Epilepsy in the elderly
L'épilepsie chez les personnes âgées

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Abstract

For a long time it was thought that epilepsy is a disease that mainly affects younger population. Epidemiological studies indicate that epilepsy is most frequently in the elderly. So we can say that epilepsy is a disease of old people because it is the most common disease affecting the brain tissue of the elderly, after a stroke and dementia. With all of this, if we consider that the quality of life, availability of medical services, reduce birth rates etc. all lead to more rapid growth in the number of people in this age group, we must pay great attention to this problem. Unfortunately there are a very small number of the conducted studies and guidelines on this topic. Since September 2008 in the literature can be found only 102 publications, of which only 50 original articles. Seizures are very often not clinically observed because the aura and secondary generalization of tonic-clonic seizures is rare in elderly patients. Besides the sudden loss of consciousness is a condition that is with age increasingly occurring for different reasons, so differential diagnosis is more challenging.

Keywords: Epilepsy- Elderly- Therapeutic approaches.

Résumé

Pendant longtemps, on a pensé que l 'épilepsie est une maladie qui touche principalement les plus jeunes. Des études épidémiologiques indiquent que l 'épilepsie est le plus fréquemment chez les personnes âgées. On peut donc dire que l 'épilepsie est une maladie des personnes âgées, car il est la maladie la plus commune affectant le tissu cérébral des personnes âgées, après un accident vasculaire cérébral et la démence. Avec tout cela, si l 'on considère que la qualité de la vie, de la disponibilité des services médicaux, de réduire les taux de natalité, etc conduisent tous à une croissance plus rapide du nombre de personnes dans ce groupe d 'âge, nous devons prêter une grande attention à ce problème. Malheureusement, il ya un très petit nombre des études réalisées et des lignes directrices à ce sujet. Depuis Septembre 2008, dans la littérature peuvent être trouvées seulement 102 publications, dont seulement 50 articles originaux. Les convulsions sont très souvent pas observée en clinique parce que l 'aura et la généralisation secondaire des crises tonico-cloniques est rare chez les personnes âgées. Outre la perte soudaine de conscience est une condition qui est de plus en plus avec l 'âge se produisent pour des raisons différentes, de sorte diagnostic différentiel est plus difficile.

Mots-clés: Epilepsie- Age avancé- Approches thérapeutiques.

Introduction

1-Etiology

Epilepsy in the elderly is usually a result of existing or newly occurred diseases of the central nervous system. For middle-aged people epilepsy usually occurs as a result of trauma, congenital malformations, encephalitis and tumors. Whereas in the case of elderly is usually consequence of stroke or neurodegenerative diseases, while tumors are much less common cause. In one third of the elderly, the cause of epilepsy remains unknown. Epidemiological studies in patients over 60 years of age without prior stroke, trauma or dementia, showed that the risk for the occurrence of epilepsy is 1.1%. This incidence is twice as high compared to the younger and still significantly lower when stroke, trauma or dementia is present [1].

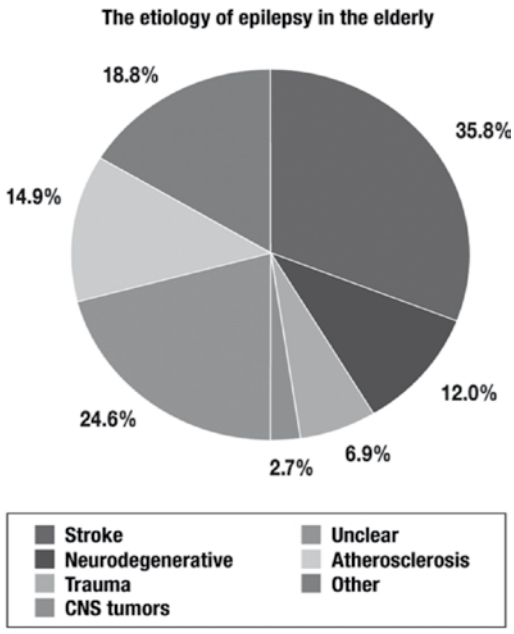

Figure 1: Causes of epilepsy in the elderly in Bosnia Herzegovina [1].

A study followed 535 respondents, with a negative history of previous seizures, after cerebrovascular incident until their death or migration from Rochester, Minnesota.

Thirty-three patients (6%) had a seizure in the first week, 78% of which was developed within 24 hours after stroke (significantly more if the case of stroke in frontal hemisphere). Twenty-seven patients had the seizure in the first week after the seizure, while 18 developed epilepsy (recurrent

late seizures). Compared with the general population, the risk of seizures during the first year after the stroke is 23 times higher for initial late seizures and 17 times higher for the occurrence of epilepsy. Distinction is here made by early seizures, which occur as acute epileptic reactions within two weeks after the stroke and delayed seizures. Cumulative possibility of developing an initial late seizure was 3.0% in the first year, 4.7% in the second year, 7.4% in the five years, and 8.9% in ten years period. Early seizures occur as a result of acute biochemical changes, exposure to the excitatory neurotransmitter glutamate. Early seizures occur in 2-8% of patients, usually within the first 48 hours after the stroke. Isolated epileptic seizures occur in 3-6% of patients after the stroke [2]. Late seizures, occurring two weeks or more after the stroke as the result of chronic events such as the loss of inhibitory function of the brain, creating scar tissue and formation of new synaptic connections.

Half of these patients develop focal epilepsy with recurrent seizures, usually in the first three years after a stroke. Focal epilepsy after a stroke occurs in 2-4% of patients and this incidence is 2-4 times higher than in the same age group without stroke. It is important to emphasize that patients with late seizures who had early seizures are a risk group with a high propensity to develop focal epilepsy.

Potential development of epilepsy depends on several factors:

- The type of stroke
- Hemorrhagic stroke
- Embolic stroke
- Ischemic stroke
- Localization of stroke
- Cortical localization
- And subcortical localization.

Also on the stroke severity (clinical manifestations and CT image of the infarcted area volume).

Epileptic seizures in the elderly may be the first sign of cerebrovascular disease. The study which surveyed 4709 respondents over 60 years of age and without a positive history of cerebrovascular disease, trauma, dementia, alcoholism, found that patients who had epileptic seizures have a five-year risk of stroke 2.89 times higher compared to the control samples without seizures [3].

It is for these reasons, that patients above 60 years of age, who had a first epileptic seizure, must be considered a candidate for a stroke.

The incidence of seizures in patients suffering from Alzheimer 's disease is increased with disease progression. The cumulative incidence in a period of 7 years is 8%. The incidence was slightly higher in younger patients (50-59 years old) compared to those who become ill at a later age (over 80). The risk of developing epilepsy, except the early emergence of dementia is itself a form of the disease with the presence of typical EEG changes. Epileptic seizures do not occupy the major complications of dementia and are not the biggest problem in therapy in these patients, but it is important to know that there is an increased possibility of their occurrence and is consequently identified. Whenever the older person appears with symptoms of unknown cause of confusion we must think also about focal epilepsy [3, 4, 5].

2-Therapeutic approaches

Pharmacotherapy in the elderly is complicated because it has to be taken into account the pharmacokinetics and pharmacodynamics that in older people due to wear and tear of the body and associated disease is significantly altered. There are no official guidelines and meta-analysis on this topic. Made are only three randomized, controlled, double-blind studies and a number of smaller studies. For this reason, most clinical decisions about the treatment of epilepsy in the elderly is based on experience and data that have been obtained for the younger population, combined with the general principles of pharmacotherapy in the elderly. Available studies suggest that lamotrigine and gabapentin are better when compared to carbamazepine in the treatment of elderly patients. This is not a result of the drug effectiveness but better tolerance. It seems that the more successful the treatment of epilepsy is in patients over 60 years compared to younger patients.

A study in which participated 622 respondents, 62% of patients over 65 years did not have any seizures for a period of two years from the start of therapy, compared with 30% of patients >40 years. A prerequisite for successful treatment and inability to tolerate the drug interactions with medications the patient is taking. Mattson et al. performed did a study in which about 64% of patients over 65 years had to discontinue antiepileptic therapy because of side effects compared with only 33% of young people. This suggests that it is imperative to find a medication that is best tolerated and least metabolized. Problems occur because of increased sensitivity to drugs and an increased possibility of interaction [5].

It is clear that enzyme-inducing antiepileptic drugs (Carbamazepine, Phenytoin, Phenobarbital,Primidone) due to its ability to interact with other drugs are not the drugs of choice for elderly patients. Changes in pharmacokinetics are visible from the moment of taking the medication, because gastric secretion, blood volume, blood flow and motility of the gastrointestinal tract are reduced in older people. Serum concentrations are directly dependent on the binding of protein (serum albumin), the concentration of which is reduced, so that the concentration of the free fraction of drug in the serum was increased. This affects not only the desired effects of the drug but also side effects, particularly marked among the drugs that are predominantly associated with proteins such as Valproic acid, Carbamazepine or Phenytoin.

The main physiological changes that occur with aging are:

Reduced hepatic mass and blood flow, which results in a decrease in hepatic metabolism and progressive reduction in renal function [6].

How well the liver metabolizes drugs depends on the capacity of the liver enzymes. Cytochrome P450 enzyme complex, one of the major pathways of drugs decomposition, losing about 10% of their functional capacity every ten years after the age of forty. The problem is that there is no single clinical parameter to measure and monitor liver metabolism. Liver enzymes such as GGT, GOT, GPT and serum

albumin concentration cannot tell us what the capacity of the liver to metabolize drugs is. With the aging also renal function decreases, but unlike the liver it can be measured biochemically. As a result, drugs that are excreted via the kidneys have an advantage in applications by older people, because they can be adapted in dose according to patient 's renal function.

When it comes to dose of drugs in elderly patients we should adhere to the the saying 'start low and aim low'.

Elderly patients are more sensitive to central and systemic side effects of antiepileptic drugs, especially side effects that disrupt cognitive function, in part because of their effect on the pharmacokinetics of cognitive abilities. This was determined in a double-blind study, compared to Carbamazepine, Gabapentin and Lamotrigine in patients above 65 years of age.

The study observed the percentage of patients who had a year in therapy and compared the effectiveness and tolerability of the medication given. It was showed that Gabapentin (49%) was significantly lower in these characteristics as compared to Carbamazepine (67% with the target dose of 400 mg daily) and Lamotrigine (73% with the target dose of 100 mg daily). From this it can be seen that there is no significant difference between Carbamazepine and Lamotrigine. When the target dose of Carbamazepine increased to 600 mg per day tolerability was less noticed so it was only 35.5% of patients that remained in the study for one year. Valproic acid has been in use for many years, there is different forms of application and is effective in focal seizures so it should be considered as a valid substitute for Carbamazepine in elderly patients [8]. The risk of Parkinsonism with cognitive decline in the use of Valproic acid is estimated to be 2% and for older patients even more than 2% but reducing fatigue, motor slowness and lack of induction of hepatic enzymes prefer Valproic acid compared to Carbamazepine in this age group [9]. Epileptologists recommend also the use of Levatiracetam because of its pharmacokinetic and few adverse effects. But still there are no controlled studies of Levatiracetam and Valproic acid in the elderly [10].

In a study involving 73 older patients, side effects were observed and how good is seizure control if the Carbamazepine/Valproic acid serum concentration levels are on the lower therapeutic limit. Conclusion and general recommendations is that when applying AEDs to patients older than 70 years target dose should be twice less than one which is recommended for younger patients and that the maximum permissible dose should reduce by half. Whenever it is possible.

Patients and methods

This study provided the elderly patients using AEDs and observed the effect of therapy on their cognitive functions and quality of life across literature.

We observed the following drugs: Pregabalin, Zonisamide, Lacosamid, Gabapentin, Lamotrigine, Oxcarbazepine, Tiagabine, Levetiracetam, Topiramate, Vigabatrin, Phenytoin, Phenobarbitone, Clobazam, Clonazepam, Felbamate, Acetazolamide, Primidone, Sodium Valproate and Carbamazepine.

Results

Lamotrigine or Carbamazepine monotherapy?

Efficiency: The statistically significant results.

Significantly more patients taking Carbamazepine were without any seizures;

Different effects-significantly higher number of patients using Lamotrigine changed therapy for various reasons because they had:

- Increased tremor (low quality);
- Losing weight (medium quality);
- Significantly more patients are taking Carbamazepine compared to Lamotrigine.
- Fatal outcome (low quality);
- Somnolence (medium quality).

Different effects: without statistically significant differences in results:

- Rash (very low quality);
- Asthenia (very low quality);
- Weakened coordination (very low quality);
- Dizziness (very low quality);
- Headache (very low quality);
- Sedation (very low quality);
- Glandular problems (very low quality);
- The increase in body weight (very low quality);
- Water retention (very low quality);
- Nystagmus (very low quality);
- Dysarthria (very low quality);
- Stroke (very low quality);
- Changes in mood and affect (very low quality);
- Cognitive disorders (very low quality);

There are no studies that show what the impact on quality of life is and there is no evidence of greater effectiveness in the use of one or the other drug.

Lamotrigine or slowly releasing Carbamazepine monotherapy?

In terms of seizure control has no significant difference.

Statistically significant number of people on slow releasing Carbamazepine therapy discontinued therapy for various reasons in relation to Lamotrigine.

Different effects. Statistically significant differences:

- Rash (very low quality);
- Dizziness (very low quality);
- Headache (very low quality).
- Cognitive effects – Not statistically significant results.

There are no studies that show what the impact on quality of life is, and there is no evidence of greater effectiveness in the use of one or the other drug.

Sodium Valproate or Phenytoin monotherapy?

In terms of seizure control, cost-effectiveness and impact of various without significant difference.

Therapy discontinuation for various reasons (very low quality);

- The incidence of agitation (very low quality);
- The incidence of drowsiness (very low quality);
- Incidence of tremor (very low quality);
- The incidence of edema (very low quality);
- Incidence of alopecia (very low quality);

•The incidence of depression (very low quality);
•The incidence of weight gain (very low quality);
•Incidence of influence on cognitive abilities (medium quality);
The test results are statistically significantly better in patients on Phenytoin monotherapy for a period of 6 months. But in all other cognitive tests, there were no significant differences in the period of 6 weeks, 3 months, 6 months and one year.
There are no studies that show what the impact on quality of life is, and there is no evidence of greater effectiveness in the use of one or the other drug.

Gabapentin or Carbamazepine monotherapy?

In terms of seizure control has no significant difference. Statistically significantly more patients on Gabapentin monotherapy had:
•Increase in body weight (medium quality);
•Water retention (medium quality);
•No statistically significant differences between the two drugs in terms of different impacts:
•Increased tremor (low quality);
•Losing weight (medium quality); significantly more for patients on Carbamazepine relative to Lamotrigine:
•Fatal outcome (low quality);
•Somnolence (medium quality).

Different effects: without statistically significantly different results:
•Dizziness (very low quality);
•Headache (very low quality);
•Sedation (very low quality);
•Glandular problems (very low quality);
•The increase in body weight (very low quality);
•Nystagmus (very low quality);
•Dysarthria (very low quality);
•Stroke (very low quality);
•Weight loss (very low quality);
Changes in mood and affect (very low quality);
Cognitive disorders (very low quality);
There are no studies that show what the impact on quality of life is and there is no evidence of more effectiveness in the use of one or the other drug.

Lamotrigine and Gabapentin monotherapy?

In terms of seizure control has no significant difference.
Statistically significantly more patients on Lamotrigine monotherapy had an increased incidence of weight loss (medium quality).

Statistically significantly more patients on Gabapentin monotherapy had:
•Discontinuation for various reasons (medium quality);
•Increase of body weight (medium quality);
•Water retention (medium quality).

No statistically significant differences in:
•Sedation (very low quality);
•Glandular problems (very low quality);
•Tremor (very low quality);
•Dizziness (very low quality);
•Headache (very low quality);
•Nystagmus (very low quality);
•Dysarthria (very low quality);
•Stroke (very low quality);
•Weight loss (very low quality);
•Changes in mood and affect (very low quality);
•Cognitive disorders (very low quality);
There are no studies that show what the impact on quality of life is and there is no evidence of more effectiveness in the use of one or the other drug.

Discussion

Epidemiological studies indicate that epilepsy is often en-

Table 1: New guidelines for the treatment of elderly patients with epilepsy

Recommendations	We should not discriminate older patients and we need to offer them services, tests and therapy as well as for the rest of the population.
Relative values of different outcomes	Different effects of medication and quality of life were considered as the most important effects of the therapy, because older people are more susceptible to side effects of medications. Effectiveness in controlling the seizures is universal for all age groups.
Ratio of clinical benefit and harm	AEL have more side effects in this group. It is assumed that the reduction in the number of seizures is the same for all age groups. It is believed that the reduction in seizures is more important than adverse events, as is the case with other age groups.
Economic considerations	Studies have shown no statistically significant difference when using the AEL between young and elderly patients.
Evidence quality	These recommendations are based on data that are in form of medium to very low quality and expertise of GDG's.
Other considerations	GDG's desire was that older people receive optimal treatment and the same opportunities as others in the best approach to therapy and specialized services, which is not always the case.
Recommendations	Particular attention should be paid to the pharmacokinetics and pharmacodynamics of drug interactions. Treatment should always start with low doses and if Carbamazepine is used offer Carbamazepine with gradual release.
Relative values of different outcomes	Incidence of various influences and effects on cognitive skills is very important.
Ratio of clinical benefit and harm	Carbamazepine showed a significantly higher incidence of death, somnolence and skin rash compared with Lamotrigine, but there were no significant differences when Carbamazepine is used in the slowly releasing form. Significantly more patients on Lamotrigine had a loss of body weight compared with Gabapentin and Carbamazepine. Significantly more patients on Gabapentin had weight gain and water retention compared to Lamotrigine and Carbamazepine. It is believed that with a dose reduction control over seizures can be retained and can minimize all of these AEL side effects. It is believed that older patients have more comorbidities and use more medications so can have adverse drug interactions. Yet the greater is the gain in seizure control in relation to the potential side effects and drug interactions.
Economic considerations	Studies have shown no significant difference when using the AEL between young and elderly patients. Should always try with low doses which reduce side effects and costs of the therapy itself.
Evidence quality	The quality of evidence is good with adequate reporting and randomization, concealment and blinding. Yet the number of dropouts was big enough to make a difference among four groups that could lead to bias.
Other recommendations	GDG supported the recommendation that the Carbamazepine controlled release of a similar efficacy as well Carbamazepine, but it is better because it avoids peak concentration. GDG considered that older people do not have such a good specialist services available, resulting in inadequate treatment and poor outcome. Therefore it is important to pay special attention when choosing the drug and dose to the patient in the elderly group.

countered in the elderly. Occurs as a result of neurodegenerative changes in dementia, tumor, and status after injury or after stroke. Nevertheless, for the one third the cause of epilepsy remains unknown. Epidemiological studies on patients over 60 years of age without prior stroke, trauma or dementia, showed that the risk for the occurrence of epilepsy is 1.1%. Cerebrovascular disease is the leading cause of epilepsy in old age [11]. We distinguish between the so-called early seizures, which occur as acute epileptic reactions within two weeks of the infarct and delayed attacks. Cumulative possibility of developing an initial late attack was 3% in the first year, 4.7% in the second year, 7.4% in the five years, and 8.9% at ten years. Early attacks occur as a result of acute biochemical changes, exposure to the excitatory neurotransmitter glutamate. Early seizures occur in 2-8% of patients, usually within the first 48 hours after the stroke. Isolated epileptic seizure occurs in 3-6% of patients after a stroke. Late seizures, occurring two weeks or more after the accident are the result of chronic events such as the loss of inhibitory function of the brain, creating scar tissue and formation of new synaptic connections [11].

In half of these patients develop focal epilepsy with recurrent seizures, usually in the first three years after a stroke. Focal epilepsy after a stroke occurs in 2-4% of patients and the same incidence is 2-4 times higher than in the same age group without stroke.

It is for the above reasons the stroke can be considered as a trigger of epileptic seizures. We regard this as a symptom associated with stroke.

The incidence of seizures in patients suffering from Alzheimer 's disease is increased with progression of the disease. The cumulative incidence of a period of 7 years is 8%. Pharmacotherapy in the elderly is complicated because it has to take account of the pharmacokinetics and pharmacodynamics that in older people due to wear and tear of the body and associated disease is significantly altered. There are no official guidelines and meta-analysis on this topic. Available studies suggest that Lamotrigine and Gabapentin improved when compared to Carbamazepine the treatment of elderly patients. This is not a result of the effectiveness of the drug has better submission. It seems that the more successful the treatment of epilepsy in patients over 60 years compared to younger patients. A prerequisite for successful treatment and inability to tolerate drug interactions with medications the patient is taking [12].

Conclusion

Ederly patients are more sensitive to central and systemic side effects antiepileptic drugs, especially side effects that disrupt cognitive function, in part because of their effect on the pharmacokinetics of cognitive abilities. There is no significant difference between carbamazepine and lamotrigine. Epileptologists recommend and use Levatiracetam because of its pharmacokinetic and few adverse effects.

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