found in 80% of patients with diabetes type 1 (37). Systemic lupus erythematosus (SLE) and diabetes mellitus type 1 have the highest risk of developing epilepsy (38). It is important to be careful about the interaction of immunosuppressants and antiepileptic therapy (38). Immunomodulators are increasingly included in the treatment of refractory epilepsy (35). Autoimmune epilepsy is often drug-resistant (36).

EPILEPSY AND BRAIN TUMORS

Sometimes, epilepsy can be the only symptom of a brain tumor (39). Epilepsy associated with brain tumors accounts for 12% of acquired epilepsies and 4-10% of total epilepsy number (40). Among all tumor types, seizures are most common with glioneuronal tumors (70–80%), especially in patients with frontotemporal or insular lesions (41). Seizures are also common in patients with glioma, with the highest rates of epilepsy (60–75%) observed in individuals with low-grade gliomas located in superficial cortical or insular regions. Approximately 20–50% of patients with meningioma and 20–35% of those with brain metastases also suffer from seizures (41). There is a specific group of tumors associated with epilepsy called "long-term epilepsy associated tumors" (LEAT). Their characteristics include a slow growth rate, early-onset drug-resistant epilepsy, neocortical localization and temporal lobe predominance. The most common LEATs are dysembryoplastic neuroepithelial tumors and gangliogliomas (39). Tumor-related seizures are symptomatic by nature. Semiologic characteristics depend on localization of tumors. Focal seizures with impaired awareness are more common in temporal tumors and focal to bilateral tonic-clonic seizures are more common in extratemporal tumors (42). Cortical tumors are associated with a higher risk of causing seizures. Additionally, frontal, temporal and parietal tumors are associated with a higher risk of causing epilepsy than occipital tumors. Infratentorial tumors are rarely associated with epilepsy (42). Epilepsy associated with tumors has a poorer response to antiepileptic therapy, which is confirmed by the fact that it is pharmacoresistant in 30% of the cases. The clinical outcome is better if surgical resection is performed. Surgical treatment should be considered as early as possible, regardless of pharmacoresistance. This would avoid long-term consequences of epileptic seizures, side effects of antiepileptic drugs and tumor progression (39). After surgical treatment, approximately 60-90% of patients is seizure free (41).

EPILEPSY AND PSYCHIATRY DISEASES

Back in the 1880's, Gowers noticed the increased frequency of behavioral symptoms and mental health issues among people suffering from epilepsy. The importance of recognizing conditions in the domain of the psychiatric disorders has become increasingly significant during the recent years. Underlying causes of the dysregulation and the consequent seizure generation may also affect the mechanisms responsible for mood and behavior control (43). According to the results of clinical studies involving patients with epilepsy and psychiatric comorbidities, the prevalence of any psychiatric disorder was observed in up to 43.3% in the general population of patients with epilepsy, in 51% of patients with idiopathic generalized epilepsy, and in 43.1% of patients with temporal lobe epilepsy. The most common psychiatric disorders associated with epilepsy include mood disorders – affective disorders (up to 40%), anxiety disorders (up to 30.8%), personality disorders (up to 11% in juvenile myoclonic epilepsy) and psychotic disorders (in about 2-9% of patients with epilepsy) (44). Mood disorders are the leading psychiatric comor-

bidity in epilepsy, followed by anxiety disorders. Although mood disorders most often occur after the epilepsy onset, some studies have proven that it can precede the development of the epilepsy. Psychosis of epilepsy is a rare comorbidity in patients with epilepsy, but one of the most prominent psychotic disorder due to another medical condition. A meta-analysis of 57 studies of people with psychosis and related disorders showed a prevalence of 5.6 to 7% in patients with temporal lobe epilepsy (44, 45). It can be classified according to its temporal relation to seizures as preictal, ictal, paraictal, interictal and postictal, with the latter being the most common, occuring in 60% of patients (44, 46). The prevalence of psychosis is highest in patients with focal epilepsy, especially those with medial temporal lobe involvement. This comorbidity presents a challenge in treatment and requires an individualized and multidisciplinary approach to improve the patient's quality of life (44).

EPILEPSY AND SLEEP DISORDERS

Sleep disturbances in people suffering from epilepsy can be caused by nocturnal seizures, sedation as a side effect of AEDs, inadequate sleep hygiene, insufficient amount of sleep and sleep disorders as comorbidities (47). The most common comorbidity in people with refractory epilepsy is obstructive sleep apnea (47). Treatment with nasal continuous positive airway pressure (CPAP) reduces hypoxia and sleep fragmentation, which consequently leads to better seizure control (48). SUDEP is a sleep-related fatal complication of epilepsy. It most often occurs in people between the age of 15 and 40. Risk factors are male sex, refractory epilepsy and polytherapy. The exact mechanism is yet unknown, but there are some evidences that generalized tonic-clonic seizures playing an important role in pathogenesis (47). There are also some indications that SUDEP is caused by postictal apnea (49). Epileptic seizures can worsen sleep architecture. However, mentioned comorbidities can cause seizure exacerbation as well. Antiepileptics can also worsen sleep architecture (50). Patients treated with lamotrigine have an increased risk of insomnia, while phenobarbitone is associated with excessive daytime sleepiness. A side effect of some antiepileptic drugs, such as valproate, is obesity (51). On the other hand, zonisamide has proven itself effective in the treatment of obese patients with epilepsy. It helps in losing weight and consequently lowers the risk of obstructive sleep apnea development (52).

CONCLUSION

Comorbidities include numerous somatic and psychiatric conditions. Although comorbidities are frequent in patients with epilepsy, there are still uncertainties in the significance of these conditions. Common risk factors and pathophysiological mechanisms of the disease are oftentimes present. Comorbidities not only affect the quality patients' life, but also the clinical course of epilepsy itself. Generally, they are associated with a less favorable clinical outcome and consequently worse quality of life. They directly increase healthcare expenditures due to more frequent hospitalizations and challenges in establishing an optimal treatment strategy. The importance of adequate screening methods and preventive measures lies in the opportunity to early detect simultaneously present diseases that may not be clinically manifest in the beginning. Enhanced comprehension of the mutual effect of these conditions could contribute to improving the effectiveness of the therapeutic approach.

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