PARADIGMS IN MANAGEMENT OF JUVENILE MYOCLONIC EPILEPSY

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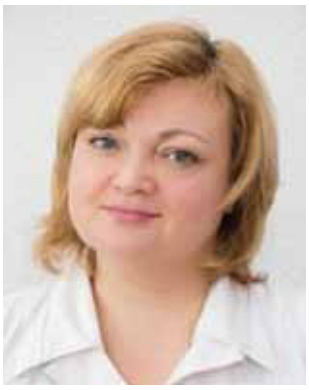

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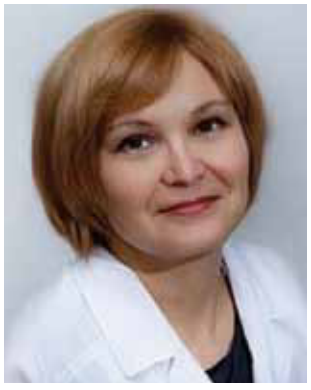

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ABSTRACT — Juvenile myoclonic epilepsy (JME) is one of the most common forms of idiopathic generalized epilepsy. In this article we describe the results of a clinical study into JME management in patients living in the Siberian Federal District. We show that late diagnosis, misdiagnosis and inadequate treatment of JME most often arise due to incompetent management of primary care, rather than as a result of the complexity of clinical symptoms. The outcomes from this study give a deeper insight into the diagnosis and prognosis of this form of idiopathic generalized epilepsy.

KEYWORDS — Idiopathic Generalized Epilepsy, Juvenile Myoclonic Epilepsy, Clinic, Management, Delayed Diagnosis, Prognosis

INTRODUCTION

Juvenile myoclonic epilepsy (JME) is one of the most common forms of idiopathic generalized epilepsy debuting in adolescence, and it is characterized by the appearance of massive myoclonic seizures arising in the period after awakening. Debut age for JME varies from 7 to 21 years, with a peak in the age range 11–15 years. In some cases, the disease can begin at an earlier

age with absence seizures or generalized seizures, with subsequent gain of myoclonic seizures in adolescence. Consciousness is maintained at the time of myoclonic seizures; they arise or become more frequent in the first minutes and hours after awakening. In 90% of diagnosed cases these coincide with generalized seizures and in 40% of patients these are additionally accompanied by short absences of juvenile kind [1, 2].

Usually establishing JME diagnosis is not difficult because of the "bright" clinical picture. However clinical practice shows that the correct diagnosis of the disease is frequently delayed [3, 4, 5].

Special statistical study of diagnostic errors in JME diagnosis in London, UK, conducted by Panayiotopoulos S.P. et al. (1992), showed that from 180 epilepsy patients examined, 15 were diagnosed with JME. Yet upon admission to hospital, diagnosis was correctly identified only in one patient. The average time of JME diagnosis was 14.5 years after the debut of epilepsy. Furthermore, seven patients were prescribed inappropriate anticonvulsants [6].

In a study by P. Genton et al. (2000), the authors found that diagnosis of JME was not made correctly in any of the cases prior to the admission of patients to a specialized epilepsy center in Marseille (France) [7].

Similarly to the aforementioned studies, our own clinical observations suggest repeated errors in the diagnosis of JME [8].

Nevertheless, the timely diagnosis of JME is crucial for the correct management of symptoms and prevention of disease development [9].

In general, excellent seizure control can be achieved in JME patients with relatively low doses of appropriate anticonvulsants [10].

Traditionally, treatment of JME in the XX–XXI centuries was carried out via administration of valproic acid (VA). High efficacy of VA in relieving all types of seizures was demonstrated in patients with JME (myoclonus, generalized seizures, absence seizures), and this drug type was firmly established as the gold standard in the treatment of this form of epilepsy.

Where effectiveness of valproate was suboptimal, they always featured in combination therapy with succinimides (in resistant absences), PB (in resistant GSP), and with clonazepam (in expressed myoclonus and photosensitivity). However, new broad-spectrum antiepileptic drugs (AEDs) have been developed in recent years (LTD, TPM, LEV) and several publications demonstrated their efficacy in JME.

Literature strongly suggests that levetiracetam may be used as a first-line drug in the treatment of JME. Levetiracetam was demonstrated to be as effective as valproate, with significant advantages over it safety criteria. Despite having favorable tolerability profile, Lamotrigine was not sufficiently effective in a monotherapy in JME patients. In addition, in some cases it led to an aggravation of seizures (in particular, myoclonus). Topiramat was shown to be highly effective for GSP, but demonstrated reduced efficacy with absences and myoclonus [11].

It is important to keep in mind that seizures may aggravate and side effects could be detrimental with ineffective treatment, which could reduce the quality of life of JME patients. When managing patients with JME, administration of diuretics and vascular drugs that increase blood flow and perfusion to the area of epileptogenesis, should be avoided, as there is no liquorodynamic dysfunction in JME.

Despite a relatively easy control of the seizures on appropriate treatment, JME is considered to be a chronic disease with a life-long duration. The issue of remission upon termination of AEDs in JME patients is currently under debate. According to Martinez-Juares et al. (2006), only 5% of JME patients who stopped AEDs demonstrated no recurrence of seizures [12]. Yet according to the observations of B. Baykan et al., this figure is about 10% [13]

Similarly, favorable prognosis in patients with JME was not confirmed by Russian groups [14]. However long-term remission with AEDs cancellation was reported in some patients [15]. According to C. Camfield & P. Camfield (2009), cessation of all types of seizures was observed in 17% of patients with JME, with only myoclonus remaining in 13% after the completion of AEDs [16]. Nonetheless, often JME is diagnosed late due to disease progression or inadequate therapy, with significant reduction in the patients' quality of life [17]. Previously, we proposed a variety of enhancements for the accurate diagnosis of JME [8, 18, 19]. In this study, we evaluated the quality of care for patients with JME in the Siberian Federal District.

Aim:

to identify and analyze problems of management and repeated diagnostic errors in JME diagnosis.

MATERIALS AND METHODS

Study Design

This study was conducted in the Neurological Center of Epileptology, Neurogenetics and Brain Research (hereinafter — NC UH) of the Voyno-Yasenetsky Krasnoyarsk State Medical University Hospital, Krasnoyarsk-city, Siberia, Russia. It was performed as part of a complex research project No. 210-16 "Epidemiological, genetic and neurophysiological aspects of nervous system disorders (central, peripheral, autonomic) and preventive medicine" (state registration No 0120.0807480).

Participants

We randomly selected 124 patients with JME, who were diagnosed between 2006 and 2016. All patients were Siberian Federal District's residents and underwent preliminary anamnestic and clinical selection using stratified randomization. In accordance with the Declaration of Helsinki, all of the participants signed informed consent. The study was approved by the local ethics committee of the Voyno-Yasenetsky Krasnoyarsk State Medical University.

Procedures

JME diagnosis was verified in all patients enrolled in this study using video-EEG monitoring with carrying out stress tests. The latter included rhythmic photo-stimulation (RPS); trigger photo-stimulation (TPS), hyperventilation (HV) and according to preliminary findings, sleep deprivation. Female participants were monitored during peri-menstrual cycle, taking into account fluctuations in estrogen levels, which have the potential to promote convulsions. Additionally we tested the level of consciousness during the functional tests (RPS, TPS and HV), with serial counting aloud while standing with outstretched arms (all necessary precautions were taken to ensure patients' safety in the event of loss of balance or consciousness). All patients underwent brain MRI (1.5 Tesla or higher). Detailed analysis of disease history for each patient included debut age, the type of epileptic seizures at debut and the dynamics of the disease progression.

Statistical Analysis

All statistical analyses were carried out using licensed software package SPSS, version 20.0 (USA). Data with nonparametric distribution were presented as median and quartile (Me [P25; P75]); otherwise, average mean and standard error were used. For a comparative analysis of quality indicators in two groups of patients, chi-squared test and Fisher's exact test (for small sample sizes) were used. Values were considered statistically-significant when $p < 0.05$.

RESULTS

We enrolled 123 patients with JME for this study, with the following geographical distribution: 50.4% were residents of Krasnoyarsk (62 cases), 38.2% — of Krasnoyarsk Territory regions (47 cases) and 11.4% were from the neighboring regions of the Siberian Federal District (14 cases). Age debut of the disease varied between 2 and 29 years, with average of 13.28 ± 0.42 years, and median of 14 (11:16) years.

Age of original diagnosis varied between 7 and 54 years old, with average age of 22.46 ± 0.73 years old, and a median of 20 (17:26) years old. The time between onset of the disease and diagnosis of JME varied between 0 and 41 years of age, with average time of 9.5 ± 0.78 years and median of 7 (2:16) years.

In 68 of 123 cases (55.3%) there were mistakes in the appropriate management of JME before enrolling to the NC UH: in Krasnoyarsk there were 34 cases from 62 (54.8%), which was the same in comparison with the cities of Krasnoyarsk Territory and other regions of the Siberian Federal District that were 27 from 47 cases (57.4%) and 7 cases from 14 (50%), respectively ($p > 0.05$). Upon review of medical errors, mistakes in the original diagnosis were identified in 40 out of 68 cases (58.8%); inadequate therapy for the disease onset was prescribed in 45 out of 68 cases (66.2%), incorrect dose of AEDs was prescribed in 14 out of 68 cases (13.6%) and irrational combination of drugs — in 14 out of 68 cases (13.6%).

In all cases, before referral to the NC UH there were no registered reports of any side effects from AEDs in the medical records, even if they had it in the past, or at the time of referral. In addition, no pharmaco-genetic profile was specified in any of the cases, including those with side effects from AEDs. It should be noted that therapeutic drug monitoring and pharmaco-genetic studies of liver cytochrome P450 isozyme genes (CYP1A1, CYP2C9, CYP2D6, CYP2E2) are readily available in Krasnoyarsk and are inexpensive.

All the patients with confirmed JME were recommended therapeutic drug monitoring (TDM) and in 54 (43.9%) of 123 cases, a blood test to study polymorphisms of cytochrome P450 isozymes genes had been advised. In 36 out of 54 cases, the analysis was performed, with compliance for a molecular-genetic study of 66.7%. In 19 cases of 36 (52.8%), adverse pharmacogenetic profile was identified (so-called "slow metabolizers") which required dose corrections, regular TDM (at least once every 3 months), or a change in AEDs, in case of serious side effects.

All identified AED side effects in patient's medical history and at the time of referral were included in the Register of the Side Effects from AEDs, which was compiled by the NC UH in conjunction with clinical pharmacologists. The Register' main aim is to analyze and provide solutions for any difficulties associated with therapeutic management of epilepsy, including JME, in the Siberian population. In accordance with the current Russian legislation (Federal Law of December 22, 2014 N 429-FL, Article 64-66), all current side effects from AEDs are recorded and sent to the National Health Control Authority.

DISCUSSION

Typical electroencephalographic abnormalities are highly supportive of the clinical diagnosis of JME.

However the clinical scenario might not be as clear as the classical description would suggest. Delayed diagnosis (and/or misdiagnosis) of JME directly impacts development of the disease. Inadequate treatment allows aggravation of seizures and worsening of the condition, alongside undesired side effects and emotional stress, all of which significantly reduce patients' quality of life.

It is essential that a patient's anamnesis is thorough and detailed. This can be facilitated by active questioning about presence of myoclonic seizures in patients, who may be ignoring (or not remembering) these episodes, especially at first presence. In addition, family members, friends, classmates and teachers could be quizzed to get a more complete picture of the disease. Awareness should be raised among GPs to flag such conditions and thoroughly investigate causes of seizures.

It is important to keep in mind the possibility of childhood or juvenile absence epilepsy transformation into JME in young patients to maximize a timely and correct diagnosis [18]. Catching JME early will enable correct management of the disease and subsequent long-term improvement in quality of life.

The selection of antiepileptic drugs for the treatment of JME depends on several factors, including the patient's comorbidities, preferences, previous history of adverse events, gender and pharmaco-genetics [20]. In most patients with JME, seizures are well controlled with monotherapy. Valproic acid has been considered the treatment of choice for JME for many years, but epileptologists are increasingly using other choices as first-line therapies. Approximately 80% of patients with JME become seizure-free with valproate monotherapy. A low-dose requirement is not unusual; in fact, the great majority of patients with JME need relatively low levels of anticonvulsants to achieve adequate seizure control (as long as it is an appropriate medication for the syndrome). A great majority of children born to women taking anticonvulsant monotherapy are healthy [22]. Valproic acid and divalproex sodium clearly pose a recognized risk of neural-tube defects (category D) that is higher than the risk associated with older anticonvulsants. Evidence suggests that supplementation with folic acid may decrease this risk.

In general, low doses of appropriate anticonvulsants are needed to successfully treat JME. Although treatment with phenytoin, carbamazepine, or phenobarbital may control some seizure components of JME (typically at high doses), these drugs may increase seizure frequency (eg, myoclonic exacerbation with carbamazepine) and occasionally precipitate new seizure types, such as absence seizures [21, 22, 23].

As this study demonstrates, JME diagnosis was established at an average of 9.5 years of age in the Siberian Federal District, which is comparable with the results of the Panayiotopoulos S.P. et al. (1992) study [6].

Errors in the management of JME, including inadequate treatment and incorrect dosage of drugs, were more common in remote regions of the Krasnoyarsk region, Siberian Federal District, compared with the city of Krasnoyarsk. At the same time, errors of the diagnostic management, including errors in diagnosis and irrational drug combinations, did not vary significantly between the regions. In all cases, modern approaches to personalized treatment of JME, including the study of pharmaco-genetic profile, were not used as a primary method. All identified errors were eliminated after the treatment of patients in a specialized neurological center of epileptology, NC UH, which improved both, the quality and the safety of treatment.

Repeat cases of prescription of sub-optimal drugs for this form of epilepsy, which could aggravate the seizures and contribute to progression of the disease, even with the correct original JME diagnosis, remain a stereotypical mistake of the neurologists around the world. [5, 7]. These mistakes are systemic, witnessed in over 50% of diagnosed cases, both in Russia and abroad. They continue to register in the XXI century and in comparison with the XX century, did not tend to decrease, despite rapid developments in the field of neurophysiology, neurogenetics, neuroimaging. Thus we can conclude that there is an imminent need to change the paradigm of JME management, with introduction of a new disease management model that will be based on years of experience and modern achievements in science and practice. Numerous domestic and foreign studies report the aforementioned issues, yet no feasible ways to resolve it have been suggested to date. We propose that to solve the problem of JME management will only be possible via combined efforts of clinicians and health managers, with organization of regular local, regional and specialized conferences aimed at review of individual cases and system errors in JME management. In addition, it is important to develop new paradigm of JME management which based on modern achievements of science and practice.

CONCLUSION

Thus, repeated mistakes in diagnosis and treatment of JME are a problem of management and continuity of patient management among physicians in primary health care. It is important to resolve this problem, both at clinical and institutional level, including medical practitioners, health administrators and clinical pharmacologists.

Specialized epilepsy centers play a key role in the identification and correction of diagnostic and therapeutic management errors of JME and organizing educational programs for primary care physicians.

Table 1. *Diagnostic and therapeutic mistakes in JME management.*

Management problem	Total (N=123)	Krasnoyarsk (n1=62)	Krasnoyarsk territory (n2=47)	Siberia district (n3=14)	P value
1	2	3	4	5	6
Mistakes in JME management	68 (55.3%)	34 (54.8%)	27 (57.4%)	7 (50%)	$p_{3,4}$=0.0003 $p_{4,5}$=0.0001 $p_{3,5}$=0.0001
Mistakes in JME diagnosis	40 (58.8%)	23 (37%)	12 (25.5%)	6 (42.9%)	$p_{3,4}$=0.0001 $p_{4,5}$=0.0001 $p_{3,5}$=0.0001
Inadequate therapy of JME	45 (66.2%)	22 (13.2%)	18 (38.3%)	5 (35.7%)	$p_{3,4}$=0.0001 $p_{4,5}$=0.0001 $p_{3,5}$=0.0001
Incorrect dose of AEDs	14 (13.6%)	4 (6.5%)	9 (19.1%)	1 (7.1%)	#$p_{3,4}$=0.0678 #$p_{4,5}$=0.3232 #$p_{3,5}$=0.6512
Irrational combination of drugs	14 (13.6%)	10 (16.1%)	4 (8.5%)	1 (7.1%)	#$p_{3,4}$=0.2284 #$p_{4,5}$=0.6823 #$p_{3,5}$=0.3951
Lack of therapeutic drug monitoring	123 (100%)	62 (100%)	47 (100%)	14 (100%)	$p_{3,4}$=0.0001 $p_{4,5}$=0.0001 $p_{3,5}$=0.0001
Lack of side effects of AEDs monitoring	123 (100%)	62 (100%)	47 (100%)	14 (100%)	$p_{3,4}$=0.0001 $p_{4,5}$=0.0001 $p_{3,5}$=0.0001
Lack of pharmacogenetic monitoring	123 (100%)	62 (100%)	47 (100%)	14 (100%)	$p_{3,4}$=0.0001 $p_{4,5}$=0.0001 $p_{3,5}$=0.0001

p = chi-square test; #p = Fisher's test.

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