Epilepsy in elderly

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Epilepsy in elderly

GRADUATE THESIS

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ABBREVIATIONS:

AEDs – anti-epileptic drugs

CAA – cerebral amyloid angiopathy

CI – confidence interval

DRE - drug-resistant epilepsy

ECG – electrocardiogram

EEG – electroencephalogram

EPS – early post-stroke seizures

ILAE – International League Against Epilepsy

LPS – late post-stroke seizures

NCSE – non-convulsive status epilepticus

NIHSS – The National Institutes of Health Stroke Scale

RBD – rapid eye movement sleep behavior disorder

SE – status epilepticus

TEA – transient epileptic amnesia

TGA – transient global amnesia

TIA – transient ischemic attack

TFNEs – transient focal neurological episodes

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Summary

Title: Epilepsy in elderly

Author: Edi Kovačević

Epilepsy is a brain disease characterized by a permanent predisposition to seizures and the neurobiological, cognitive, psychological and social consequences of recurrent seizures, caused by abnormal excessive or synchronous neuronal activity in the cortex of the brain. It is one of the most common neurological diseases, The frequency of epilepsy increases with aging, occurs more often in males and in developing countries. Epilepsy is not a single disease, not even an individual syndrome, but rather a wide range of clinical symptoms - epileptic seizures, which can be manifested in the sensory, motor, experiential or autonomic-vegetative sphere, often with loss or disturbance of consciousness. Epilepsy may have structural, genetic, infectious, metabolic, immune or unknown etiology. Among elderly, the most common known risk factors are cerebrovascular disease, dementia, cerebral neoplasms and head trauma. There are several guidelines as well as classifications for epilepsy that are set and keep being updated by the ILAE. However, concerning the epilepsy in elderly population, the researchers are still trying to find some answers. The number of elderly population is rising in the developed part of the world, so it is a topic that needs to be addressed. A large portion of older people suffer from epilepsy of unknown onset. There is a long list of differential diagnoses possible in these individuals, so it can be easily misdiagnosed. Until now, it is known that older people are more compliant with less frequent dosing of therapy, have less adverse effects on monotherapy and should take lower doses of AEDs. The therapy in elderly patients should be individualized. Nonetheless, there are not complete guidelines regarding management of epilepsy in elderly. Many elderly also suffer from comorbidities, which further complicates the selection of therapy. With the recent development of new AEDs it opens even more possibilities. Therefore more researches need to be conducted and evidence to make the decision making easier for the physicians in selecting the optimal path of treatment.

Key words: seizure; epilepsy; elderly; diagnosis; therapy

Sažetak

Naslov: Epilepsija kod starijih osoba

Autor: Edi Kovačević

Epilepsija je bolest mozga koju karakteriziraju trajna sklonost nastanku epileptičnih napada te neurobiološke, kognitivne, psihološke i socijalne posljedice recidiva napada. Uzrokovana je abnormalnom prekomjernom ili sinkronom aktivnosti neurona korteksa mozga. To je ujedno jedna od najčešćih neuroloških bolesti. Učestalost epilepsije raste u starijoj životnoj dobi, češće se javlja kod muškaraca i u zemljama u razvoju. Epilepsija nije jedinstvena bolest, čak ni pojedinačni sindrom, već obuhvaća širok spektar kliničkih simptoma - epileptičnih napada, što se može očitovati u osjetnoj, motoričkoj, doživljajnoj ili autonomno-vegetativnoj sferi, često uz gubitak ili poremećaj svijesti, odnosno svjesnosti. Epilepsija može biti strukturalne, genetske, infektivne, metaboličke, imunološki posredovane ili nepoznate etiologije. Kod osoba starije životne dobi, najčešći poznati čimbenici rizika su cerebrovaskularne bolesti, demencija, cerebralne neoplazme i traume glave. Postoji nekoliko smjernica kao i klasifikacija epilepsija koje postavlja i stalno ažurira ILAE. Međutim, što se tiče epilepsije u starijoj populaciji, istraživači još uvijek pokušavaju pronaći neke odgovore. U razvijenom dijelu svijeta raste broj starijeg stanovništva, pa je to tema koja bi trebala biti aktualna. Velik dio starijih ljudi pati od epilepsije nepoznatog početka. Popis mogućih diferencijalnih dijagnoza kod tih osoba je dug, tako da se lako može pogrešno dijagnosticirati. Do sada je poznato da starije osobe više pristaju na rjeđe doziranje terapije, rjeđe razvijaju nuspojave ako se primjenjuje monoterapija i trebaju uzimati niže doze antieplieptičkih lijekova. Terapija u starijih bolesnika treba biti individualizirana. Ipak, ne postoje potpune smjernice za liječenje epilepsije u starijih osoba. Mnoge osobe starije životne dobi pate i od ostalih komorbideta, što dodatno otežava odabir terapije. Nedavnim razvojem novih antiepileptika otvara se još više mogućnosti. Stoga je potrebno provesti više istraživanja i dokaza kako bi se liječnicima olakšalo donošenje odluke u odabiru optimalnog liječenja.

Ključne riječi: napad; epilepsija; osobe starije životne dobi; dijagnoza; terapija

Introduction

Epilepsy is a brain disease characterized by a permanent predisposition to seizures and the neurobiological, cognitive, psychological and social consequences of recurrent seizures. With written records reaching back to 4000 BC, epilepsy is one of the world's earliest known disorders. It is also one of the most common neurological diseases, a chronic non-communicable brain illness that affects around 50 million individuals around the world (1). Epilepsy is characterized by a specific and diverse etiology that is an integral part of the current classification according to the International League Against Epilepsy (ILAE). Epilepsy is not a single disease, not even an individual syndrome, but rather a wide range of clinical symptoms - epileptic seizures, which can be manifested in the sensory, motor, experiential or autonomic-vegetative sphere, often with loss or disturbance of consciousness. This disease is still a significant medical and public health problem, especially in specific groups of patients such as pregnant women and the elderly. For years, epilepsy has been associated with fear, misunderstanding, prejudice, and public unfairness. The social stigma still persists in many countries today, affecting the quality of life for persons living with this condition and their families (1). It is caused by abnormal, excessive or synchronous neuronal activity seen on EEG that will result in seizure episodes. They can also vary in frequency, from less than one per year to several per day. Interestingly, up to 10% of people around the world will experience at least one seizure during their whole life, but a single seizure does not indicate epilepsy (1). According to the ILAE, the operational (practical) clinical definition of epilepsy from 2014 is defined by any of the following: 1. In case that an individual has two or more unprovoked or reflex seizures that occur more than 24 hours apart from each other. 2. One unprovoked or reflex seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years. 3. Diagnosis of an epilepsy syndrome. It is thought that in order for epilepsy to be resolved in individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years (2).

Epidemiology

Regarding the epidemiological situation, the occurrence of epilepsy varied from 50.4 to 81.7 per 100,000 people per year, measured between the 1990 and 2016 (3). Due to the developments and improvements in the health care during the past years, people have been able to survive even after severe head injuries, strokes, intracranial infections and at the same time live while being diagnosed with primary and secondary brain tumors, which cause increased likelihood of epilepsy. Before the newer medical diagnostic procedures as well as treatment of patients' with preparations and drugs, for instance, tissue-plasminogen activator, antibiotics, antivirals, magnetic resonance imaging, focused radiation and so on, numerous of these would not have lived until the point of time, where they would be diagnosed with epilepsy. As for some other diseases, same can be seen in the case of epilepsy, that its' frequency and rate depend on the state of the country as it is more common in the countries with low-income countries that are much more affected (4,5). In poorer countries higher incidence of parasitic infections, increased rates of head trauma and lack of available treatment can be observed and these are specific factors that have an impact toward this result. There have also been assumptions that genetic differences could also affect this phenomenon, but that needs to be further proven with future studies, in order to determine, how the genetics are connected to epilepsy (4). Nevertheless, the most impactful variable causing the increase in epilepsy incidence in developing world is the shortage of anti-epileptic drugs (AEDs). The cheapest AEDs are usually inaccessible in developing countries even though several AEDs have been presented into the market in the past years. It was shown that almost 70% of persons who are living with the burden of epilepsy could be without seizures if they have been properly diagnosed and treated, according to the estimation by the World Health Organization (1). Epilepsy occurs in both genders equally, however it does not affect people of different ages equally. It has a rather bimodal distribution, where one peak is seen in children from 5 to 9 years old and the second one in elderly people, around 80 years of age (6,10).

Seizure classification

According to the ILAE there are two classifications of seizures: a basic version and an expanded one. Firstly, let's discuss the basic version of the ILAE classification of seizure types. The main division of seizures is defined by concerning the onset of seizures. The seizures can be either focal, generalized, unknown, or of unclassifiable origin. A focal seizure is a seizure that begins with a single point of focus. In the past these kinds of seizures were termed "partial" seizures. By using the term "focal" it is more precisely defined that it is pertaining regarding seizures that begin from a focus. On the other hand the term "partial" better describes that these seizures originate from only a part of the body. The second group of seizures is "generalized" seizures, meaning that at the initiation of the seizure occurs in both cerebral hemispheres. The seizures with asymmetrical onset are also classified as "generalized", as long as both hemispheres influence the beginning of the seizure. In cases, where it is impossible to properly categorize the seizure into focal or generalized, even though the patient's anamnesis and different diagnostic modalities have been used, then the seizure is thought to be of unknown onset. The ability to classify a seizure as one of "unknown onset", is to allow the physicians to describe other characteristics of the seizure, although its' onset is not specifically known. For instance a bystander, such as a family member, could spot an individual lying on the floor with whole body tremors, unconscious, a person that is drooling a tongue biting. In that case the onset of the seizure is unknown, thus this can be example of an "unknown onset to bilateral tonic-clonic seizure. The mentioned seizure may have been of a focal or of a generalized onset and that type of seizure would have been unclassifiable in the past, but in the current times it is possible to classify it. There is still a need for the so called unclassifiable seizure, although they are now a subcategory of seizures that are of an unknown onset. Next step in classifying the seizure, after placing it into the right category after its onset, is the state of consciousness. The focal seizures are further subdivided according to the individual's consciousness into either aware or a seizure with an impaired awareness. Thus these seizures can be either called "focal aware seizures" or "focal impaired awareness seizures". Focal aware seizures used to be named simple partial seizures and the latter were known in the past as complex partial seizures. These changes were made in order to make it clearer to the patients, because it was thought that classifying according to the awareness impairment, is

better understood than a seizure that can be simple or complex. Even though they are different and might have various driving consequences, none of these is more complex or simple than the other. Therefore, this alteration is expected to cause better understanding from the patients' perspective. Furthermore, many driving laws are based on the level of consciousness in their criteria, so an individual will immediately realize why he or she is unable to drive in the situation of having focal impaired awareness seizures. In case of generalized seizures there is no distinction between seizures regarding the awareness, as any seizure that is classified as generalized, is one where an individual has impaired consciousness. The basic seizure classification's last differentiation is regarding the fact, depending on the matter of motor component of a focal or generalized seizure. With further addition of word "motor" focal, generalized and seizures of unknown onset can be divided into motor and nonmotor. In situation of generalized and unknown onset seizures the motor component can be further split into "tonic-clonic" or "other motor." It is important to mention that focal seizures should be termed motor only if they are of motor onset, focal seizures that extend from the focus and pertain both hemispheres are classified as "focal to bilateral tonic-clonic." There is another change from the previous classification as the term "generalized" is used strictly in the cases where seizures are of generalized onset. The addition of the "unknown" category enables more information (such as whether there is a motor component) to be specified. This ILAE 2017 classification relies on the type of the onset and thus seizures should be classified accordingly. A physician should be 80% assured whether a seizure is of focal onset, otherwise the seizure should be categorized as "unknown onset." Due to the false-negative rate that usually occurs in clinical statistics, the 80% cut-off value was designated.

The expanded seizure classification is an upgraded division of basic classification by providing more specification within the motor and nonmotor groups of seizures. These should be used whenever the seizures could be described more in depth. These labels are decided according to the manifestation of the initial symptom or sign seen on the person suffering the seizure. The initial signs are not always the most noticeable ones. Although there is one type of seizure where it necessary that the most prominent sign has to be visible and that is the case in "behavioral arrest" seizures. Sometimes an individual seizure cannot be obviously classified into one of

the possible groups and in that instance the next best description should be used or another description that can offer more details about the said seizure. There are further guidelines in how to properly and more in detail classify seizures in “The instruction manual for the ILAE 2017 operational classification of seizure types” (8). These signifiers as well as other free text descriptions are not exactly part of the classification, however they can additionally describe the seizure.

Table 1: ILAE 2017 Classification of Seizure Types Expanded Version

Focal Onset		**Generalized Onset**	**Unknown Onset**
Aware **Impaired**	**Awareness**	**Motor**	**Motor**
		tonic-clonic	tonic-clonic
Motor Onset		clonic	epileptic spasms
automatisms		tonic	**Non-Motor**
atonic [2]		myoclonic	behavior arrest
clonic		myoclonic-tonic-clonic	
epileptic spasms [2]		myoclonic-atonic	
hyperkinetic		atonic	
myoclonic		epileptic spasms	
tonic		**Non-Motor (absence)**	
Non-Motor Onset		typical	
autonomic		atypical	
behavior arrest		myoclonic	
cognitive		eyelid myoclonia	
emotional			
sensory			
focal to bilateral tonic-clonic			**Unclassified [3]**

[1] Definitions, other seizure types and descriptors are listed in the accompanying paper and glossary of terms

[2] Degree of awareness usually is not specified

[3] Due to inadequate information or inability to place in other categories

Adapted from Fisher RS, Cross JH, D'Souza C, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. *Epilepsia*. 2017;58(4):531-542.

Epilepsy classification

To continue with, the classification of epilepsy should follow the designation of seizure to the proper group. There are three main groups in the classification of epilepsy, they can be either focal, generalized, a combination of focal and generalized or unknown. In order to assign the type of epilepsy, all of the patient's seizures should be written down grouped and classified so the epilepsy can be classified accordingly (9). For example in a patient with focal aware cognitive to bilateral tonic clonic seizures that arise from the left and right temporal lobes, his or her seizures would be classified as focal epilepsy. In the case of focal and generalized seizures concurrently, these seizures would be put in the combined focal and generalized epilepsy group (10). After establishing the type of epilepsy, the next step is defining its etiology. The epilepsy can be categorized into one of the six groups, which are the following structural, genetic, infectious, metabolic, immune, and that of unknown etiology. Individual's epilepsy can be of multiple etiologies (9). In order to define epilepsy as one of a structural etiology there should be some structural finding on a diagnostic modality that can prove that this is the most probable cause (11). For instance, a person's seizures that are originating from the left frontal lobe, which are caused by a glioblastoma in the left frontal lobe would be classified as epilepsy due to a structural etiology. In cases where a specific disease, such as a defined abnormal gene or copy number results in epilepsy, they would be termed as ones of genetic etiology. Sometimes a patient's family history, EEG, and seizure semiology align with the diagnosis of genetic epilepsy and therefore in these occasions genetic testing is not needed. Such a situation occurs when a patient has focal aware auditory to bilateral tonic clonic seizures with EEG findings of right lateral temporal seizures, in a family where multiple relatives have identical semiologic findings and thus can be diagnosed based on this presentation with familial autosomal dominant lateral temporal lobe epilepsy (10). This is due to approximately 80% penetrance and because of a mutation in leucine-rich glioma inactivated protein 1 (LGI-1) on chromosome 10q. Family history of genetic epilepsy is not obligatory in order to diagnose a patient's epilepsy as one of genetic etiology, they can also happen due to de novo mutations. Genetic anomalies are not the only ones that can cause this kind of etiological epilepsy (12). Another etiology that might arise is an Infectious agent, which causes epilepsy occurrence. Some of these infectious culprits

can be neurocysticercosis, human immunodeficiency virus, cytomegalovirus and cerebral toxoplasmosis. It is known that most of these infections cause structural abnormalities, however as the initial cause is infection, the latter would be the best term used for describing etiology of this particular epilepsy. Individuals who suffer seizures chronically, after the acute onset of meningitis or encephalitis due to an infection are also diagnosed with infectious epilepsy. The brain imaging often seems structurally intact and the only clue pointing towards infectious etiology is a history of meningitis without any residual structural abnormalities (13). Furthermore, some specific metabolic imbalances may be the source of epilepsy and in these instances the epilepsy is of metabolic etiology. Such occur in situations where patient has pyridoxine-dependent seizures and cerebral folate deficiency caused seizures (14). In the case of pyridoxine-dependent seizures, the etiology is of utmost importance as its recognition allows the physician to start with the proper treatment. Last identifiable etiological causes of epilepsy are autoimmune diseases. One of the diagnoses that is becoming increasingly prevalent and might cause epilepsy is antibody-mediated limbic encephalitis. Moreover, there are several antibodies that have been identified as causes of epilepsy, the most common ones being N-methyl-D-aspartate receptor (NMDAR), LGI-1, anti-neuronal nuclear antibody type 1 (ANNA-1), Ma, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), γ-aminobutyric acid-B (GABA-B), and metabotropic glutamate receptor 5 (mGluR5) (10,15). Similarly to pyridoxine-dependent seizures mentioned above, recognizing an immunologic cause of epilepsy should not be overseen due to its treatment. Managing seizures due to limbic encephalitis is specific, as they respond very poorly to AEDs. These types of seizures usually improve only after introducing immunologic agents. These medications are such as steroids, immunoglobulins, plasmapheresis, and rituximab (16). Though some epilepsy cannot be classified according to one of the described etiologies, therefore they are put in a category as epilepsy of unknown etiology. It is not rare that the reason of epilepsy's manifestation is unable to be identified. A few recent studies tried to determine the etiology of epilepsy in cohort studies of children and adults and according to them, it was found that approximately 40% of epilepsy, their etiology remained unknown (17,18). However, this is not an unanticipated result, as many patients with seizures have no known family history of epilepsy, a normal MRI/CT scan, normal complete metabolic panels, a clinical history that does not correlate with any known genetic syndrome, and no known infectious or autoimmune

disease (10). In both studies, in children and adults, it is noticeable that unknown etiology was most common, followed by genetic and then structural causes in children (17). But, in adults as well as elderly, second most common etiology was structural, such as different types of strokes and tumors, followed by genetic etiology (18,19). Lastly, it is important to mention that this classification also takes into consideration the comorbidities that are present in the patient, which then affect the decisions regarding treatment of epilepsy.

Epilepsy in elderly

Epidemiology, incidence and prevalence

Firstly, regarding the elderly, it is essential to define this age group. Most frequently elderly are people above 60 to 65 years old or older. These cutoff values are based on the nineteenth century, because that is when it was established by law in some European countries, as the age at which a person became eligible to receive pension. Nowadays, the United Nations uses 60 years as a cutoff to refer to elderly people, while most high-income countries use 65 years (20,21). Globally, the fastest growing age group is actually people aged older than 65 years. There are predictions that amount of old age people in the USA alone is expected to increase from 43.1 million in 2012, to 83.7 million by 2050, as well as growing numbers of those older than 90 years (23). Even though there are no agreed definitions of epilepsy in older people, machine learning defined approximate age period. According to the artificial intelligence applied to a prospective cohort database to examine various attributes associated with late-onset epilepsy, it defined a threshold of 65–70 years as likely to be the most optimal to explain late-onset epilepsy (24). These findings however need further evaluation. Incidence increases continuously in people aged older than 50 years and the highest incidence can be observed in people that are older than 75 years (25-27). The Global Burden of Disease report on epilepsy and the data once it was age-standardized, indicated a similar pattern in high-income and low-income countries, as well as reported epilepsy prevalence of 5.4 per 100 people in older populations (26). In another study, the Cardiovascular Health Study, an incidence of approximately 25 cases per 1000 person years was observed in a cohort of almost 6000, mostly white, older people. At the most recent follow-up, epilepsy prevalence

was 5.7 per 100 people, which is much higher compared to the lifetime active epilepsy prevalence (28,29). Some studies have stated a point prevalence of more than 7.5% in cases, where elderly are living as nursing home residents (30). Administrative database studies indicate that the incidence and prevalence increase with age and are the highest in African American and lower in Asian and Native American populations compared to the white people (31,32). The explanations for these differences remain undefined.

Etiology and risk factors

The increased incidence of epilepsy rate among the elderly is a consequence of high rate of numerous significant epilepsy risk factors. Among these the most frequent are cerebrovascular disease, dementia, cerebral neoplasms and head trauma are the most common central nervous system disorders that concern new-onset epilepsy in elderly people (33). Even though there have been many developments in order to try identifying the cause of epilepsy, in more than one-third of epilepsy cases in older individuals these causes cannot be specified (34).

Regarding the predictors of new-onset epilepsy in people that are above 65 years old, the most important independent determinant is cerebrovascular disease (35, 36). In occurrences, in which the elderly have suffered of cerebrovascular disease beforehand, this represents up to 65% of new-onset epilepsy patients, which is more than five times higher incidence compared with individuals of the same age (36). Another study has shown that in older aged patients who previously had stroke have more than three times greater relative risk of developing new-onset epilepsy than other individuals above 65 years of age (28). Because of the variance in supposed pathophysiology and risk of recurrence, the differentiation between early post-stroke seizures (EPS) that occur within first seven to fourteen days after a stroke and late post-stroke seizures (LPS) is essential. Early post-stroke seizures occur due to cellular membrane instability and the release of glutamate-mediated excitotoxicity. On the other hand late post-stroke seizures are triggered by gliosis, neuronal deafferentation and collateral sprouting (37). EPS are the consequence of an acute cerebral insult and thus convey a decreased risk of recurrence. In roughly a third of EPS cases the adults develop epilepsy, according to hospital-based studies, while in LPS the development of epilepsy is over 90% (38). However after a stroke, the

chances of experiencing either EPS or LPS are approximately the same, because one of these might occur in up to 6% of elderly patients (37,39). There are several risk factors that increase the chances of developing EPS and LPS and are termed as Independent seizure predictors. Firstly, risk factors that influence the probability of both are the size of the total anterior circulation infarct, hemorrhagic stroke, cortical involvement and clinical stroke severity, in situations where NIHSS is more than 14. Hemorrhagic transformation of ischemic stroke, hyperglycemia and alcoholism are risk factors for EPS, while incidence of LPS increases in cases of patients younger than 65, recurrent strokes and in people with history of early post-stroke seizures (21). Development of cerebrovascular disease can also apparently be predicted by the presence of epilepsy. When comparing older people with a history of seizures with elderly of the same age group with no such history, those individuals that experienced seizures in the past have a relative risk of stroke of 2.89 (95% CI: 2.45, 3.41) (40). This event has been named “vascular precursor epilepsy” by some experts. There is higher load of risk factors connected with the vascular system in adults diagnosed with epilepsy when compared to the people of same age (41). When matching individuals with childhood-onset epilepsy to the control group, they also have greater cerebrovascular changes at 45 years of age that are seen on the magnetic resonance imaging (42). Among the factors that can affect the pathogenesis of epilepsy, besides the ones mentioned are neurodegenerative diseases. Due to the several different structural and biochemical changes that occur in the central nervous system, such as the loss of inhibitory neurons in hippocampal and neocortical areas, glutamate-mediated excitotoxicity, disturbances in neurotransmitters and ion channel dysfunction (43).

Old age patients with dementia have a risk of developing new-onset epilepsy, which is two to ten times higher (33,44). Alzheimer's disease and vascular dementia reportedly carry similar risk according to the estimates (45). In patients with Alzheimer's disease at least one unprovoked seizure will be manifested during the lifetime of ten to 22% of these patients. Risk factors associated with development of epilepsy include early-onset Alzheimer's disease and familial presently I or amyloid precursor protein gene mutations that have been described in late-onset myoclonic epilepsy in Down syndrome (43). Hyperphosphorylated tau pathology has been shown in older individuals with DRE and progressive cognitive decline with the

observation of temporal lobe resections (46). Furthermore, greater amyloid deposition at 50-year follow-up can be detected in individuals with childhood-onset epilepsy compared to the control group (47). As reported by a prospective population-based study, a relative risk of 1.5 (95% CI: 1.4, 1.7) is seen in persons that are 50 years old or older of developing dementia over 8 years (48).

Finally, other CNS lesions, such as cerebral neoplasms or remote traumatic brain injury, seen in elderly individuals increase the risk of new-onset epilepsy development by approximately two fold (33). In adults 20–40% of cerebral neoplasms present with seizures as the first sign of the disease (49). Traumatic brain injuries occur more commonly in elderly people, due to the increased risk of falls in old age (50).

Presentation

Approximately 40–50% of new cases of seizures in the older patients are classified as focal impaired awareness seizures (51- 53).

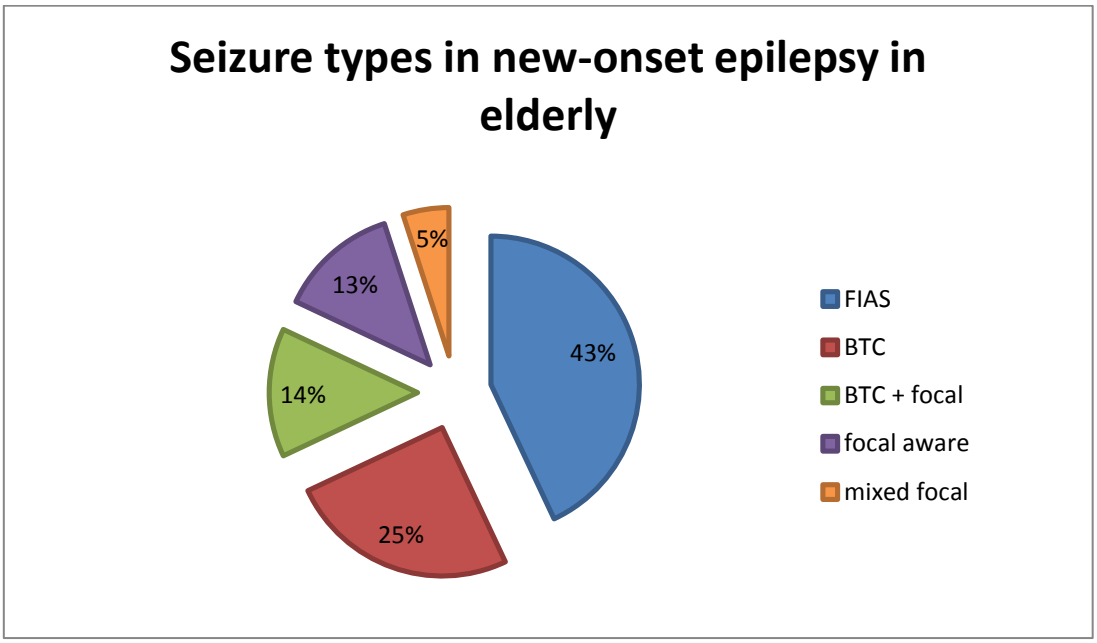

Figure 1: Seizure types in new-onset epilepsy in the elderly. BTC = Bilateral tonic–clonic; FIAS = Focal onset with impaired awareness seizure

Adapted from Lezaic N, Roussy J, Masson H, Jetté N, Keezer MR. Epilepsy in the elderly: Unique challenges in an increasingly prevalent population. *Epilepsy Behav.* 2020;102:106724.

Signal emitted from temporal location are most often seen while using electroencephalography (41). Researches have shown some differences regarding the presentation in elderly compared to the younger demographic. Auras and automatisms are less commonly seen, motor features are infrequent, the signs in cases of focal seizures with impaired awareness are simpler and shorter. On the other side, subtle episodes of transient confusion are more frequent and postictal state after a secondarily generalized seizure is longer than just fifteen minutes that is seen in younger individuals, it can last from hours until days (34, 54-56).

Late-onset generalized epilepsy has been shown with a supposed genetic cause arising after the age of 60 years. One prospective multicenter study acknowledged only a single patient (1.3%) with generalized epilepsy of presumed genetic origin within 79 old aged individuals with late-onset epilepsy. In the same study there were 9 such cases (13%) in the group elderly with early-onset epilepsy, whereas in younger adults it was even higher approximately one out of five (18%) have developed it due to the genetic cause (34). Patients with early-onset generalized epilepsy of supposed genetic culprit commonly have long dormant periods during their lives, until they reach older age, in which they start relapsing (57).

Regarding elderly patients that present with status epilepticus (SE) in hospital-based studies, approximately 30% of all individuals will present with first seizures as SE. Predicted general mortality of SE in the elderly ranges around 35% and increases up to 50% after age 80 years (58). Predicting mortality is comprised of factors such as de novo status, status severity and duration, presence of an underlying CNS structural lesion and a greater amount of comorbidities (58,59). The cause of SE that is seen most often in the elderly is ischemic stroke (58). Most common presentation of SE in old age patients is non-convulsive status epilepticus (NCSE) with impaired awareness (83%), while the smaller proportion of these individuals (17%) present with motor symptoms (59). However, the frequency of NCSE could be overestimated due to the comorbidities affecting the neurological status of the patient and controversies concerning electrophysiological standards for status epilepticus on EEG (60). Prolonged confusional episode mimicking delirium, psychosis, or unexplained coma, with a paucity of distinguishing features can all be possible manifestations of non-convulsive status epilepticus. Patient’s history of seizures, cerebrovascular disease, nonvascular dementia and acute medical illnesses, which

can be of cardiac, respiratory or hepatic origin or metabolic derangements of sodium are all risk factors of SE in the elderly (60). Reactivation of generalized genetic epilepsy from patient's medical history is what commonly describes late-onset absence SE in the elderly (61). Late-onset absence SE in individuals with no previous history of seizures, more frequently seen in women, has also been reported after alcohol or benzodiazepine withdrawal or beginning of therapy with medications that lower the seizure threshold (61-63). Rarely these latter SE may occur without any identifiable triggers (57). Due to the fact that worsening may occur with the administration of intravenous phenytoin, proper diagnosis of absence SE is essential (64). Until present time only a few studies have researched about treatment of SE in people of old age (65). More than fifty percent of NCSE in the elderly are triggered by acute illness and therefore a reversible etiology should be searched accordingly. Higher levels of neurotoxicity can be seen in the elderly when comparing to younger adults with aggressive administration of AEDs. Depending on the age of the patient, previous response to AED, potential for drug interactions and their comorbidities, there should be an individual approach regarding the treatment. Observing the AED serum levels for efficacy and toxicity can be used to lead the progressive AED escalation. With data from general adult population with SE it has been concluded that benzodiazepines are first-line medication followed by phenytoin and valproate as second-line treatment. On the contrary due to higher potency of adverse effects and drug interactions, the use of phenobarbital should be avoided (65).

Challenges and differential diagnosis

Shown by an average delay of 1.7 years from the occurrence of symptoms to an actual diagnosis, making the accurate diagnosis of epilepsy in the elderly is quite challenging (51). Epilepsy was a part of differential diagnosis after initial assessment by a primary care physician or internist for only 73% of persons eventually diagnosed with epilepsy, concluded by a large study in older veterans. Among possible diagnoses are altered mental status, confusion, blackout spells, memory disturbance, syncope, dizziness, and dementia (55). With the presence of cognitive deficits there might be challenges due to untrustworthy history-taking. Because of the fact that older individuals live alone based on studies from the USA, obtaining reliable source of information is crucial (66). The evaluation of seizures is commonly difficult. Comorbid dementia or delirium can be misdiagnosed instead of subtle FIAS (43).

Diseases such as Alzheimer's and dementia with Lewy Bodies can present as non-epileptic episodes of without any responsiveness. Patients affected by an acute CNS insult can simultaneously suffer from delirium and seizures. Delirium as well as seizures can occur with myoclonus and hallucinations. Stroke can be misdiagnosed instead of postictal Todd's paresis, whereas delirium may be incorrectly mixed with postictal confusion (34). Seizures can be mistakenly identified as comorbid cerebrovascular and cardiovascular disease, some of the most common examples being stroke or syncope and the other way round (67). Sometimes limb-shaking transient ischemic attacks (TIAs) mimicking focal clonic movements can actually be manifested due to focal cerebral ischemia instigated by high-grade carotid stenosis. Similarly seizures or TIAs may be falsely mistaken for one another because they can both be manifested as sudden speech arrest or aphasia. Sleep disorders can be deceptively thought of being nocturnal seizures, as is the case in rapid eye movement sleep behavior disorder (RBD), which increases in frequency with age and can be mistaken for nocturnal seizures. Up to 13% of the elderly with epilepsy have also an undiagnosed RBD (68).

The differential diagnosis of epileptic seizures in the elderly is quite extensive. Out of the several diseases some of them will be presented more thoroughly in the following text, these are syncope, amyloid spells, and transient epileptic amnesia (TEA). To begin with syncope, first step in determination of cause in a situation where elderly person presents with falls is to evaluate the consciousness and if it is impaired. Syncope and epilepsy cannot be excluded from potential diagnosis in the cases of unwitnessed falls with an unreliable history that can occur with cognitive impairment or amnesia. Elderly more commonly develop incontinence or injury as a result of syncope when comparing to younger adults. Cardiac syncope can happen in the supine position (69). Sustained hypotension can manifest as prolonged confusion during recovery, which can resemble a postictal state (67). In case of impaired cognition in the elderly, they may be unable to identify or recollect prodromal symptoms. The frequency of autonomic prodromal and postdromal symptoms, such as for example nausea or feeling of cold stated by the elderly is much lower than in younger individuals. Even though less commonly reported in the elderly when compared with the younger adults, most people will develop tonic posturing and myoclonic movements during the syncopal phase (69,70). Different types of syncope

with indicative characteristics can be grouped accordingly. Beginning with first group, the neurally mediated syncope or drop attacks. It can be further divided into vasovagal syncope that has a typical prodrome, emotional or orthostatic triggers, patients have normal results on examination and ECG, but positive tilt-table test; carotid sinus syndrome, which causes prodromal signs on head turning, wearing tight collars and shaving, with positive monitored carotid sinus massage; situational syncope cause by either cough, micturition, defecation, pain, stretch or weight-lifting; and lastly glossopharyngeal neuralgia, which is caused by swallowing, with pain in the base of the tongue, pharynx, larynx or ear. Belonging to the second group are neurological/CNS syncope, for example cerebrogenic cardiac arrhythmias, idiopathic drop attacks, vertrobasilar ischemia etc. Thirdly, postural hypertension presenting in prodrome with prolonged standing, positive orthostatic blood pressure measurements. This can be induced by drugs, volume loss, dehydration or shock, small fiber neuropathy that can occur due to diabetes and other causes (71).

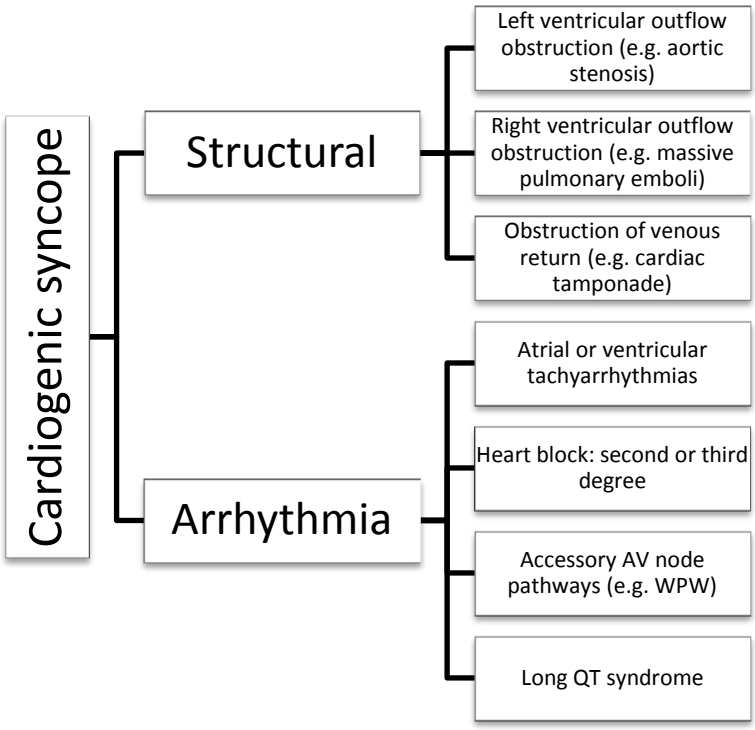

Figure 2: Cardiogenic syncope division and its causes

Adapted from Lezaic N, Roussy J, Masson H, Jetté N, Keezer MR. Epilepsy in the elderly: Unique challenges in an increasingly prevalent population. *Epilepsy Behav.* 2020;102:106724.

The last major group of syncope is that of cardiogenic origin, which is properly divided in Figure 2 (71). Physical examination with orthostatic blood pressure measurements and a 12-lead electrocardiogram (ECG) should be included in proper cardiovascular evaluation. Depending on the degree of clinical suspicion some additional cardiac tests can be made, for example ECG or tilt-table test. If episodes are recurrent and frequent, even though routinely ECGs can be false-negative a more prolonged recording such as 24–48 hour Holter should be carried out (72). EEG between seizures has an extremely low diagnostic significance in distinguishing seizures from syncope and it seldom affects the management (73). In order to confirm neurally mediated syncope or autonomic dysfunction, tilt-table testing can be used (72). Recent guidelines from the European Society of Cardiology recommend that individuals with high-risk history, examination, or ECG findings should have intensive and prompt evaluation either in an observation unit or hospitalized (72). A comprehensive list of what are considered “high” as opposed to “low” risk factors are presented in these guidelines (72).

Another disease among the differential diagnosis is cerebral amyloid angiopathy and its transient focal neurological episodes (TFNEs). Progressive deposition of beta amyloid in the wall of cortical and leptomeningeal small arteries of older individuals defines this vascular disease. Lobar intracerebral hemorrhage and progressive cognitive deficits is frequently present among patients suffering from cerebral amyloid angiopathy (CAA). Less common presentation of CAA, seen in 14% of patients, are transient focal neurological episodes (TFNEs), which are sometimes termed “amyloid spells” (74). These can mimic focal seizures when presenting with positive neurological symptoms or TIAs in the case of negative neurological symptoms. Usual descriptions of positive symptoms are recurrent, stereotyped, spreading paresthesias that spread smoothly over adjacent body parts in the course of 1 to 15 minutes; positive visual phenomena either as flashing lights or “zig-zags”; or limb-jerking. Episodes typically last fewer than 30 minutes (74).

Finally, often misdiagnosed in elderly as non-epileptic transient global amnesia (TGA), which is actually transient epileptic amnesia (TEA) that presents with brief episodes of anterograde and/or retrograde amnesia. Characteristically attacks last less than 1 hour that often occur along with olfactory hallucinations, automatisms, and a short-term loss of responsiveness (75). The duration of episodes was not

helpful in differentiating TEA from TGA, but instead recurrences, associated confusion and language disorders, along with 24-hour EEG are the most helpful in distinguishing TGA from TEA according to evidence from a recent study (76). Transient epileptic amnesia commonly is usually connected to temporal lobe epilepsy starting in late-middle to old age. Transient epileptic amnesia can be seen on EEG testing as either an ictal and/or a postictal epileptic phenomenon. Usually reported symptoms are interictal cognitive symptoms, among them being accelerated long-term forgetfulness. Positive response towards to low doses of AED monotherapy has been reported in majority of individuals (77).

Evaluation

Concerning the diagnostic evaluation of a first seizure and new-onset epilepsy in the elderly, there should be a particular algorithm to reach and confirm the diagnosis. As in every other disease in medical profession, the first step is to acquire a precise history and in the case of suspicion of first seizure in an elderly individual, it should be taken from an eyewitness, concurrently a thorough neurological examination to exclude a seizure mimic should be performed. While a routine EEG can be deceptive and is not crucial in the elderly, a prompt cardiovascular evaluation should be done. Reversible etiologies should be sought and ruled out, if the likelihood of a seizure is great, beginning with routine blood tests. Among the latter is complete blood count, complete electrolytic profile, thyroid studies, renal and hepatic function tests (35). Whereas in situation of symptoms or signs indicative of a CNS infection, an infectious work-up, comprising of lumbar puncture is performed. Brain imaging, either computerized tomography, magnetic resonance imaging or perhaps both should be conducted. Sometimes polysomnography can be used, for example when it is difficult to differentiate parasomnias from nocturnal frontal lobe seizures (68). Because older individuals have increased cognitive deficits before AED initiation, a part of routine testing should also be cognitive screening test, such as for example Mini mental status exam (75).

In elderly routine EEG recordings, normal variants are commonly incorrectly classified as epileptiform abnormalities and they occur in up to fifty percent of older individuals (78). Moreover, with the use of routine EEG interictal epileptiform abnormalities are detected in only about 35% of elderly with preexisting epilepsy and

26% of elderly with new-onset epilepsy (79). In contrary, prolonged video-EEG observation with a mean value of 3 to 4 days in the elderly is useful for differentiating epileptic from non-epileptic events, an example of the latter being psychogenic seizures, however the cost of such an supplementary test may be absurdly high (52).

Due to high frequency of structural etiologies, all elderly with possible seizures should undergo brain imaging using computed tomography (CT) or magnetic resonance imaging (MRI) (80,81). Brain CT is faster, cheaper and more available in emergency situations, while MRI is considered to have higher sensitivity and favored in non-emergency situations. Underlying focal lesions, most often ischemic stroke is found in approximately half of brain CTs and MRIs performed in elderly-onset epilepsy (81). No association between common age-related MRI findings including leukoaraiosis, abnormal change in appearance of white matter near the lateral ventricles and epilepsy in elderly has been found until present time.

Lastly regarding evaluation, there is increasing importance in consideration of immune-mediated processes as the cause of seizures and epilepsies during diagnostic procedure. More than fifteen intracellular and surface antigen-targeting autoantibodies that can be accountable for epilepsy have been identified by different investigators (82). Particularly relevant to epilepsy in elderly are antibodies against the voltage-gated potassium complex, for example LGI1 or CASPR2 antibodies. Conversely, in patients with high probability of a paraneoplastic syndrome, anti-Hu as well as other onconeural antibodies should be of substantial consideration (82,83). In individuals with higher risk autoantibody testing in serum and cerebrospinal fluid should be done on time. Autonomic dysfunction, a viral prodrome, faciobrachial dystonic seizures and associated oral dyskinesias are among clinical features that are predictive of positive autoantibody testing (84).

Treatment

According to evidence-based guidelines published in 2015 adults in the general population with a first unprovoked seizure have a seizure recurrence risk of 21–45% over the next 2 years (85). Most likely concluded from LPS studies, some authors have reported recurrence as high as 90% in individuals that are 65 years and older (38,55). On the other hand, large prospective observational studies have shown a similar risk of recurrence at 1 year in the elderly when comparing to the younger age

groups (86). The cumulative risk of recurrence at five years of follow-up is higher in older individuals, however that difference is insignificant (86). Independent seizure predictors that carry a risk of recurrence ≥60%, such as epileptiform abnormalities on EEG, abnormal findings on neurological exam, nocturnal seizures and a remote symptomatic cause, are comparable to those found in younger adults (85,86). While the risk of recurrence after a first seizure is similar to younger population, due to potential of higher incidence of falls and fractures, as well as other consequences of seizures in the elderly, this can lead to different, more negative outcomes.

The choice of the initial AED in the elderly with new-onset epilepsy is still developing due to the availability of newer agents. According to a US survey completed by epilepsy professionals recently there has been rise in prioritizing lamotrigine (LTG) or levetiracetam (LEV) in the elderly with epilepsy, contrary to that there is declining preference of choosing phenytoin (PHT), when comparing the year 2005 with 2016 (88). First-line AED therapy in the elderly with new-onset epilepsy coinciding with the majority of guidelines is most commonly comprised of LTG, LEV or gabapentin (GBP), following the data from randomized controlled trials (RCT) (21). Elderly with epilepsy show better tolerance toward LTG than carbamazepine (CBZ) with equivalent efficacy shown by a recent comprehensive meta-analysis of RCTs of AEDs (89). Even though LEV-treated participants had a slightly higher possibility of avoiding future seizures, there were no differences in tolerability between LEV and LTG. Information and evidence associated to other AEDs in the elderly with epilepsy is more scarce (89). The preference of AED therapy in the elderly with epilepsy should be through individualized approach. When discussing adverse effects (AEs) caused by AEDs, these can be divided into two groups. The first one being dosage-dependent AEs, which are comprised of confusion, dizziness, lethargy, unsteadiness, visual disturbance and the other drug-specific AEs such as hyponatremia, tremor, cardiotoxicity, ataxia, polyneuropathy and osteoporosis. All of these should be cautiously evaluated. Pharmacokinetic processes are altered in elderly, there is a reduction in liver and renal function, decreased plasma protein levels and total body water, as well as an increase in body fat. This can affect the plasma AED concentrations either as increase levels of free fractions of AEDs or longer half-life (87). Therefore, the route of drug metabolism or elimination, the method of administration, the frequency of administration, cost, a person's comorbidities and

other therapy taken by the patient should be a part of considerations. The target geriatric AED dose should be about 50–75% of that used in a young adult, according to suggestions of some experts (90). Monotherapy is the preferred option over combined therapy in elderly in order to diminish drug interactions as much as possible (90). It is easier to achieve compliance in older patients with cognitive deficits by reducing the frequency of administration (90). There is also an increased risk of osteoporosis and bone fractures connected with the use of enzyme-inducing agents such as phenytoin, carbamazepine, phenobarbital and valproate (91). Elderly women living the community of their own that were treated with continuous PHT have been shown to have a 1.8 times increased mean frequency of bone loss with a 29% higher risk of hip fracture in the next 5 years, compared to individuals of the same age (93). Increased risk of vascular disease, such as increased carotid intima thickness is associated with the use of before mentioned enzyme-inducing AED agents (93). This could be observed in people with epilepsy as one of the causes of the increased risk of sudden cardiac death (94).

Cognitive adverse events have been reported in several elderly, either as comorbid dementia simultaneously with epilepsy and/or are those suffering from potential adverse effects that occur with AED therapy. Preexisting cognitive deficits may be revealed or worsened when starting a new AED medication in an elderly person. Only one RCT has been identified during a recent systematic review of the treatment of epilepsy in people with Alzheimer's disease (95). Elderly individuals with Alzheimer's disease and new-onset epilepsy that were put on therapy with phenobarbital displayed a diminishment of cognitive function at 6- and 12-month follow-up, when compared with similar patients that were treated with LEV or LTG. Another RCT examining 15 healthy elderly applicants showed a moderate difference, where CBZ immediate-release consequently caused increase number of cognitive AEs compared with gabapentin (GBP) (96). However, one RCT evaluating older individuals with approximate mean age of 58 that compared LTG with topiramate as adjunctive AEDs found no major differences in cognitive AEs (97). In general adult population, when phenytoin is compared to CBZ, the prior is associated with greater cognitive AEs (98).

AEDs, which induce liver enzymes, may interact with other groups of medications that are commonly used by the elderly population. Among these are oral

anticoagulants, antiarrhythmic, antihypertensive, hypolipidemic and antiplatelet drugs. The physicians should take particular care when prescribing AEDs that block sodium channels, these drugs are - CBZ, oxcarbazepine (OXC), PHT and lacosamide (LCS), as they are contraindicated in the case of atrioventricular block. Therefore, AEDs that do not affect liver enzymes should be used, such as zonisamide (ZNS), LTG, topiramate (TPM) or LEV (105). A recent study has confirmed increased risk of bleeding in patients with atrial fibrillation on novel oral anticoagulant therapy that were concurrently taking valproic acid (VPA), PHT or LEV. Moreover, therapy with CBZ or PHT for three months has shown increased levels of cholesterol and low-density lipoprotein (LDL), which rises cerebrovascular risk in elderly patients (107). Thus, in order to avoid post-stroke epileptic events that are common in the elderly population, ZNS, as well as LTG, LCS or GBP are the favored options (108).

There has been a limited data concerning epilepsy surgery in patients older than 50 years with varied results. The possibility of curing seizures completely and postoperative risk is similar in elderly and younger age groups according to some studies (99-101). On the other hand, other conducted studies showed a lower efficiency of epilepsy surgery in older individuals and furthermore, even a marginally higher presence of cognitive, neurological and other medical outcomes postoperatively (101-103). Therefore, even though epilepsy surgery in elderly patients is not absolutely contraindicated, the ultimate decision should be made depending on whether there is any other comorbidity, as well as the presence of cognitive or functional deficits in these individuals.

Conclusion

The etiology of new-onset epilepsy remains unknown in about one-third to one-half of the elderly individuals, although there have been several progresses in neuroimaging (33,53). The mechanisms connecting the development of epilepsy with dementia are scarce. Further research of epilepsy development and its risk factors in the older patients could help lead the clinicians' decision making and provide new information. The prevalence of epilepsy in the elderly is high and this age group is quickly growing in high-income countries, however there is still a lack of high-quality evidence to guide its management. Examination of the efficacy and tolerability of the newest

AEDs such as for example brivaracetam through randomized controlled trials and properly conducted studies could enlarge the therapeutic possibilities in older patients with epilepsy. The definitive consequences of particular comorbidities, such as neurodegenerative disease and cerebrovascular disease, have not been researched yet. It is thought by some experts that these comorbidities may increase the susceptibility of the aging brain to drug-related adverse effects, influence drug adherence and the method of administration in particular situations (104).

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Biography

I was born on 20th May 1994 in Ljubljana, the capital city of Slovenia. After successfully finishing elementary and high school in my hometown, I had high goals for the continuation of my education. I enrolled into pharmaceutical University in Ljubljana, however my primary plan was to study medicine. Fortunately during my first year there a colleague told me about the Medical Studies in English on University of Zagreb. Therefore during the same year, I studied for the entrance exam instead, which I passed in Zagreb that allowed me to enroll into the program the following study year.