

Article

Clinical and genetic characteristics of juvenile myoclonic epilepsy

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Citation: Shilkina, O.S.; Zobova, S.N.; Domoratskaya, E.A.; Dmitrenko, D.V. Clinical and genetic characteristics of juvenile myoclonic epilepsy. *Personalized Psychiatry and Neurology* 2021, 1 (2): 95-105.
<https://doi.org/10.52667/2712-9179-2021-1-2-95-105>

Chief Editor: Nikolaj G. Neznanov,
D Med Sci, Professor

Received: 29 October 2021
Accepted: 10 November 2021
Published: 15 November 2021

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Abstract: Juvenile myoclonic epilepsy (JME) is reported as a clinically and genetically heterogeneous disease with a high risk of inheritance. The aim of the study was to establish phenotype features and genetic risk factors for juvenile myoclonic epilepsy to advance existing approaches of prevention, treatment, and observation of patients with JME. Methods: anamnestic; clinical; neurophysiological (EEG); neuroradiological (MRI), neuropsychological; laboratory (DNA-diagnostics). JME starts with absences more frequently in females as compared to males (32.0% vs. 15.4%), and with GTCS and myoclonic in males as compared to females (46.2% and 36.5% vs. 36.0% and 31.2%, respectively). The 1st phenotype of JME was more frequently encountered in male individuals in comparison with female ones (55.8% vs. 34.7%), and the 2nd phenotype was more frequently encountered in female individuals in comparison with male ones (16.9% vs. 5.8%). Homozygous carriage of the T allele of the *GJD2* gene (rs3743123) was associated with the development of JME in the study population, OR = 2.66 (95% CI 1.24 to 5.74). 41.5% of patients with JME have a slow metabolizer pharmacogenetic status, which is a risk factor for pseudo-pharmacoresistance and the development of adverse drug reactions.

Keywords: juvenile myoclonic epilepsy; phenotype; neuropsychological testing; rs206787; rs1516535; *BRD2* gene; *Cx-36* (*GJD2*) gene; pharmacogenetic profile.

Introduction

The share of juvenile myoclonic epilepsy (JME) is 5-10% of all cases of epilepsy in children and adolescents and 20-27% of all forms of genetic generalized epilepsy (GGE) [1-6]. Despite the fact, that pharmacy induced remission is achieved in 80-90% of cases of JME, the recurrence rate associated with withdrawal of antiepileptic drugs (AEDs) is still high. This is a socially and clinically significant feature of epilepsy and a concern of modern neurology, despite the emergence of new AED generations [7-9]. Genetic aspects of the disease are currently insufficiently studied. [10].

At the beginning of the 20th century, mutations in genes associated with mono-genic forms of JME and single nucleotide variants (SNVs) associated with an increase in the risk of JME were identified [1, 2, 11]. It is believed that the carriage of the variant of one of the Mendelian genes is enough to inherit a particular phenotype of JME [12]. Two-focal coding of JME with non-Mendelian inheritance type is assumed [13]. Currently, 9 chromosomal loci associated with JME are identified (Mendelian Inheritance in Man - OMIM, 2017) [14]. In some publications, 11 JME-associated loci are mentioned [12], but not in all of that genes are identified and not for all of them the type of inheritance is specified. Variable phenotypes of JME are also genetically determined [15]. The combination of predisposition gene variants can determine the type of JME course and its evolution. Thus, JME is reported as a clinically and genetically heterogeneous disease with a high risk of inheritance. All of the above explains the relevance of the present study.

Objective

The aim of the study was to establish phenotype features and genetic risk factors for juvenile myoclonic epilepsy to advance existing approaches of prevention, treatment, and observation of patients with JME from the perspective of personalized medicine. The objectives of the study were: to analyze the frequency of JME phenotypes; to analyze the association of such SNVs as rs206787, rs516535 *BRD2*, rs3743123 of the *GJD2* gene with JME; to investigate pharmacogenetic and pharmacokinetic profiles in the patients with JME by the example of the SNVs of the *CYP2C9**2 and *CYP2C9**3 carriage in the *CYP2C9* gene coding the isozyme 2S9 of liver's cytochrome P450.

Materials and Methods

The study was conducted at the Department of Medical Genetics and Clinical Neurophysiology of V.F. Voino-Yasenetsky Krasnoyarsk State Medical University as part of comprehensive research on the subject №. 210-16 "Epidemiological, genetic and neurophysiological aspects of the nervous system (central, peripheral and autonomic) and preventive medicine", registration number 0120.0807480.

Clinical and laboratory examinations were performed in 2015-2018 on the basis of the neurological center of epileptology, neurogenetics, and brain research of the University Clinic (NC UC). Molecular genetic studies were performed on the basis of the Interdepartmental Research Laboratory of Medical Genetics at V.F. Voino-Yasenetsky Krasnoyarsk State Medical University. Clinical exome sequencing was performed on the basis of the Forest Genomics Laboratory of the Institute of Fundamental Biology and Biotechnology at the Siberian Federal University.

The study was approved by the Ethical Committee of V.F. Voino-Yasenetsky Krasnoyarsk State Medical University (protocol №65/2015 dated 11.11.2015). Adults and legal representatives of children included in the study had signed voluntary informed consent to process personal data and conduct all stages of the study.

The main group (177 patients with JME (male 29.4%, female 70.6%), mean age 27.74 ± 0.62 years, Me 27.0 (22.0: 33.0) years. Inclusion criteria: patients with JME; residents of the Siberian Federal District; compliance with the study protocol. Exclusion criteria: other forms of epilepsy; residents of other regions of the Russian Federation; low compliance of patients or their legal representatives to the study protocol. The control group (150 healthy volunteers, age and gender comparable to patients in the main group, $p > 0.05$). Inclusion criteria: healthy subjects; residents of the Siberian Federal District; compliance with the study protocol. Exclusion criteria: epilepsy; residents of other regions of the Russian Federation; low compliance with the study protocol. Stages of the study: retrospective analysis of outpatient records (according to NC UC, 2003-2018); prospective observation and examination of patients with JME (2015-2018); statistical processing and analysis of the results.

Research methods: anamnestic; clinical (examination of somatic and neurological statuses), clinical and genealogical; neurophysiological (EEG video monitoring); neuroradiological (MRI of the brain according to epilepsy protocol), neuropsychological (Beck Depression Scale, V.A. Braitwaite emotional excitability scale, modified by A.A. Rukavishnikov, "Selfassessment of anxiety, frustration, aggressiveness and rigidity" scale; methodology "Memory for numbers", "Schulte-Platonov red-black tables", "Kraepelin tables"), laboratory (DNA-diagnostics, therapeutic drug monitoring). Determination of the rs206787 and rs516535 of the *BRD2* gene on chromosome 6p21 and rs3743123 of the *GJD2* gene on chromosome 15q14, the SNVs I359L (*3) A>C and R144C (*2) C > T of the *CYP2C9* gene was performed by PCR-RT (Rotor-Gene 6000, Australia) using TaqMan

technology and fluorescent probes (Applied Biosystems, USA). The library for the Clinical Exome study was prepared using the Clinical Exome Solution by SOPHiA GENETICS for Illumina MiSeq kit (Switzerland). Library amplification was performed using the KAPA HiFi Library Amplification Kit (USA). DNA quality was analyzed by the High Sensitivity DNA Kit by the Bioanalyzer 2100 electrophoretic system (Agilent Technologies, USA). To start the sequencer, MiSeq used the set "MiSeq Reagent Kit v2 (300-cycles)" (MS-102-2002, Illumina, USA).

Statistical methods. For database building the MS Excel 2013 was used; the analysis was performed using SPSS Statistics (Version 22.0) and the online calculator "Gene Expert" (http://geexp.ru/calculator_or.php). The distribution of genotypes was checked for Hardy-Weinberg equilibrium. In the pairwise comparison of genotype frequencies, χ^2 criterion was used. The risk of JME was assessed by odds ratios (OR, 95% CI). For parametric indicators mean, error of mean, median, and interquartile range Q25: Q75 were calculated; for nonparametric indicators proportion and error of proportion were calculated. Inter-group differences were considered statistically significant at $p < 0.05$. If expected frequencies were less than 5, Fisher's exact test was used and considered statistically significant at $p < 0.05$.

Results

4.1. Frequency of occurrence and peculiarities of clinical phenotypes of juvenile myoclonic epilepsy

The average age of patients with JME is 27.74 ± 0.62 years, Me 27.0 (22.0: 33.0) years. Distribution of patients by sex and age: males - 52 (29.4%), average age 26.3 ± 1.14 years; females - 125 (70.6%), average age 28.36 ± 0.74 years. The ratio of males to females is 1: 2.4. The average age of onset of JME is 13.52 ± 0.38 years, including: males - 14.16 ± 0.53 years old, females - 13.25 ± 0.48 years (Table 1).

Table 1. The distribution of patients with JME by sex and age (in years)

Characteristics samples	Average age, $M \pm m$	Me (Q25: Q75)	Average age of onset of JME, $M \pm m$	Median of age of onset of JME, Me (Q25: Q75)
Total	$27,74 \pm 0,62$	27,0 (22,0: 33,0)	$13,52 \pm 0,38$	14,0 (11,0: 16,0)
Male, n = 52	$26,3 \pm 1,14$ p=0,131	24,0 (20,0: 32,3)	$14,16 \pm 0,53$ p=0,205	14,0 (12,0: 16,0)
Female, n = 125	$28,36 \pm 0,74$ p=0,131	28,0 (22,0: 33,0)	$13,25 \pm 0,48$ p=0,205	13,0 (10,0: 16,0)

Note. Differences in the studied indicators were calculated using Student's test.

Analysis of seizure onset characteristics with regard to patient gender showed that in females, JME was statistically significantly more often onset with absences (32.0% vs. 15.4%, $p < 0.05$), and in males, with generalized tonic-clonic seizure (GTCS) and myoclonic (46.2% and 36.5% vs. 36.0% and 31.2% in females). Mean age at onset of GTCS was 15.8 ± 0.36 years, including 15.8 ± 0.69 years for males and 15.8 ± 0.42 years for females, $p > 0.05$ (Figure 1).

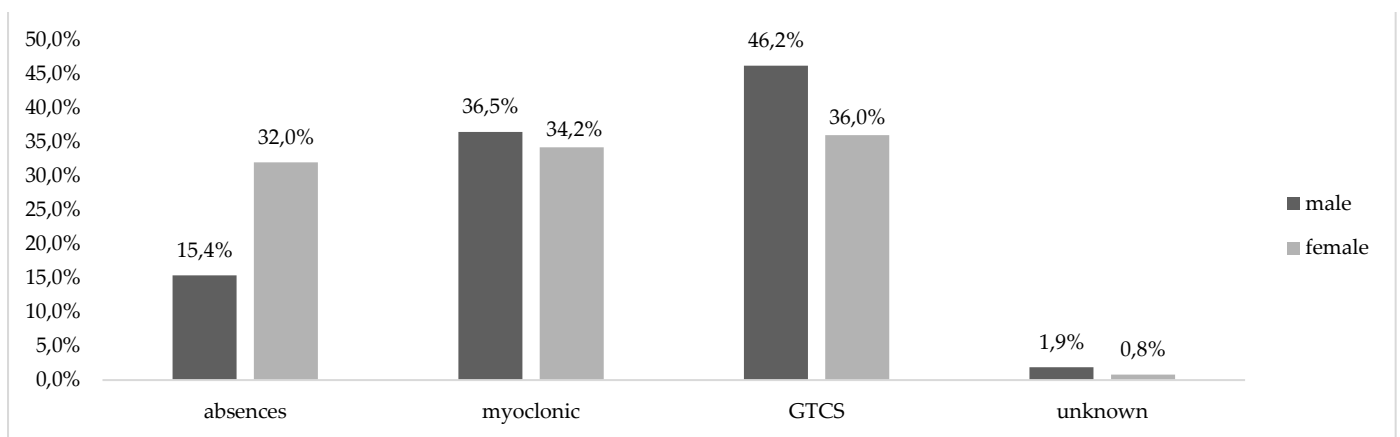


Figure 1. Seizure onset in patients with juvenile myoclonic epilepsy distributed by patients' gender

Analysis of JME phenotypes showed that the 1st (classical) phenotype was statistically significantly more frequent in male vs. female patients (55.8% vs. 34.4%, $p < 0.05$). The most unfavorable in terms of achieving remission, the 2nd and 3rd phenotypes of JME were 2.8 and 2.9 times more common in females vs. males (5.8% versus 16.1% and 5.8% versus 16.9%, respectively), with the 2nd phenotype being statistically significantly more prevalent in females ($p < 0.05$) (Table 2).

Table 2. Influence of patient gender on the JME phenotypes, n (%)

JME phenotype	Total N=177	Male n1=52	Female n2=125	p (χ^2)
I type	72 (40,7)	29 (55,8)	43 (34,4)	$p_{3,4}=0,009^*$
II type	25 (14,1)	3 (5,8)	22 (17,6)	$p_{3,4}=0,04^*$
III type	23 (12,9)	3 (5,8)	20 (16)	$p_{3,4}=0,044$
IV type	57 (32,2)	17 (32,7)	40 (32)	$p_{3,4}=0,929$

Note. *Statistically significant intergroup differences among males and females ($p < 0,05$)

In 93 (48.9%) cases remission against the background of AEP hasn't been achieved; remission of GTCS and myoclonic seizures has been achieved in 43 (22.6%), remission of GTCS, myoclonic seizures, and absences has been achieved in 39 (20.5%). The 2nd phenotype of JME was the most unfavorable in terms of achieving remission, $p < 0,05$ (Table 3).

Table 3 Frequency of remission in JME (per 100 patients)

Remission	Remission hasn't been achieved	Seizure remission	Seizure and EEG remission	p (χ^2)
Total, n=175	93 (53,1)	43 (24,6)	39 (22,1)	
I type, n=71	41(57,8)	14 (19,7)	16 (22,5)	$p=0,444$
II type, n=25	14 (56)	10 (40)	1 (0,4)	$p=0,027^*$
III type, n=23	11 (47,8)	7 (30,4)	5 (21,7)	$p=0,774$
IV type, n=56	27 (48,2)	12 (21,4)	17 (30,4)	$p=0,211$

Note. *Statistically significant intergroup differences ($p < 0,05$)

A typical EEG pattern was registered in 81 patients (45.8%); a combination of a typical pattern with at least one atypical pattern was registered in 96 patients (54.2%).

4.2. Neuropsychological testing of patients with juvenile myoclonic epilepsy

The sub-sample of 64 people was divided into 2 groups: the main group - 32 (50%) patients with JME and without adverse reactions on the background of AEP administration; the control group - 32 (50%) healthy volunteers. The mean age in the main group was 25.9 ± 1.4 years, in the control group - 23.53 ± 0.4 years ($p = 0.117$).

The V.A. Braitwaite scale, used for assessing emotional excitability included four sections: general emotionality, anger, timidity, and lack of emotional control. Average score in the main group: male - 36.75 ± 2.86 , (4-5, tendency to moderate emotional arousal); female - 47.3 ± 2.35 , (5-6, medium emotional excitability); in the control group: male - 36.73 ± 2.88 , female - 38.71 ± 1.39 (4, tendency to low emotional excitability). The main group significantly increased the level of neuroticism compared to the control group, $p < 0.05$.

Results for anxiety testing score with the C.D. Spielberger questionnaire: mean ST score in the main group and control groups was 38.31 ± 1.37 and 34.81 ± 1.29 , respectively ($p > 0.05$); mean LT score 43.72 ± 1.72 vs. 37.44 ± 1.58 ($p < 0.05$).

The total score for results of methodology for the diagnosis of self-assessment of mental states, interpreted as a measure of overall LT, was 112.47 ± 2.74 in the main group, vs. 108.91 ± 2.49 in the control group ($p > 0.05$). The total score on the A.T. Beck questionnaire in the main group was 10.06 ± 1.79 , corresponding to moderately severe depression; in the control group, 3.97 ± 0.68 (no depressive symptoms), $p < 0.05$. In the main group: on the cognitive-affective scale, 7.25 ± 1.27 (moderate severity of symptoms), in the control group, 2.78 ± 0.529 (normal); score on the somatization scale in the main group, 2.81 ± 0.66 , (borderline normal) versus 1.38 ± 0.28 in the control group (normal), $p > 0.05$.

The mean number of correct answers on the "Number Memory" scale in the main group was 7.44 ± 0.32 , mean score - 4 ± 0.135 ; in the control group 8.56 ± 0.291 and 4.44 ± 0.127 respectively ($p < 0.05$), that is, in both groups the effectiveness of short-term memory was optimal, but statistically significantly lower in the JME group. Stability of attention according to Schulte tables technique, in the main and control groups were statistically insignificant ($p > 0.05$). The average coefficient of mental performance according to Krepelin's technique in the main group was 1.137 ± 0.06 , in the control group - 1.072 ± 0.018 , which corresponded to the norm, $p = 0.303$. But 19 (59.4%) patients with JME had an irregular work capacity graph (a sign of emotional tension) against 7 (21.9%) healthy volunteers ($p < 0.05$).

4.3. Genetics of juvenile myoclonic epilepsy

Sequencing was performed in 4 patients with JME (Table 4).

It was expected that mutations at a specific locus of JME would be detected, but in all cases the disease was polygenic, as SNVs associated with JME and other generalized genetic epilepsies, including highly pathogenic ones, were identified. In a patient with JME code 86, 5 SNVs with an established highly pathogenic effect were identified: 2 SNVs in the *EFHC1* gene (locus EJM1), 1 SNV in the *CHRNA4* gene (locus EJM2), 2 SNVs in the *BRD2* gene (locus EJM3), and 10 SNVs with unspecified significance in loci associated with the development of JME were identified. In a patient with JME code 87, 4 pathogenic mutations were identified: in the *EFHC1* (locus EJM1), *BRD2* (locus EJM3), *GABRD* (locus EJM7), *CLCN2* (locus EJM8) genes, as well as 11 SNVs of unspecified significance in EJM loci. In a patient with code 69 JME, 4 pathogenic SNVs in the *EFHC1* (locus EJM1), *BRD2* (locus EJM3), and *JRK2* genes, as well as 8 SNVs with unspecified significance were identified. In a patient with JME code 71, 2 pathogenic SNVs in the *EFHC1* gene (EJM1 locus)

and 11 SNVs with unspecified significance were identified. DNA sequencing of patients with JME confirms the polygenic nature of the disease, which complicates clinical interpretation of sequencing results in burdened families and determination of the risk of disease transmission to offspring.

Table 4. Characteristics of patients with JME

Patient code	86 JME	87 JME	69 JME	71 JME
Date of birth	11.06.1999	30.12.1997	07.10.1997	11.02.1997
Sex	Female	Male	Male	Male
Onset age (years)	8	12	14	15
Onset	Absences	Myoclonic	Myoclonic	GTCS
JME phenotype	2	1	1	1
Onset of GTCS	12	14	15	15
Photosensitivity	+	-	+	+
Heredity for epilepsy	Not burdened	Burdened (father's side)	Burdened (father's side)	Not burdened
MRI	Pituitary microadenoma	No pathology	Wasn't performed	Lateroventricular asymmetry
Interictal EEG. (typical patterns)	Diffuse spike-poly-spike waves 3.5 – 4 Hz	Diffuse polyspike waves 3.5 Hz	Generalized spike-polyspike waves 3.5 - 4 Hz	Diffuse polyspike waves 3.5 - 4 Hz
Interictal EEG. (atypical interictal patterns)	Interhemispheric asymmetry of discharges; focal discharges	Interhemispheric asymmetry of discharges	Interhemispheric asymmetry of discharges	Focal initiation of discharges; generalized paroxysmal fast rhythm

Clinical and genealogical analysis showed unburdened heredity in 62.7% of patients with JME; in 8.5% - burdened heredity (by father's side); in 9.6% - by mother's side; 1.1 – both by father's and mother's sides, 18.1% - unknown; it was revealed that the 2nd phenotype of SME is associated with maternal transmission.

4.3.1 The association of rs206787 and rs516535 of the BRD2 gene and juvenile myoclonic epilepsy

The frequency of BRD2 gene rs206787 T allele carriage in the main group was 62.0%, in the control group - 64.8% (OR 0.89; 95% CI 0.58 to 1.35; $p = 0.58$); A allele in the main and control groups - 38% and 35.2% respectively (OR 1.13; 95% CI 0.74 to 1.74; $p = 0.58$). The frequency of TT genotype carriage was 35.4% in the main group and 38.3% in the control group; AT genotype was 53.2% in the main group and 53% in the control group ($p > 0.05$); AA genotype was 11.4% in the main group and 8.7% in the control group. The frequency of BRD2 gene T allele rs516535 carriage in the main group was 62%, in the control group - 64.8% (OR 0.89; 95% CI 0.58 to 1.35); allele C in the study and control groups - 38% and 35.2% respectively (OR 1.13; 95% CI 0.74 to 1.71). The incidence of TT genotype carriage was 35.4% in the main group and 38.3% in the control group; ST genotype was

53.2% in the main group and 53% in the control group; CC genotype was 11.4% in the main group and 8.7% in the control group ($p > 0.05$). No statistically significant differences in the incidence of both alleles ($\chi^2 = 0.31$; $p = 0.58$) and genotypes ($\chi^2 = 0.45$; $p = 0.8$) of SNV rs206787 and rs516535 of the *BRD2* gene were revealed, but a full unequal linkage between loci was observed both in patients with JME and in healthy volunteers.

The frequency of haplotypes with AA genotypes of rs206787 and CC rs516535 in men with JME tended to increase in comparison to controls but without statistically significant gender differences ($p > 0.05$). No statistically significant intergroup differences ($p > 0.05$) were found in the study of gender differences in the carriage of SNV rs3743123123 of the *GJD2* gene. No statistically significant association of the carriage of the examined *BRD2* gene haplotypes with the phenotypes and MRI changes in patients with JME was revealed as well ($p > 0.05$). The association of TT/TT haplotype carriage with photosensitivity was revealed in patients with JME (OR=3.6; 95% CI 1.37 - 9.48; $p=0.02$). The carriage of the AT/CT haplotype had no statistically significant effect on photosensitivity (OR = 0.47; 95% CI 0.19 to 1.17). Similar results were obtained for the AA/CC haplotype (OR = 0.32; 95% CI 0.06 - 1.65). No statistically significant gender differences were found in the frequency of photosensitivity and its association with the carriage of the studied *BRD2* gene SNVs in patients with JME.

4.3.2 The association of Cx-36 (*GJD2*) and juvenile myoclonic epilepsy.

The frequency of allele C carriage in the main group was 58.2%, in the control group - 66.7% (OR 0.7; 95% CI 0.47 - .04); allele T carriage in the main group - 41.8%, in the control group - 33.3% (OR 1.43; 95% CI 0.96 - 2.13). There were no statistically significant differences in allele carriage ($\chi^2 = 3.19$; $p = 0.07$). The CC genotype was found in 38% of cases in the main group and in 42.7% of cases in the control group ($p > 0.05$); the CT genotype was found in 40.5% of cases in the main group and in 48% of cases in the control group; the TT genotype was found in 21.5% in the main group and in 9.3% in the control group ($p = 0.04$). The OR for the TT genotype was 2.66 (95% CI 1.24 to 5.74), for the ST genotype 0.74 (95% CI 0.42 to 1.28), and for the CC genotype 0.82 (95% CI 0.47 to 1.44). Homozygous carriage of T allele of *GJD2* gene (rs3743123) was statistically significantly associated with the development of JME in the main group, OR = 2.66 (95% CI 1.24 - 5.74); $p = 0.04$. No statistically significant intergroup differences ($p > 0.05$) were detected in the study of gender-specific features of SNV rs3743123123 carriage of the *GJD2* gene.

4.3.3 The analysis of the pharmacogenetic profile of patients with juvenile myoclonic epilepsy

DNA testing was performed for 53/177 (30%) patients: 58.5% were common metabolizers (CYP2C9*1/*1 genotype); 39.6% were slow metabolizers (CYP2C9*1/*2, CYP2C9*1/*3 genotypes); 1.9% were ultraslow metabolizers (CYP2C9*2/*2, CYP2C9*3/*3 or CYP2C9*2/*3 genotypes). Toxic levels of valproic acid in blood were recorded more frequently in slow metabolizers compared to common metabolizers (40.9% vs. 12.9%, $p < 0.05$) (Table 5).

This study identifies further prospects for the use of association genetic studies of rs206787 and rs516535 SNPs carriage of the *BRD2* gene to identify groups of patients at high risk of photosensitivity and for the wider implementation of clinical exome sequencing to search for common haplotypes in different ethnic groups in Russian Federation.

Table 5. Results of therapeutic drug monitoring (TDM) in patients with JME

TDM Results	Common metabolizers, n=31	Slow metabolizers, n=22	P (Fisher criterion)
Valproic acid < 100 µg/ml	25 (80,6 %)	13 (59,1 %)	-
Valproic acid > 100 µg/ml	4 (12,9 %)	9 (40,9 %)	p<0,05*
Unknown	2 (6,5 %)	-	-

Note. *Statistically significant intergroup differences (p<0,05)

Discussion

JME is a widespread form of GGE, which includes myoclonic seizures, sometimes other seizure types (generalized tonic-clonic seizures, absences), onset in adolescence, and typical EEG changes as generalized spike and polyspike waves 4-6 Hz discharges with a normal background EEG [16, 17]. The age of onset of JME covers a wide range from 8 to 36 years of age, with a peak onset from 12 to 18 years of age [4, 5, 18].

Despite the bright clinical picture, there are different variants of JME, which determine the formation of certain phenotypes based on 2 components - predisposition gene mutations and environmental factors. Nowadays, against the background of the rapid development of molecular genetics, there are many studies aimed at identifying the JME genetic predisposition. It was supposed that there were genes with Mendelian (monogenic type of inheritance), two-locus model of inheritance [19], but nowadays, JME is considered to be a multifactorial disease, which is also confirmed by our study of clinical sequencing. However, due to the small sample size, it is difficult to analyze the contribution of susceptibility gene mutations to the formation of any disease trait. However, there are prospects of this study in the future.

The results of the molecular-genetic study of the carriage of SNVs rs206787 and rs516535 of the *BRD2* gene showed no connection to the development of JME in the studied population that is in agreement with the study carried out by D.K. Pal et al. in 2006 and Cavalleri G. et al. in 2013 [19-24]. However, these research groups have established an unbalanced linkage of the *BRD2* gene loci, which is also confirmed by our study.

In contrast to Lorenz S. et al. who established an association of the 6 SNVs of the *BRD2* gene in the predisposition to a photoparoxysmal response, our data do not confirm the association of the carriers of the SNVs rs206787 and rs516535 of the *BRD2* gene with photosensitivity in patients with JME, and also do not confirm the influence of this SNVs on the formation of certain phenotypes of JME and structural changes in the brain detected by MRI [25, 26].

We confirmed that homozygous carriage of T SNV of the Cx-36 gene (rs3743123) was associated with the development of JME in patients living in the Siberian Federal District. Also this SNVs are a risk factor for the development of JME, OR = 2.66 (95% CI 1.24-5.74); p = 0.04. A clinically significant association of these SNVs of the Cx-36 gene with the development of JME has also been previously demonstrated in two independent studies [27, 28].

In 2006, I. E. Martínez-Juárez et al. identified four phenotypes of JME: type 1 - the classic JME phenotype (72%); type 2 - childhood absences epilepsy with transformation to JME (18%); type 3 - JME with absences (7%), and type 4 - JME with atonic seizures (3%) [15, 29]. Thus, type 1 - the classic phenotype of JME was the most common, which agrees with our data. Comparable data were obtained for 2 and 3 phenotypes of JME. In addition, we confirmed the data on the unfavorable prognosis in type 2 of JME with regard to achieving seizure and EEG remission, as well as maternal inheritance.

Many researchers have described anxiety disorders as one of the features of JME [30-32]. Despite being aware of the factors that cause seizures, many patients cannot cope with their emotions independently. A decrease in stress tolerance leads to difficulties in falling asleep and, consequently, to such undesirable lack of sleep [33]. These disorders can be caused by concomitant non-psychotic psychiatric disorders, which are often described in JME. These include different types of anxiety and mood disorders: generalized anxiety disorder, phobias, depression, dysthymia, and psychosomatic disorders [34-36]. The data are consistent with ours: the incidence of depressive symptoms is higher in patients with JME compared to people without epilepsy.

The data on cognitive impairment in patients with JME are inconsistent - according to many authors, the presence of cognitive impairment is not typical for JME, but in general, epilepsy is often accompanied by cognitive impairment [11, 12, 37]. According to our data, the main indices of cognitive functions in patients with JME are lower than in those without JME but correspond to the normative ones.

The diagnosis of JME is often made late which leads to a significant reduction in the quality of life of patients [38]. According to our data, the diagnosis of JME was made after an average of 10.5 years, which is comparable with the findings of Panayiotopoulos S.P. et al. in 1992 [21, 39].

Thus, the literature review on the state of the JME problem indicates that this problem is far from being resolved. At the same time, in recent years the greatest interest of researchers is given to the issues of early diagnosis of the disease, especially in burdened families. It is believed that modification of the external trigger factors, which lead to severe seizures, their serial and status course, is an urgent problem of modern neurology.

Conclusion

The incidence of JME is lower among males than among females (ratio of males to females 1: 2.4). The average age at the onset of JME is 13.52 ± 0.38 years. The disease starts with absences more frequently in females as compared to males (32.0% vs. 15.4%), and with GTCS and myoclonic in males as compared to females (46.2% and 36.5% vs. 36.0% and 31.2%, respectively). The 1st phenotype of JME was more frequently encountered in male individuals in comparison with female ones (55,8% vs. 34,7%), and the 2nd phenotype was more frequently encountered in female individuals in comparison with male ones (16,9% vs. 5,8%). The 2nd phenotype of JME is characterized by a low frequency of achieving remission. The incidence of anxiety-depressive disorders is higher in patients with JME compared to those without JME.

JME is a polygenic disease, which limits the interpretation of sequencing results and screening for JME in burdened families. There is no association of carriage of the *BRD2* rs206787 and rs516535 SNVs with the development of JME in the studied population. The association of TT/TT haplotype carriage of the SNVs rs206787 and rs516535 of gene *BRD2* and photoparoxysmal reaction in patients with JME was revealed. Homozygous carriage of the T allele of the *GJD2* gene (rs3743123) was associated with the development of JME in the study population, OR=2.66 (95% CI 1.24 to 5.74).

41.5% of patients with JME have a slow metabolizer pharmacogenetic status, which is a risk factor for pseudopharmacoresistance and the development of adverse drug reactions.

Author Contributions: Conceptualization, D.V.D.; methodology, D.V.D.; validation O.S.S.; data processing, O.S.S.; investigation, O.S.S. and S.N.Z.; writing—original draft preparation, O.S.S.; writing—review and editing, O.S.S. and E.A.D.; project administration, D.V.D. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Krasnoyarsk State Medical University named after prof. V.F. Voino-Yasenetsky (protocol code №65/2015 dated 11.11.2015).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Samples of the compounds are available from the authors.

Acknowledgments: The authors express their gratitude to Natalia A. Shnayder, Doctor of Medical Sciences, Professor, for her supervision of this article.

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