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MODERN VIEWS OF THE CLINICAL PICTURE OF POST-TRAUMATIC EPILEPSY AGAINST THE BACKGROUND OF CONCOMITANT SOMATIC DISEASES

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Abstract
The features described above determine a different course of the epileptic process in the elderly compared to younger patients, because epileptic brain is closely related to the self-regulation processes of the CNS. It should be noted that the peculiarities of the physiology of organism functioning in old age determine not only the pathomorphosis of the disease, but also a qualitatively different effect of drugs on the body.

Keywords: epilepsy, Binswanger's encephalopathies, dementia, CNS, craniocerebral injuries

Introduction

Multiple pathologies against the background of marked age-related changes in metabolic processes and body functions significantly alter pharmacokinetics and pharmacodynamics of drugs - absorption, distribution, biotransformation, excretion as well as their therapeutic activity, and increase the appearance of negative side effects - allergies and drug disease. Thus, therapy for the elderly is characterised by a number of special features that require the physician to have an in-depth knowledge not only of the age-specific mechanisms of action of the drugs prescribed, but also of possible complications, side-effects and contraindications. These are due to changes in plasma protein concentration, decreased hepatic blood flow, renal function, gastrointestinal changes, decreased muscle mass and increased fat tissue. After dementia and stroke in the elderly, epilepsy is the third most common neurological problem. In this age group, the incidence of epilepsy increases from around 50 years of age, reaching 50 and 75 cases per 100,000 population at ages 60 and 75 years,

respectively. Some researchers consider these figures to be somewhat of an underestimate. A recent trial, based on a computerised database, gave a more detailed breakdown of the incidence of epilepsy: 76, 147 and 159 cases for ages 60/69, 70/79, 80 years and over, respectively, with an average of 117 cases per 100,000 of the population over 60 years. Approximately half of elderly patients with epilepsy have early-onset disease. The etiology of epilepsy in this group of patients is heterogeneous: genetic, idiopathic, symptomatic, associated with perinatal pathology, vascular disease, etc. In elderly patients with epilepsy, the most frequent etiological factors are cerebrovascular disease (about 50% of patients) and dementia (11¬16%), including Binswanger's subcortical encephalopathy and vascular malformations. It has been shown that epileptic seizures are not related to the severity of lacunar infarction, but primarily to the degree of cognitive impairment, which may be a reflection of a neurodegenerative process. Various authors have reported that 2.3¬14% of patients with stroke experience epilepsy, but only 2¬4% of post-stroke patients develop post-stroke epilepsy.

A third cause of epilepsy in the elderly is neurosurgical pathology, including brain tumours (4%), craniocerebral injuries (1¬3%), and neurosurgical interventions for haematomas, tumours and intracerebral haemorrhages. It is possible that vascular manifestations and craniocerebral injuries can cause the development of cerebral hypoxia, contributing to the detection of "old" hidden epileptic foci, which in these conditions play the role of a trigger - the "pacing mechanism" of an epileptic seizure. In addition, toxic-metabolic syndromes such as hypoglycaemia and non-ketotic hyperosmolar coma, seizures associated with alcoholism and drug dependence can be causes of epileptic seizures in elderly patients. It should be noted that in the elderly the toxicometabolic changes develop more frequently not due to alcohol intake and withdrawal, which is typical for people from 40 to 60 years, but after long-term use of drugs, which are triggers for the development of epileptic activity of the brain. In elderly patients, some evidence suggests that 15% of epileptic seizures were dysmetabolic, and 14% were due to intoxication. Drugs that can provoke an epileptic seizure in the elderly when used in sub-toxic doses include: Penicillin- and cephalosporin-type antibiotics, aminoglycoside antibiotics, TB drugs, caffeine, ephedrine, ergotamine, haloperidol, insulin, isoniazid, non-selective monoamine oxidase inhibitors, sulfonamides, tri- and tetracyclic antidepressants, x-ray contrast agents. The presence of so many drugs that can provoke an epileptic seizure in the elderly is evidence of a significant dysfunction of the antiepileptic brain system in this category of patients. About 25% of first-onset epilepsy in elderly patients can be classified as idiopathic epilepsy. Seizures occur for no apparent reason, it is not

possible to determine whether a seizure is generalised or whether there is a secondary generalisation of a partial seizure, and the etiological factor for epilepsy cannot be identified, even with a thorough examination of the patient. The presence of this "idiopathic" group of patients is most often explained by deficiency of inhibitory systems in the prefrontal cortex in old age due to its progressive involution. The principles of epilepsy diagnosis in the elderly do not differ significantly from those in younger patients. Although it should be noted that epileptic seizures have a higher proportion in the structure of paroxysmal states in elderly patients than in young patients and are comparable in frequency to those in children of the first five years of life. In addition, it should be borne in mind that the risk of developing epilepsy increases significantly in proportion to age in persons over 65 years of age. The differential diagnosis of epileptic seizures in the elderly is most often made with syncope and transient ischaemic attacks. Therefore, the following diagnostic tests should be performed in elderly patients with a first-time seizure: electroencephalogram (EEG), electrocardiogram (ECG), sonography and brain scanning (CT and MRI), and a detailed somatic examination.

Diagnosing epilepsy in older patients may be more difficult than in younger patients, for a number of reasons. For example, older people are more likely to have seizures that are not noticed by others because they are less socially active, more often out of work and live alone. Often elderly patients have seizures at night, which may explain the longer period of time that patients go without epilepsy diagnosis and treatment. It should be remembered that the awareness and understanding of symptoms may be poor in elderly patients and they may not be able to accurately report symptoms to the clinician. Furthermore, subtle symptoms, such as a momentary lapse of consciousness with a frozen stare or stopping to speak, may be dismissed as normal features of old age by those around the patient.

We would like to emphasize the difficulties of diagnosing late-onset epilepsy, as the clinical picture is dominated by focal components (often only in the form of aura), automatisms, atypical absences and unilateral seizures with the development of postictal Todd's palsy. This may be interpreted by clinicians as the presence of conditions of a non-epileptic genesis (e.g. psychomotor agitation or brain infarcts).

A feature of epileptic seizures in the older age group is frequent hospital admissions with misdiagnosis of stroke. It is not uncommon for physicians to mistake epilepsy in elderly patients for neurological disorders, tremors, or other conditions such as vascular disease, syncope, transient and ischaemic attacks, etc.

On the other hand, it should be remembered that loss of consciousness of non-epileptic aetiology is not uncommon in the elderly, making a differential diagnosis

difficult. Cardiovascular events in the form of vasovagal syncope, bradycardia or psychogenic seizures may resemble epileptic seizures. Patients are prescribed anti-epileptic drugs (AEDs), which if inevitably ineffective, lead to the erroneous conclusion that seizures are pharmacoresistant when treated with anti-epileptic drugs. ECG and EEG examinations with blood pressure monitoring may be helpful in making the correct diagnosis in these cases.

Compared with younger patients, a much higher proportion of elderly patients (over 90%) have partial seizures, which are more likely to be secondary to generalized seizures. Patients with partial seizures often have a combination of simple partial and complex partial seizures, simple partial and secondary generalized seizures, and a combination of all types of partial seizures. Less frequently than in younger patients, older patients present with primary generalized seizures, which are tonic-clonic in nature, or occasionally with a predominantly tonic or clonic component.

While seizures in younger patients have mainly negative social consequences, in older patients, seizures may provoke and cause somatic or neurological disorders. The post-seizure period can be longer and more severe in older patients than in younger ones. For example, focal motor deficits (prolapse symptoms) in the form of Todd's palsy (up to several days), confusion (hours to 1-2 weeks), states of psychomotor agitation (requiring psychiatric consultation to rule out psychiatric pathology), transient amnesic syndrome in the form of disoriented retrograde and anterograde amnesia are noted. This determines that one of the features of epileptic seizures in the elderly is the frequent hospitalization with misdiagnosis of stroke.

A severe postictal period was observed in 85% of elderly patients and approximately 15% of younger patients. A prolonged prodromal preictal state, which usually worsens the condition and well-being of patients, and which suggests with a high degree of probability the imminent development of a seizure, is observed in 25-30% of elderly and, very rarely, young patients. It should be noted that the presence of a severe postictal period and a prolonged prodromal preictal state in almost all patients can be regarded as an indicator of a severe clinical course of epilepsy, even in rare seizures.

In elderly patients, the course of epilepsy is complicated by epileptic status 3 times more often than in younger patients, and 2 times more often than in children. This determines the need to prescribe anticonvulsants even after single epileptic seizures and when patients have rare simple partial seizures, which is also associated with an extremely high risk of recurrent seizures in this category of patients.

An important argument for the need for early treatment of epilepsy in the elderly is the high rate of seizure fractures with particularly severe outcomes.

Older patients with epilepsy often present with other symptoms of nervous system damage in addition to epileptic seizures. The most common clinical features of patients were clinical signs of cerebrospinal hypertension, which in most cases were confirmed not only clinically, but also by CT scan and nuclear MRI of the brain. The severity of cerebrospinal hypertension was higher in those with decompensated epilepsy. Pyramidal symptoms were observed in more than half of the patients. In addition to stroke and tumour patients, other patients with epilepsy also have these symptoms. They are most often accompanied by central sensory disturbances. When motor pyramidal and sensory symptoms are combined, complex partial seizures often predominate in the neurological status of patients.

Clinical signs of venous dyshemia are not uncommon in patients, and are more common in those with poorly curative secondary generalized seizures. Static and coordination disorders are seen in about a third of elderly epileptic patients. The presence and severity of vestibuloatactic syndrome, coordination disorders and clinical features of epilepsy are usually unrelated. It should be noted that it is not always the case that patients have neurological symptoms that can only be explained by the presence of the neurological disease that led to the development of epilepsy. Long-standing epilepsy itself seems to cause or exacerbate focal neurological symptoms in elderly patients.

The difficulties in pharmacotherapy of epilepsy in the elderly are related to the diseases causing it, concomitant pathology, the interaction of PEP with other drugs taken by the patient due to somatic disorders, as well as age-related physiological changes. Treatment of patients in this age group is very difficult due to poor compliance. This is complicated by specific pharmacokinetics, frequent polypragmasy, and the unusual sensitivity of elderly people to PEPs.

When deciding whether to initiate therapy, it is always necessary to consider the potential dangers of taking PEPs, the duration of therapy for which is on average 2 to 5 years.

It is not advisable to prescribe PEPs if patients have:

-Reflex (stimulus-dependent) seizures;

-Situation-dependent seizures (e.g., when alcohol is consumed or withdrawn);

-Drug-induced seizures;

-Early single post-traumatic or post-stroke seizures (in the acute phase of a brain injury or stroke)

-Single seizure or series of seizures throughout the day, which equates to a single seizure

-Frequently recurrent seizures without a severe postictal period.

The initiation or resumption of treatment may be withheld if the patient has previously had rare (1 or 2 per year) seizures, more than 6 months after the last seizure and the end of anticonvulsant medication, and if the EEG shows no epileptiform or focal pathological activity. Initiation of therapy includes elimination of triggering factors such as sleep deprivation, alcohol intake, and elimination of a specific stimulus in reflex epilepsies. The basic criteria for the selection of a PEP, in relation to its perceived efficacy, do not differ from those in other age groups, but are determined more by the type of epileptic seizure than by the form of epilepsy. The choice of PEP in elderly patients is driven not only by high efficacy, but also by a number of requirements, as presented below.

1.High efficacy for partial and secondary generalised seizures.
2.The possibility of rapid dose escalation.
3.No effect on cognitive function.
4.No adverse effect on the course of comorbidities.
5.Can be prescribed no more than 2 times a day to avoid irregularities.
6.No significant effect on other medications used by patients.
7.Drug interactions should be well studied.
8.High awareness of the presence of specific side-effects in elderly patients.

The above suggests a more differentiated approach to PEP selection in elderly patients than in those of younger age. A special role should be given to consideration of drug interactions due to forced polypragmasy in this category of patients.

The principles of pharmacotherapy to avoid side effects and drug complications in elderly patients with epilepsy are the same as for any elderly patient who requires polypragmatic prescribing.

Because the metabolism of a number of PEPs is reduced in the elderly compared to younger patients, similar doses of PEPs create higher blood concentrations in elderly patients. This makes it necessary to start treatment of elderly patients with low doses of the drug and titrate them carefully. It is necessary to use on average smaller daily doses of carbamazepine in patients in this age group in order to avoid increasing the blood concentration of the drug with associated toxic effects. Thus, the recommended starting dose of PEP in elderly patients should be 30-50% lower than in younger patients. When prescribing PEPs, it is necessary to consider the presence of side effects and contraindications for prescribing these drugs, which is especially important for elderly people, as the risk of adverse reactions to injected drugs in patients in this age group increases by 1.5 - 2 times compared to those aged 30 - 40 years. If PEPs are well tolerated, it is recommended that retarded (prolonged) forms

of the drugs be taken 1¬2 times a day, which in elderly patients due to the convenience of use in some cases allows for better adherence to the treatment regimen.

Since various partial seizures with/without secondary generalisation predominate in the elderly, it is necessary to briefly review the first- and second-line drugs of choice for this seizure type.

A common opinion is that carbamazepine is the only seizure drug of choice, with a proven high efficacy. The efficacy of carbamazepine therapy in the elderly is comparable to that in younger patients, but some side effects limit its use in elderly patients. The adverse effects on cognitive function are less pronounced with carbamazepine than with phenytoin and phenobarbital, but even these minimal effects often limit its use in older patients. In addition, carbamazepine affects cardiac conduction, which makes it impossible to use in atrioventricular block and limits its use in other rhythm disorders. Carbamazepine also causes sedation, dizziness and ataxia, which increases the likelihood of falls in elderly patients. In addition, carbamazepine, due to the fact that it binds to blood plasma proteins and affects hepatic enzymes, has significant pharmacokinetic interactions with drugs of other pathology, in clinical practice no less important is the impact of epilepsy on the clinical course of any acute and, especially, chronic somatic pathology, as well as the effect of PEPs that the patient takes on the clinical course of a particular disease. And all these questions must be answered by an epileptologist, who sees a patient with epilepsy, rather than by doctors of other specialties involved in the treatment of concomitant pathology. This situation changes somewhat when a patient develops a chronic illness that requires constant monitoring by another specialist. For example, a patient with diabetes mellitus, hypertension or severe angina should ideally be seen by two specialists who work closely together, although, unfortunately, this is not always the case.

The management of epilepsy in the presence of comorbidities is highly complex and remains largely open, but some of the following points may help to address this difficult clinical issue.

1.Monotherapy or rational duotherapy.

2.The use of PEPs that have linear pharmacokinetics and minimal interaction with other drugs.

3.Using PEEPs that do not affect the functional state of body organs and systems (heart rate, hormone metabolism, lipid metabolism, other types of metabolism, liver function, female reproductive system etc.).

4.The use of PEPs that have minimal negative effects on the CNS, as developed somatic pathology can exacerbate the side effects of anticonvulsants (especially on cognitive function).

Thus, epilepsy in the elderly has a number of features, which include the predominance of partial seizures with/without secondary generalisation, the combination of epilepsy with other nosological forms in almost all patients, which determines the need for polypragmasy. In the choice of treatment modalities in patients, good efficacy of therapy is noted. Despite the constantly expanding arsenal of PEP, prolonged valproic acid drugs can be considered as one of the main drugs of choice for epilepsy treatment in elderly

Drug groups, which is essential in elderly patients in whom prolipragmasia is inevitable. The hyponatremia induced by this drug is also undesirable in elderly patients.

Numerous multicentre studies have shown that valproic acid is no less effective for partial seizures than carbamazepine. Valproic acid also has a number of side-effects, but side-effects such as hair loss, effects on the menstrual cycle, and weight gain are less limiting in older patients than in younger patients. At the same time, valproic acid has a number of advantages for use in the elderly:

-does not affect cognitive function;
-does not affect heart rate;
-Well-studied drug interactions with other medications;
-Impacts on types of epileptic seizures;
-Does not cause hyponatremia;
-Could be rapidly escalated in dose; -has high efficacy in partial seizures;
-High efficacy for partial and secondary generalized seizures;
-Well-studied side effects;
-Can be taken 1 or 2 times a day.

However, by its pharmacokinetic properties non prolonged forms of valproic acid are less acceptable for treatment of elderly patients than prolonged form - depakine-chrono, which pharmacokinetic properties are as follows: absorption - almost 100%, binding to plasma proteins - 78¬94%, metabolism - in the liver; elimination half-life - 11¬20 hours; therapeutic concentration in blood - 50¬100 mg/l; time to reach peak concentration in blood - 3¬6 hours, concentration is not associated with food intake.

The use of 'new' generation drugs, which are the first-line drugs of choice, was seen as more promising when they became available on the market than when they were subsequently used clinically. However, with low seizure rates, the use of lamotrigine and topiramate in elderly patients is promising and has already been confirmed by a

sufficient number of multicentre clinical trials. Lamotrigine use is limited by the need of extremely slow titration (it takes approximately 2 months to reach the therapeutic dose according to the instructions) and high frequency of skin manifestations - skin rash, up to Stevens-Jones syndrome. Topiramate use also requires extremely slow titration and is also limited by negative effect on higher mental functions. Although it should be noted that as experience is gained with these two PEPs in the elderly, the number of patients receiving them for epilepsy will increase. The second-line drugs of choice, phenytoin and phenobarbital, are difficult to use because of their very poor tolerability in elderly patients. Side effects such as dizziness, ataxia, nystagmus, tremor, double vision, dysarthria, stupor, agitation, respiratory disorders, reduced attention, memory, intelligence, haemotoxic disorders, hyperglycaemia, hypocalcaemia, hirsutism, megaloblastic anaemia, hyperplasia of gums and facial tissue, facial pigmentation and allergic reactions make their use difficult in people over 65, especially with some form of comorbid pathology.

Gabapentin is well tolerated by elderly patients, but its efficacy is significantly lower than that of carbamazepine and other first-line drugs of choice, and it is not recommended for monotherapy. The use of levetiracitam in elderly patients seems promising because of its high efficacy and good safety spectrum, but more research on its efficacy and safety and experience in routine clinical practice in elderly people with epilepsy is needed to make it the first-line choice for this category of patients. It is important to note that the use of original or reproduced PEPs with proven bioequivalence is desirable, as elderly patients are particularly sensitive to drug quality.

An extremely important and significant feature of epilepsy in elderly patients is the combination of epilepsy with somatic pathology and, often, with more than one nosological form. This necessitates, on the one hand, the need to take into account the mutual influence of the pathogenetic links of epilepsy and other pathological conditions, and on the other hand, the need for polypragmasy, taking into account the mutual influence of medications. The problem of concomitant somatic pathology in people with epilepsy is particularly relevant because the epileptic process in patients is lifelong, and even in cases of successful treatment cessation, patients remain at high risk of seizure recurrence, particularly because of any factor that may be a somatic disease or therapeutic complex for it.

Conclusions

Acute somatic pathology in patients with epilepsy certainly influences epileptogenesis, as does the presence of concomitant chronic pathology, especially

that which directly or indirectly affects brain metabolism. In addition to the mutual influence of the two pathological processes, the interaction of anticonvulsants with the drugs used to treat the concomitant pathology must be considered. Only a detailed consideration of the above factors will make the treatment of epilepsy in elderly patients not only effective but also safe, and will not worsen the clinical course of epilepsy and other existing pathology in the patient.

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