PPN

Personalized Psychiatry and Neurology

Lecture

Juvenile myoclonic epilepsy: current state of the problem

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Abstract: Due to the high prevalence of the disease, its genetic and clinical heterogeneity, the need for lifelong therapy and the emergence of new views on the pathogenesis and course of JME, it is necessary to provide primary care physicians (general practitioners, district therapists, neurologists) with up-to-date systematized information about the most common form of genetic generalized epilepsy (Herpin-Janz syndrome). JME is a genetically determined disease of the brain, accompanied by a triad of seizures (absences, myoclonia, generalized tonic-clonic seizures), and developing mainly in adolescence and young age. In recent years, monogenic and multifactorial forms of JME have been identified, but questions about the genetics of JME are far from being resolved. JME is characterized by the preservation of intelligence, life expectancy with adequate therapy does not differ from the average population, but the frequency of failures of pharmaco-induced remission is high when taking anticonvulsants is canceled. This explains the need for lifelong pharmacotherapy, individual selection of anticonvulsants. About 30% of patients with JME have non-psychotic mental disorders, disorders of the sleep and wake cycle, which in turn leads to an aggravation of epileptic seizures mainly in the first half of the day. This review presents an analysis of full-text publications in Russian and English over the past five years in the databases eLibrary, PubMed, Web of Science, OxfordPress, Springer, and Clinicalkeys. In addition, the review includes earlier publications of historical significance.

Keywords: *juvenile myoclonic epilepsy (JME); generalized tonic-clonic seizures; absence; myoclonia; genetic epilepsy.*

Introduction

According to the World Health Organization (WHO), five million people are diagnosed with epilepsy every year in the world. At the same time, in high-income countries, there are 49 cases of epilepsy per 100,000 people annually, and in low-and middle-income countries, this figure can reach 139 per 100,000. This is probably due to an increased risk of endemic diseases, such as malaria or neurocysticercosis; a higher frequency of road traffic injuries; birth-related injuries; as well as changes in the medical infrastructure, the availability of preventive health care programs and affordable medical care [1].

Epilepsy is a brain disease that corresponds to any of the following conditions: 1) at least two unprovoked (or reflex) epileptic seizures with an interval of more than 24 hours; 2) one unprovoked (or reflex) epileptic seizure and the probability of repeated seizures corresponding to the overall risk of relapse after two unprovoked epileptic seizures is more than 60%; 3) the established diagnosis of a specific epileptic syndrome [2].

According to the Global Burden of Disease studies (GBD, 2019), an assessment of the burden of epilepsy in 195 countries and territories from 1990 to 2016 showed that in 2016 the number of patients with epilepsy reached 45.9 million people, including genetic and secondary forms, worldwide. The age-standardized prevalence of cases of active epilepsy (with persistent epileptic seizures) was 621.5 per 100,000 [95% confidence interval (CI): 540.1 - 737.0]. Of these, 24000,000 people had active genetic (idiopathic) epilepsy (prevalence - 326.7 per 100,000 [95% CI: 278.4 – 378.1]) [3]. Significant progress in reducing the burden of epilepsy, in general, and genetic epilepsy, in particular, can be expected from improving the level of training of primary care doctors on the problem under consideration, improving early diagnosis and timely selection of adequate therapy for the disease [4]. However, to date, management errors of genetic generalized epilepsy (GGE) persist all over the world [5, 6], leading to a decrease in the quality of life of patients, the development of therapeutic resistance and/or pseudo-resistance to antiepileptic drugs (AEDs), an increase in direct and indirect economic costs [7].

It is important to remember that GGE is a common form of epilepsy [8], it includes several electro - clinical syndromes that are diagnosed and classified according to clinical features, electroencephalographic (EEG) characteristics. A characteristic EEG pattern in GGE is bilateral synchronous, symmetric and generalized polyspike slow-wave discharges [9]. Polyspike and polyspike slow-wave discharges are also often recorded [10].

Juvenile myoclonic epilepsy (JME) has been the subject of intensive research for many years, since it is the most common archetypal syndrome of GGE [11] with a fairly homogeneous manifestation and a largely unknown etiology, and the elucidation of probably multiple genetic mechanisms of the pathogenesis of JME is a continuous scientific process [12, 13]. JME cannot qualify as "benign" epilepsy, but in most patients, epileptic seizures can be treated adequately, while patients will not experience serious restrictions regarding their life expectations. The risk of relapse of epileptic seizures in JME is higher than 80% with the abolition of AEDs, therefore, lifelong treatment is usually necessary [14].

History of Juvenile Myoclonic Epilepsy

JME, also known as Janz syndrome in Europe and Castels-Mandilaharsu syndrome in South America, is the most common form among all forms of epilepsy in juvenile and young people, in general, and among GGE, in particular [11, 15]. The share of JME is 5-10% of all cases of epilepsy in children and adolescents and 20-27% among all forms of GGE.

JME was discovered in stages in Switzerland and France in the XIX century, adequately described in Germany and Uruguay in the 1950s and rediscovered in North America in the early 1980s. The disease was first described in 1854 by Delasiauve ("motor petit mal"). In 1867, Theodore Herpin described a 13-year-old boy suffering from myoclonic twitching (“impulsions, commotions”), which after three months developed into generalized tonic-clonic seizures (GTCS). In 1957, Janz D. and Christian W. published an article in the journal describing several patients with JME. As a tribute to the first author of the first extensive and detailed clinical description of JME, the disease is called Janz syndrome [16].

The name "Juvenile myoclonic epilepsy" was proposed in 1975 and adopted by the International League Against Epilepsy (ILAE). In accordance with the proposal for a revised Classification of epilepsies and epileptic syndromes in 1989, the ILAE Classification and Terminology Commission defined the definition of JME (impulsive petit mal) as follows: "Impulsive petit mal appears during puberty and is characterized by seizures with bilateral, single or repeated, arrhythmic, irregular myoclonic contractions, mainly in the hands. Jerks can cause some patients to suddenly fall. Violations of consciousness are invisible. There are often GTCS and, less often, infrequent absences. Usually, seizures occur shortly after waking up and are often triggered by sleep deprivation [17, 18].

Etiology of Juvenile Myoclonic Epilepsy

The exact cause of JME remains unknown, although at present the disease is attributed to GGE. Specific mutations in various genes with a complex type of inheritance were identified in JME. Most likely, several genes lead to a similar electro-clinical syndrome [19, 20]. Although most studies have shown that JME is an autosomal dominant disease (i.e., with a 50% risk of inheritance), it has incomplete penetrance. Some clinically healthy individuals may be carriers of mutations of candidate genes of predisposition to JME. However, their children who inherited these mutations will have clinical symptoms of JME. For an untrained observer, the disease seems to skip generations. For relatives of a patient with JME, the risk of clinical symptoms of the disease is low: 3.4% - in parents; 7% - in brothers and sisters; 6.6% - in children. Despite the similar genetic load, the JME phenotype may vary among relatives, as in the case of identical twins who had a proband of JME (myoclonus and GTCS), but the identical twin had only absence epilepsy in childhood. Currently, there is no doubt that the burden of the disease really varies depending on the spectrum of people with JME [3, 21].

The results of routine pathological analyses of brain samples from patients with JME are usually normal. However, histology sometimes reveals an increased number of partially dystopian neurons in the molecular layer, the white matter, the hippocampus and the cerebellar cortex; an indistinct boundary between the cortex and the subcortical white matter, as well as between plates 1 and 2, can also be detected. These data are called microdisgenesis and are interpreted as a manifestation of minimal developmental disorders [22-24]. According to the data of neuroimaging using structural and functional magnetic resonance imaging (MRI) in patients with JME, the following can be detected: a decrease in the volume of the medial parts of the frontal frontal cortex; a decrease in the volume of the precentral gyrus cortex and the additional motor lobule (AMD); violations of functional connections in the thalamo-motor neural networks; a decrease in the volume of the thalamus nuclei; changes in the white matter of the medial - frontal region of the brain [25-29].

Onset of Juvenile Myoclonic Epilepsy

JME is characterized by an age-dependent onset with upper limb jerks in adolescence, as well as GTCS in most cases. The most typical age of JME onset is between 12 and 18 years of life, but the symptoms of the disease can be observed in a wider age range - from 6 to 36 years [12, 30].

In most patients, JME debuts around puberty with myoclonic seizures preceding the first GTCS for an average of 3.3 years. In about 25% of cases, GTCS develops before the onset of myoclonic seizures, rarely with a delay of several years, and in about one third of cases, myoclonic seizures and GTCS have a simultaneous onset (Fig. 1) [31].

JME persists throughout life at most patients, the burden of epileptic seizures associated with JME seems to decrease in adulthood and with aging. It is not known whether patients outgrow JME, compared with other GGE, at a later age (i.e. > 60 years). To solve this issue, an epidemiological study is necessary. At the same time, rare cases of late debut of JME were recorded already in the eighth decade of life [12, 13, 47].

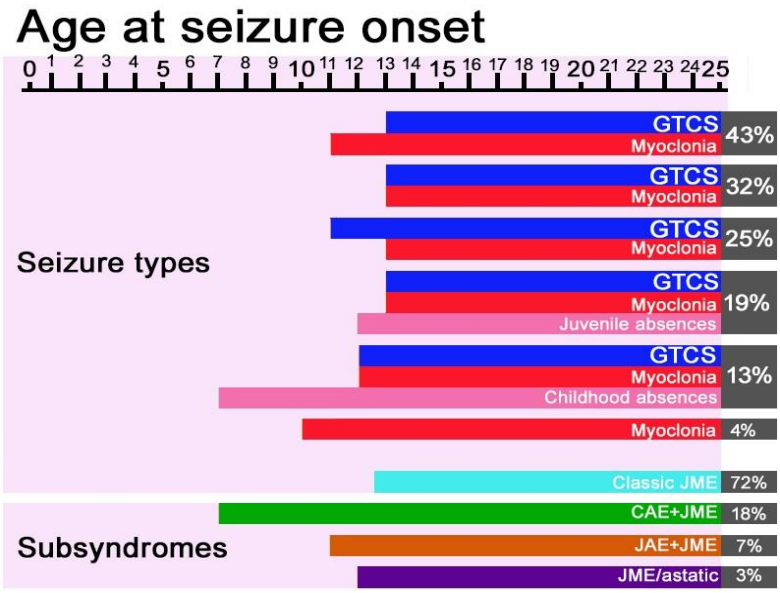

Figure 1. General characteristics of epileptic seizures in juvenile myoclonic epilepsy and subsyndromes (phenotypes) of the disease (according E. M. Yacubian, 2017 [31]; modified by K. V. Petrov, 2021): GTCS – generalized tonic-clonic seizures; JME – juvenile myoclonic epilepsy; CAE – childhood absence epilepsy; JAE – juvenile absence epilepsy.

Diagnostic Criteria for Juvenile Myoclonic Epilepsy

The official definition of JME in the ILAE classification of epilepsy and epileptic syndromes is as follows: "*Impulsive Petit Mal appears around puberty and is characterized by seizures with bilateral, single or repetitive, arrhythmic, irregular myoclonic jerks, predominantly in the arms. Jerks may cause some patients to fall suddenly. No disturbance of consciousness is noticeable. The disorder may be inherited, and sex distribution is equal. Often, there are GTC seizures and, less often, infrequent absences. The seizures usually occur shortly after awakening and are often precipitated by sleep deprivation. Interictal and ictal EEG have rapid, generalized, often irregular spike-waves and polyspike-waves; there is no close phase correlation between EEG spikes and jerks. Frequently, the patients are photosensitive. Response to appropriate drugs is good"* [32].

Initially, it was believed that JME is easy to diagnose, in recent years, the interest and range of manifestations of this syndrome have been significantly expanded. Two meetings of international experts (Avignon, 2011 and The Hague, 2012) ended with a consensus definition, according to which the symptom required for the diagnosis of JME is myoclonic seizures without loss of consciousness, which usually occur after waking up. After this mandatory diagnostic criterion is met, it will be possible to establish 2 diagnostic classes of JME: one narrower and one wider [33, 34].

The diagnostic criteria of class I include: myoclonic seizures without loss of consciousness, occurring exclusively during or during the first two hours after awakening; EEG with a normal background and typical ictal generalized high-amplitude polyspikes and slow waves accompanying myoclonic seizures; normal intelligence; age of debut between 10 and 25 years of life [18].

Diagnostic criteria of class II: myoclonic seizures that usually occur after waking up; myoclonic seizures provoked by sleep deprivation and stress and provoked by visual stimuli or praxis, or GTCS, which were preceded by myoclonic seizures; normal background on the EEG and at least a single interictal generalized paroxysm "polyspike wave", with some permissible asymmetry, with or without registration myoclonic seizures; no mental retardation or deterioration of intelligence; broader terms for the age of debut are from 6 to 25 years [18].

JME is characterized by three types of generalized epileptic seizures, which (in the classical course of the disease) are combined into the so-called Herpin-Janz triad (Fig. 2): absences; myoclonic seizures; GTCS.

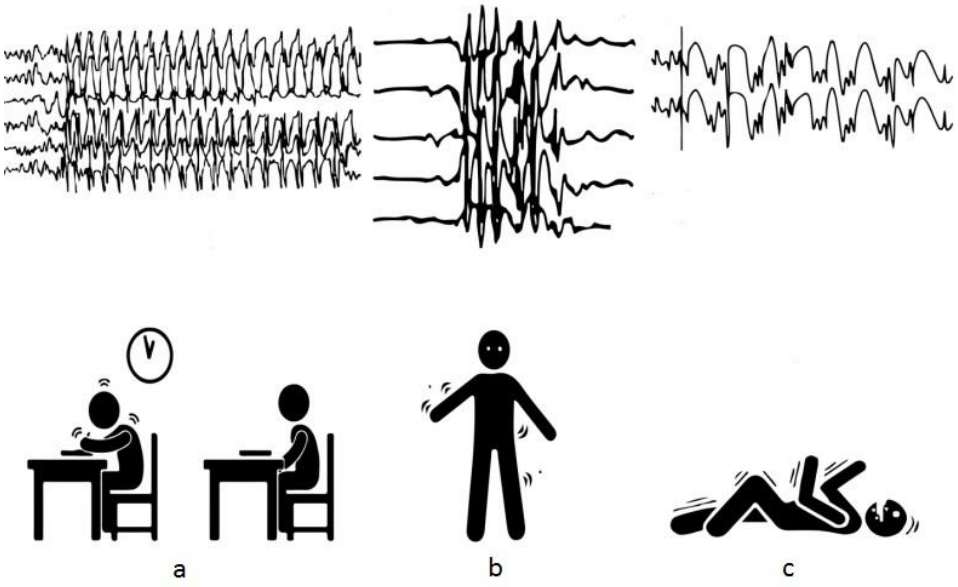

Figure 2. The Herpin-Janz triad - three characteristic types of epileptic seizures in juvenile myoclonic epilepsy: a) absence; b) myoclonic seizure; c) tonic-clonic seizure.

Absence is a non - convulsive generalized epileptic seizure with a sudden cessation of the action started, a stop of the gaze (an empty look), a lack of awareness of what is happening around, a lack of real (verbal) contact with people around them. Patients may blink rapidly, roll their eyes up, move their lips, or gently pull or rub their clothes. Absences begin and end very suddenly. When the patient regains consciousness, he may not realize that he had a non-convulsive generalized epileptic seizure (absence). In some cases, especially in children, a parent or teacher may not always notice absences, as they can easily be confused with dreams ("ideas"). Absences were described in 31.9% of patients (in 12.8% - with the debut of JME from the first decade of life, in 19.1% - with the juvenile debut of JME). Absences may precede the onset of myoclonic seizures, being on average 4.5 ± 2.5 years ahead. In general, absences in patients with JME are rare and short duration, so they are often ignored by patients and their family members, including due to incomplete, if any, disorders of consciousness. At the same time, the actual frequency of absences in JME is higher than previously assumed, before the introduction of video monitoring – EEG and specific load tests and protocols, including cognitive-motor ones, into clinical practice [31, 35].

Myoclonic seizures (jerks) are very short duration, often lasting up to several seconds, twitching of the upper (more often) or lower (less often) limbs, facial muscles, and tongue. As a rule, the patient does not lose consciousness during myoclonic seizures. Myoclonic seizures can involve individual parts of the body or spread to the entire body of the patient. Myoclonic seizures that occur in full consciousness in patients with JME, which are necessary for the diagnosis of the disease, prevail in the upper extremities. They are spontaneous, short duration, sudden, isolated, or occur in short arrhythmic clusters with a characteristic chrono-dependence, usually defined as "epilepsy on awakening". More often, myoclonic seizures in JME develop after waking up in the morning, especially after a lack of night sleep (deprivation) or are provoked by a sudden awakening. They can also occur during relaxation periods later in the day. This feature of JME caused the figurative name "Cinderella syndrome" [36, 37] (Fig. 3).

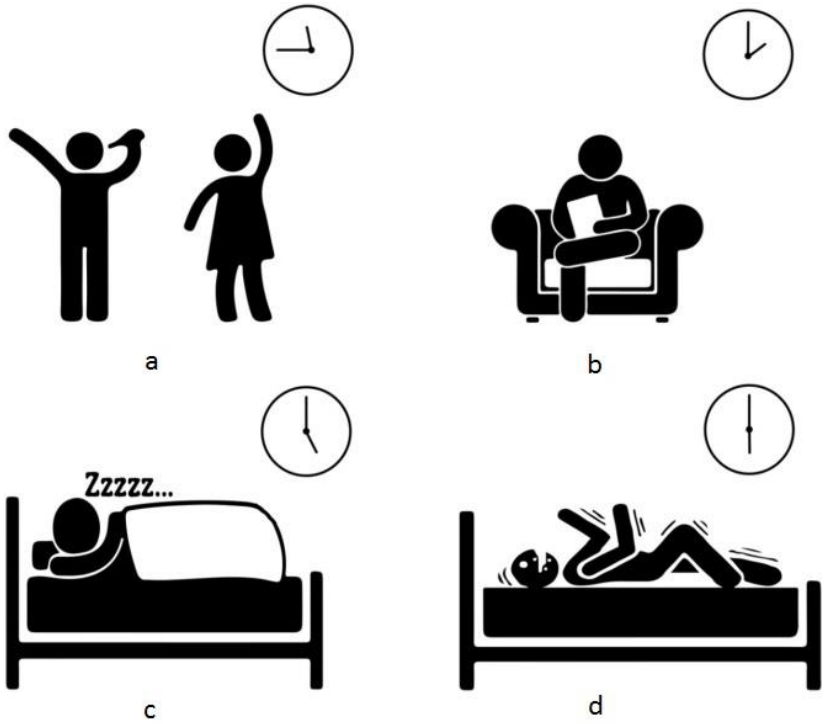

Figure 3. Cinderella syndrome-characteristic triggers of epileptic seizures associated with a violation of the sleep-wake cycle in patients with juvenile myoclonic epilepsy: a) nighttime activity (especially in combination with alcohol intake); b) late falling asleep; c) reduction of the duration of night sleep; d) early awakening.

Roughly symmetrical jerks in the extremities can lead to an imbalance and a patient falling, falling or throwing objects out of his hands during morning hygiene or breakfast. Praxis-induced reflex myoclonic seizures are possible. They may predominate in the hand that performs the movement, but, in general, more often with the participation of the dominant side. Rarely, myoclonic seizures involve the lower extremities, sometimes the muscles of the trunk, including the diaphragm, causing an inspiratory noise, a sudden short cry (screaming), hiccups, which makes such an epileptic attack look like a fright reaction. Myoclonic seizures may remain the only type of seizures in patients with JME, which is observed from 4% to 17% of cases. However, this number is probably underestimated, since most of these patients may never seek medical help from a neurologist [38].

GTCS is a consequence of generalized epileptiform activity involving the entire brain, so the patient loses consciousness immediately. GTCS consists of two phases: first, the tonic phase develops, during which the movements stop and the person falls to the ground; then follows the clonic phase with rapid jerky movements of the body. GTCS usually lasts up to 1-3 minutes. Sometimes, before GTCS, a person may experience what is known as an aura, which serves as a warning sign of an impending epileptic attack, giving patients time to prepare. Not always aura lead to GTCS and may occurs independently [12].

Usually, accumulation of the negative influence of provoking factors (triggers) causes the first GTCS, which, as a rule, is the reason for seeking medical help for most patients. 80-95% of patients with JME have GTCS, and they can follow a long cycle of myoclonic seizures, with an increase in their amplitude and frequency, resulting in the tonic phase of intense and especially long GTCS [39].

A feature of JME are reflex signs (Fig. 4, 5), including [40, 41]: 1) sensitivity to light stimulation (photosensitivity), which is clinically rather not pronounced, occurs on average in 38% of patients with JME (from 8% to 50-90% of cases, depending on age, treatment and the modality of photostimulation) [42]; 2) sensitivity to eye closure in the form of registration on the EEG of the appearance of polyspike wave discharges and eyelid

myoclonia during the first two seconds after eye closure occurs in 15-20% of patients with JME [42, 43]; 3) sensitivity to praxis, which is characterized by the occurrence of epileptic seizures or epileptiform discharges on the EEG when performing complex, cognitively-controlled tasks, often associated with visual-motor coordination and decision-making, occurs on average in 30% of cases (from 29% in Brazilians, 31% in Europeans, up to 47% in Japanese); 4) sensitivity to speech activity - myoclonic orofacial reflex in the form of lightning-fast jerks in the perioral muscles, tongue, throat and jaw, which are provoked by the movement of the tongue, mainly reading and talking, occurs on average in 25-30% of patients with JME, due to the hyperexcitability of the neural network supporting linguistic communication [44].

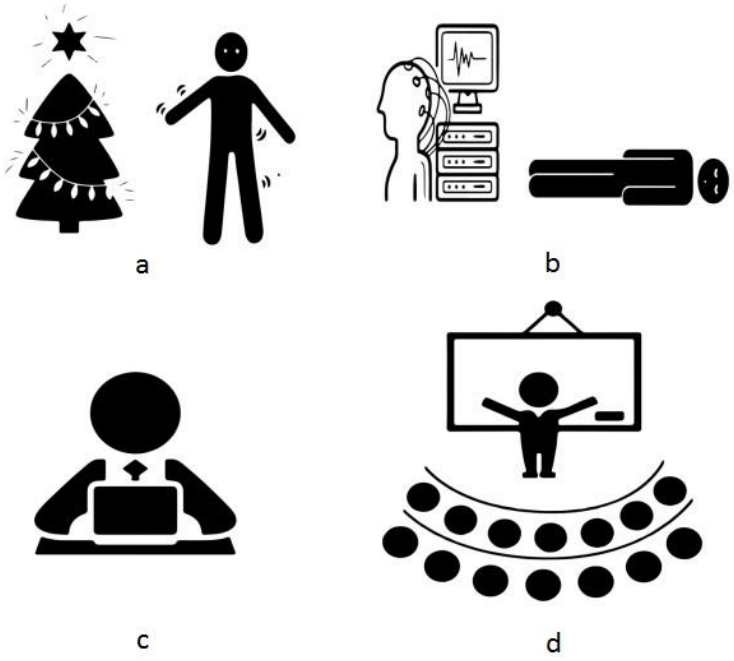

Figure 4. Four reflex signs characteristic of juvenile myoclonic: a) sensitivity to light stimulation; b) sensitivity to eye closure; c) sensitivity to praxis; d) sensitivity to speech stimulation

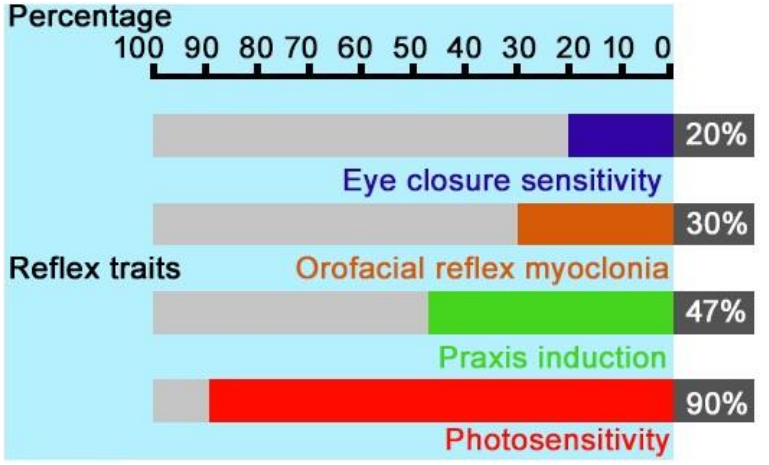

Figure 5. Frequency of occurrence of four reflex signs of juvenile myoclonic epilepsy (according to E. M. Yacubian, 2017 [31]; modified by K. V. Petrov, 2021).

Phenotypes of Juvenile Myoclonic Epilepsy

JME is characterized by clinical heterogeneity, which can complicate differential diagnosis. To date, there are four main phenotypes of JME [19, 45, 46].

The classical phenotype of JME (62.5% of cases) is characterized by the onset of the disease in the adolescent period with isolated myoclonic awakening attacks that appear as the first type of attack or after the debut of GTCS, as well as the classical Herpin-Janz triad (absences, myoclonia, GTCS) [47].

The JME phenotype with transformation from childhood absence epilepsy (10% of cases) is characterized by the onset of the disease from absences in children, followed by the addition of myoclonic seizures and GTCS, more often in adolescence. This phenotype is characterized by a high risk of therapeutic resistance [47].

The phenotype of JME with the juvenile onset of absences (2.5% of cases) and the addition of GTCS and myoclonia in subsequent years resembles the clinical course of juvenile absence epilepsy (JAE) in the first years after the onset of the disease [47].

The phenotype of JME with astatic attacks (25%) is a rare phenotype of the disease, characterized by the debut of astatic attacks independently of myoclonic attacks [47].

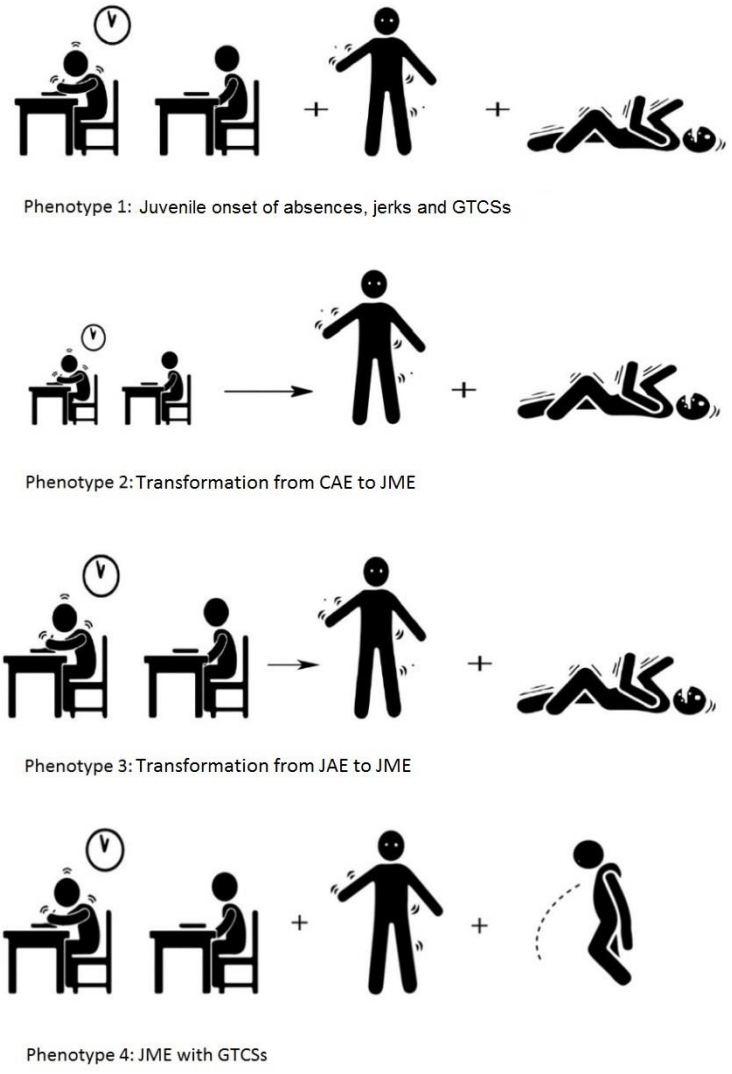

Figure 6. Four phenotypes of juvenile myoclonic epilepsy.

Comorbid Disorders and Juvenile Myoclonic Epilepsy

Behavioral and mental disorders, especially unstable mood, anxiety, and personality disorders, are present on average in 30% of patients [48-50], in connection with which a number of authors figuratively call JME – "a wolf in sheep's clothing" (Fig. 7). These disorders, which are a consequence of frontal dysfunction in a number of patients, can lead to poor compliance with doctor's recommendations and unhealthy behavior, which affects their treatment and rehabilitation of patients with JME. The intelligence of patients with JME does not suffer, but in 20-25% of cases there are comorbid cognitive disorders [51].

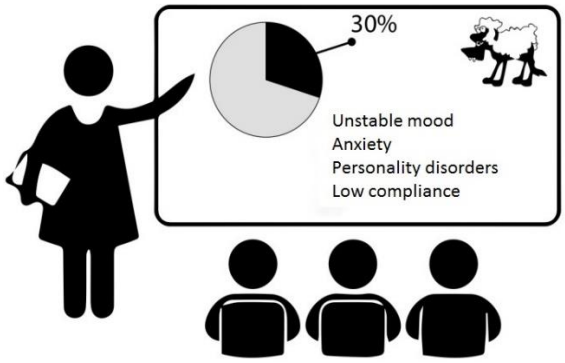

Figure 7. Wolf in sheep's clothing syndrome-characteristic behavioral disorders in patients with juvenile myoclonic epilepsy that affect their treatment and rehabilitation: unstable mood; anxiety; personality disorders; poor compliance with doctor's recommendations.

Treatment of Juvenile Myoclonic Epilepsy

JME is a heterogeneous epileptic syndrome, given the reaction to AEDs and the long-term consequences. The treatment of JME is based on a balance between avoiding provoking factors (triggers) and the proper use of AEDs [52].

Lifestyle advice is an integral part of the treatment and rehabilitation of patients with JME, including recommendations for eliminating common triggers such as sleep deprivation, fatigue, alcohol consumption, early and/or sudden awakening, and emphasis on the importance of following the AEDs regimen.

Since the 1980s, valproic acid (VA) and levetiracetam (LEV) have been the first-choice AEDs for JME with a percentage of prescribability up to 60-80% and 20-30%, respectively (Table 1). Some AEDs, especially sodium channel blockers, such as phenytoin, carbamazepine, oxcarbazepine, lamotrigine, less often - gabapentin, pregabalin, tiagabine and vigabatrin, can worsen the course of JME, especially myoclonic seizures [53].

Prognosis of Juvenile Myoclonic Epilepsy

JME is considered, in general, sensitive to adequate treatment (Fig. 8), has therapeutic resistance rates of about 15%, and pseudoresistance - near 10%. Long-term remission is more real than previously thought possible: about 60% of patients with JME remain free from epileptic seizures for at least five years until the last attack. Among them, 72% receive AEDs and 28% do not receive AEDs. About 26-28% of patients with JME are free from epileptic seizures on the background of regular use of AEDs for 20 years or more. However, up to 50% of patients with JME have at least one serious adverse social outcome, such as inability to finish high school, unplanned pregnancy, depression, unemployment or loneliness, low physical activity [12, 54].

Table 1. Antiepileptic therapy options, suggested dosage ranges, evidence, and precautions for the treatment of juvenile myoclonic epilepsy (according to M. J. Brodie, 2016 [53]; modified by N. A. Shnayder, 2021).

AED	Mean daily dose (in adult)	Efficiency	Safety
Valproates	400-3000 mg	The most effective choice based on clinical experience; positive psychotropic effects.	Monitoring of weight gain (in about a third of patients; more common in women) and dysmetabolic syndrome. Monitoring of impaired liver function and the risk of thrombocytopenia (risk of bleeding). Monitoring of heart rhythm and conduction disorders (especially with a burdened family history).
Phenobarbital	60-180 mg	Before the presence of valproic acid, the effectiveness is up to 80% of patients.	Sedation. A strong inducer of liver cytochrome P450.
Levetiracetam	500-3000 mg	It is likely to be less effective than valproic acid in the control of absences that coexist with other types of epileptic seizures in about 30% of patients with juvenile myoclonic epilepsy.	Monitoring of psychiatric side effects that may occur at the start of therapy. Monitoring of heart rhythm and conduction disorders (especially with a burdened family history).
Lamotrigine	100-400 mg	Probably less effective than valproic acid. Synergistic effect with valproic acid. It can be effective for myoclonic seizures.	Slow titration of the drug due to allergic risks. Monitoring of heart rhythm and conduction disorders (especially with a burdened family history).
Topiramate	100-400 mg	It can be effective for generalized tonic-clonic seizures.	Monitoring of neuropsychiatric side effects. Monitoring of the level of potassium in the blood serum. Monitoring of heart rhythm and conduction disorders (especially with a burdened family history).
Zonisamide	100-500 mg	It can be effective for myoclonic seizures and generalized tonic-clonic seizures.	Sedation, depression. Gastrointestinal side effects. Allergic rash, exacerbation of atopias. Monitoring of heart rhythm and conduction disorders (especially with a burdened family history).
Perampanel	6-12 mg	It can be effective as an additional drug for generalized tonic-clonic seizures.	Monitoring of adverse behavioral effects.
Klobazam	10-40 mg	It can be effective as an additional antiepileptic drugs.	Sedation.

Clonazepam	4-8 mg	It can be effective as an additional antiepileptic drugs.	Sedation. Monitoring of the development of tolerance to the drug.
Acetazolamide	500-1000 mg	It can be effective as an additional antiepileptic drugs.	Allowance. Monitoring of the level of potassium in the blood serum. Monitoring of heart rhythm and conduction disorders (especially with a burdened family history).

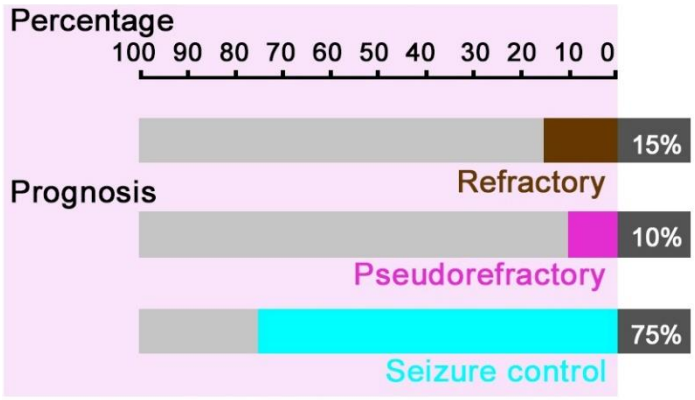

Figure 8. Prognosis of juvenile myoclonic epilepsy y (according to E. M. Yacubian, 2017 [31]; modified by K. V. Petrov, 2021).

Predictors of the worst prognosis in JME are: long-term duration of the disease; a combination of three types of epileptic seizures; non-classical clinical manifestations, such as childhood absences that evolve in JME; focal anomalies on the EEG; concomitant behavioral disorders and other psychiatric disorders; expression of four reflex features of JME; carriage of single-nucleotide variants F229L, R182H and R294H of the *EFHC1* gene [19, 31].

Despite these predictors, predicting at an early stage of the development of the disease which of the patients with JME will have epileptic seizures refractory to AEDs is still a problem in this complex epileptic syndrome [55].

Rehabilitation of Patients with Juvenile Myoclonic Epilepsy

Currently, the arsenal of non-drug methods of rehabilitation of patients with JME is expanding and being introduced into clinical practice, fundamental and clinical approaches to physical rehabilitation of patients are being revised. However, doctors of physical and rehabilitation medicine, neurologists, general practitioners do not have formal education / training regarding the benefits of exercise and sports for patients with epilepsy. This is one of the reasons for unjustified restrictions and low physical activity of patients with JME [56].

In order to improve the quality of life of patients with JME and their social functioning, it is necessary to identify, analyze and classify the patient's problems, both related to life and health, and with factors of a social and personal nature and individual environment. Identification and conceptual classification of these problems can give an idea of the life perspective of patients with JME and help them mitigate the long-term consequences of the disease. It is extremely important to study these issues from the point of view of the patient himself, since his opinion, the opinion of his family members (parents, friends, children, etc.) and clinicians (neurologists, doctors of physical and rehabilitation

medicine) may differ in relation to the importance attached to the outcomes of the disease and the impact of regular physical activity and sports on health and quality of life [56-60].

The identified problems related to the health of a patient with JME should be considered from the point of view of the International Classification of Functioning, Disability and Health (ICF, 2001) [61-65]. ICF is a multi-purpose classification of the components of health, disability and functioning (Fig. 9). ICF can be used to formulate a rehabilitation diagnosis that is associated with the condition of a patient with JME at the time of examination. In general, the rehabilitation diagnosis of JME is a list of significant problems of the patient that determine his functioning.

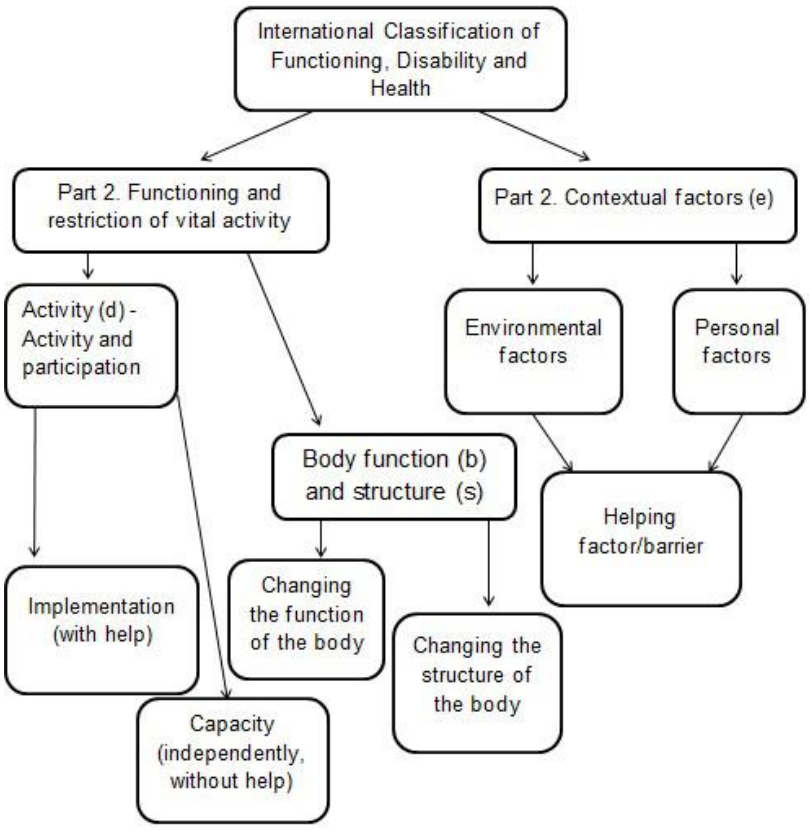

Figure 9. Block diagram of the International Classification of Functioning, Disability and Health (2001)

Rehabilitation assessment of patients with JME is a starting point for making medical decisions and developing personalized programs of physical and rehabilitation medicine (PRM) for a particular patient [66].

Terminologically, the word "assessment" includes the procedures and techniques of the ICF and the measurement of parameters specific to a particular person, in general. Such an assessment allows us to reach final decisions regarding the patient's needs through this classification and its tools (measurements), which can mutually influence each other (positively or negatively).

The diagnosis according to the ICF (2001), in contrast to the diagnosis according to the ICD (1995), gives a more complete picture of the existing problems in a patient with JME, both directly related to his health, and with incorrect attitudes of the family, environment, and the patient himself, requiring appropriate corrective intervention by a rehabilitologist, coordinated with the attending epileptologist (neurologist or psychiatrist).

So, the plan of rehabilitation measures for a patient with JME may include: psychocorrecting methods in connection with the anxiety and low compliance detected in him; educational work with the patient's relatives; explanatory conversations with the patient and his relatives on the normalization of sleep, a balanced diet, maintaining physical

activity and regular visits to the attending epileptologist; explanation to the patient and his relatives of the need for classes with a rehabilitation doctor, due to the low tolerance of the patient's body to physical exertion, overweight and associated with an increased risk of obstructive sleep apnea/hypopnea syndrome; informing the coach about the clinical and rehabilitation diagnoses of the patient and modern approaches to the admission of patients with epilepsy to certain sports (athletics belongs to group 1-there is no significant additional risk), in connection with which the patient can continue training in the mode of the usual training process (Table 2, 3) [66].

Table 2. Classification of sports by the level of risk of injury or death for patients with epilepsy or for other persons if an epileptic seizure occurs during a sport events [66].

Group 1 (no significant additional risk)	Group 2 (moderate risk)	Group 3 (high risk)
	Alpine skiing	
	Archery	Aviation sports
	Athletics (pole vault)	Rock climbing
Athletics (except for the sports listed in Group 2)	Biathlon, triathlon, mod-	Diving
Bowling	ern pentathlon	Horse racing
Most contact types of martial arts (judo, wres-	Kayaking and canoeing	Auto-motorsport
tling, etc.)	Contact types of martial	Parachuting
Team sports on land (football, basketball, volley-	arts associated with po-	Rodeo
ball, rugby, field hockey, baseball, cricket, etc.)	tentially serious injuries	Scuba diving
Ski racing	(for example, boxing,	Ski jumping from a ski
Curling	karate, etc.)	jump
Dances	Cycling	Solo swimming (sailing)
Golf	Fencing	Surfing, windsurfing
Rocket sports (lawn tennis, table tennis,	Gymnastic	
badminton, squash)	Horse riding	
	(for example),	
	Olympic equestrian	
	disciplines-dressage,	
	show jumping, triathlon)	
	Ice hockey	
	Bullet shooting	
	Skateboarding	
	Snowboarding	
	Ice skating	
	Swimming	
	Weightlifting	
	Water skiing	

Table 3. Recommendations on the choice of sports for patients with juvenile myoclonic epilepsy [57, 67-72, modified by N. A. Shnayder and K. V. Petrov, 2021].

Type of sport	Recommendation
Swimming and water sports	Always swim in indoor pools under the direct supervision of trained specialists (for cardiopulmonary resuscitation) who are aware of the patient's / athlete's health status (the fact of the presence of JME). Do not swim in open waters without the supervision of relatives, friends, coaches and other adults who can swim, who have basic training in cardiopulmonary resuscitation and are aware of the health status of a patient with JME. Always wear a life jacket while in a boat, water skiing, or when doing any other water sport. Do not engage in water sports in closed or open artificial or natural reservoirs alone. Avoid these sports with uncontrolled epilepsy (with the first detected JME before taking AEDs, in the early morning hours, especially after exposure to provoking factors the night before, at night and / or in the morning, with the development of adverse reactions of AEDs, when taking any doses of alcohol on the eve or on the day of water sports, in the perimenstrual period in patients with JME of fertile age). It is not recommended to engage in scuba diving (in most cases, JME).

	It is not recommended to engage in hang gliding and skydiving. You can practice horse riding under the supervision of trained specialists in providing first aid for epileptic seizures (or as a type of non - drug therapy – hippotherapy). It is allowed to engage in certain sports (cycling, gymnastics on uneven bars or performing acrobatic elements, rock climbing) only for patients with JME with seizures controlled against the background of taking AEDs (with the duration of remission of all types of seizures typical for JME for a period of 12 months or a 3-fold period from the last attack between attacks with oligoepilepsy).
Sports at a height	Admission to certain sports (cycling, gymnastics on uneven bars or performing acrobatic elements, rock climbing) should be individually evaluated for a patient with a controlled JME with recommendations for their performance with the necessary protective equipment. Engage in the above-mentioned sports at altitude (subject to admission to them) using personal protective equipment against the risk of injury (helmet, elbow pads, knee pads, insurance, etc.). Avoid busy roads and sports tracks when cycling.
Auto-motorsport	It is not recommended to practice for those patients with JME who have any uncontrolled epileptic seizures (absences, jerks, GTCSs). There are no formal restrictions if JME is controlled against the background of taking AEDs (with the duration of remission of all types of seizures typical for JME for a period of 12 months or a 3-fold period from the last attack between seizures in oligoepilepsy) and the issuance of a driver's license meets all the regulations adopted in each individual country. Avoid busy roads and sports tracks when doing auto and motor sports. Take into account the safety of other road users (athletes, coaches, referees, fans, bystanders).
Shooting sports	It is not recommended to engage in those patients with JME who have uncontrolled epileptic seizures (absences, jerks, GTCSs).
Contact sports	It is possible to engage only in patients with JME with controlled seizures while taking AEDs (with the duration of remission of all types of seizures typical for JME during a period of 12 months or a 3-fold period from the last attack between seizures in oligoepilepsy), provided that the type of epileptic seizures and the type of weapon are evaluated. Take into account the safety of other participants in training and competitions (athletes, coaches, referees, fans, bystanders). It is not recommended to engage in those patients with JME who have uncontrolled epileptic seizures (absences, jerks, GTCSs). You can practice all contact sports of group 1 (judo, wrestling). It is usually possible to engage in all contact sports of group 2 (karate) with the exception of boxing (a sport for which there was no general consensus as to whether it is harmful or not for patients with epilepsy).
Aerobic sports	It is allowed to engage in most aerobic sports: walking; running; football; basketball; volleyball; rugby; field hockey; cross-country skiing; lawn tennis; table tennis; aerobics; gymnastics, not related to height. It is allowed to work out in the gym (walking and running on a treadmill, classes on exercise bikes and steppers, etc.), provided that there are no uncontrolled jerks and GTCSs. There are no restrictions on the use of appropriate sports equipment in the gym. The use of personal protective equipment to ensure the safety of the patient/athlete from the risk of injury in cases where this is recommended by the instructions for the simulator.

International recommendations in some cases differ from the legislation of the Russian Federation, in particular with regard to driving vehicles [73] and possession of weapons [74].

Conclusion

So, JME is a common polygenic form of GGE. This disease continues to be actively studied. We are increasingly aware of the genetic, pathophysiological and microstructural changes in the brain in JME. However, the implementation of the results of molecular genetic diagnosis of JME is difficult to real clinical practice due to the large number of causal genes, monogenic forms of JME and single-nucleotide variants of candidate genes associated with the development of JME. In addition, at present, the question of the duration of taking AEDs and the prognosis of JME is debatable, and the issues of rehabilitation of patients with JME are far from being resolved.

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