PPN

Personalized Psychiatry and Neurology

Article

Hepatolenticular Degeneration: Intrafamily Heterogeneity

Elena V. Ovchinnikova[1,2]

[1] Far Eastern Federal University, 690950 Vladivostok, Russia
[2] Primorsky Regional Clinical Hospital No. 1, 690091 Vladivostok, Russia

* Correspondence: ovchinnikovaelv@mail.ru; Tel.: +79140697335

Citation: Ovchinnikova, E.V. Hepatolenticular Degeneration: Intrafamily Heterogeneity. *Personalized Psychiatry and Neurology* **2025**, *5 (4)*: 77-92. https://doi.org/10.52667/2712-9179-2025-5-4-77-92

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

Received: 25 October 2025
Accepted: 12 December 2025
Published: 15 December 2025

Publisher's Note: V.M. Bekhterev NMRC PN stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Abstract: The article studies the clinical manifestations of hepatolenticular degeneration (HLD) in first-degree relatives of patients with genetically confirmed neurological forms of the pathology (a total of 37 representatives from 16 families). Molecular genetic testing was performed using Sanger sequencing. It was found that first-degree relatives in each of the examined families differ only in the severity and timing of the pathology with the same type of mutations in the *ATP7B* gene, and a clear similarity in the manifestations of the neurological defect. Early manifestation of the neurological defect was confirmed. Its occurrence was noted against the background of signs indicating changes in other organs and systems that mask brain tissue damage and extrapyramidal motor disorders. It has been shown that examination of first-line relatives of patients with neurological forms of HLD allows diagnosing the pathology at the preclinical stage (in 58.8%) or at its initial manifestations (in 35.3%), reducing the delay in diagnosis by 10 years or more. This guarantees early treatment and social adaptation of patients. The conducted studies allow us to recommend practical healthcare to include examination of first-line relatives in the standard of care for patients with HLD for early diagnosis and prevention of unfavorable outcomes.

Keywords: *hepatolenticular degeneration, Wilson disease, family clinical screening, genetic heterogeneity*

1. INTRODUCTION

Hepatolenticular degeneration (HLD) or Wilson's disease (WD, OMIM277900) remains one of those hereditary pathologies for which the issues of clinical diagnosis cannot be considered resolved [1]. According to clinicians, this is hindered not so much by the polymorphism of HLD manifestations, but by differences in the age of onset, the nature of manifestation, the sequence of appearance of signs of damage to individual systems, and the types of progression of the pathology [2]. The focus is always on clarifying the reasons for the severity of neurological and/or abdominal pathology. The assumption that copper accumulation in the brain develops secondarily after the liver is overloaded with copper is contradicted by evidence of the absence of liver damage symptoms in patients with neurological forms of HLD in more than 40% of observations [3]. At the same time, while the mechanism of development of the abdominal form is understood and deeply studied, the reasons for the increased sensitivity of brain tissue to copper toxicity require further study. Some researchers explain the susceptibility of the basal ganglia to copper toxicity by the high content of copper and iron in them. They justify this by stating that the basal ganglia, being a depot of catecholamines, which contain both neuromelanin and metals, block resistance to oxygen and additionally accumulate metals themselves. [4]. Others believe that the basis of nerve tissue damage in HLD lies in the formation of so-called "false neurotransmission" due to the emergence in the intestines of HLD patients of such precursors of mediators as phenylethylamine, tyramine, and octopamine, which, by

replacing true neurotransmitters (norepinephrine and dopamine), hinder normal neurotransmission [5].

The discovery of the *ATP7B* gene, responsible for the defect in copper metabolism, has played a special role in expanding the understanding of the mechanisms of formation of different forms of HLD [6]. This was followed by studies that expanded the understanding of the mutational landscape of *ATP7B*. It was established that, unlike the liver, where there is a full-size form of R-type ATPase, in the structures of the brain there is another - a short form of R-type ATPase. It is a product of alternative splicing of brain *ATP7B* and, being a water-soluble protein, is not associated with membranes and can freely move in the cytosol and perform a different function than in the liver. Therefore, one of the mechanisms of the development of neurological symptoms in HLD is due to the lack of mRNA of R-type ATPase in the brain capillaries. The involvement of this enzyme in the synthesis or regulation of ceruloplasmin function in the listed structures is confirmed by its presence in the neurons of the hippocampus, olfactory bulb, cerebellum, cortex, and nuclei of the brainstem [7].

Moreover, it has been proven that the diversity of HLD depends not only on the heterogeneity of mutations in the *ATP7B* gene but also on the gene responsible for the synthesis of ceruloplasmin (CP), which are different genes located on different chromosomes (specifically on the 3rd and 13th) [8]. It has been found that the expression of these genes occurs in a coordinated manner during fetal development, but it is not possible to trace the patterns of their relationships in a multicellular organism later on [9]. At the same time, a dependence of the clinical manifestations of HLD has been established not only on the disruptions in the relationships of these genes but also on the individual nature of metabolic processes in a given organism. It became clear that for research, it is necessary to select observations with a predominance of neurological or abdominal pathology. The need to account for all the listed factors dictates the necessity of studying the clinic of HLD not only in individuals with the same forms (neurological and abdominal) but also in representatives with closely related metabolic processes, that is, in individuals with familial ties. However, throughout the history of studying HLD, insufficient attention has been paid to the peculiarities of its intrafamilial clinical manifestations. Even after the publication by Bear A.G. (1960) on the results of analyzing the manifestations of pathology in representatives with HLD from 30 families, the number of such studies has increased only slightly. Most of them were conducted in China, and the number of examined descendants in families is limited to 7-10 representatives [9, 10, 11]. This situation can be explained by the difficulty of conducting large-scale screening studies and the lack of consensus among specialists in choosing unified methodological approaches to genetic research.

The introduction of DNA typing for HLD in the Primorsky region in 2020 allowed the use of a unified methodology to identify mutations in the *ATP7B* gene during the study of WD's clinical and genetic features. This provided the opportunity to conduct research on first-degree relatives in families of patients with genetically confirmed various forms of HLD WD.

2. OBJECTIVE

The main purpose is to study the clinical manifestations of HLD in first-degree relatives in families of patients with genetically confirmed neurological forms of the pathology.

3. MATERIALS AND METHODS

The subjects of the study were first-degree relatives of 16 patients with genetically confirmed neurological forms of HLD (a total of 37 individuals from 16 families). All examined individuals were of European descent.

Molecular genetic study was conducted using the Sanger sequencing method, [12]. Clinical assessment was carried out according to the Leipzig scale requirements, 2001 [13]. The determination of neurological forms of HLD was based on the classification by N.V. Konovalov (1960), which identifies four of them (arrhythmo-hyperkinetic, extrapyramidal-cortical, trembling, and trembling-rigid) [14]. All subjects underwent EEG, micro-ophthalmoscopy to detect the Kayser-Fleischer ring on the cornea, ultrasound examination (US) of the abdominal organs and kidneys, MRI of the brain to identify MRI phenomena typical for HLD [15], blood tests for serum ceruloplasmin (CP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), copper content in 24-hour urine, and genetic testing to identify mutations in the *ATP7B* gene.

The severity of neurological manifestations of WD was assessed considering the defects in activities of daily living (ADL) and the total score of seven symptoms (dysarthria, tremor, ataxia, rigidity/bradykinesia, chorea/dystonia, cognitive deficit, epileptic seizures), which were evaluated on a 3-point scale: 0 points – absence of symptoms; 1 – one or two symptoms; 2 – three or four symptoms; 3 – five to seven symptoms.

When determining the degrees of severity of clinical manifestations, the following scoring indicators were considered: mild - 1 point and absence of ADL defects; moderate – 2-3 points, but no ADL defects; severe – 2-3 points with ADL defects.

The duration of follow-up observation ranged from 3 to 15 years with quarterly frequency of repeated consultations. All patients received comprehensive therapy, including chelates (D-penicillamine and/or Zinc therapy, or their combined use), and symptomatic treatment.

For statistical accounting of signs, absolute values and percentage relationships were used. In the analysis of intergroup differences, the parametric Student's t-test and Fisher's test, the non-parametric Mann-Whitney U-test, and the $\chi 2$ method with a known number of degrees of freedom were used.

4. RESULTS

Molecular genetic study of mutations in the *ATP7B* gene in 37 subjects revealed them in a heterozygous state in only 4 cases (10.8%). The remaining 33 (89.18%) were found to be homozygous and compound heterozygous carriers (Figure 1, Table 1). This allowed for a detailed investigation of these 33 representatives.

Among 33 representatives with homozygous and compound heterozygous mutations, two groups were identified: the first (main) group consisted of 16 probands, and the second (comparison group) included 17 representatives from the first line of their kinship. The comparison of mutation types in the probands and representatives from the first line of kinship in each family revealed their uniformity. The maximum (45.9%) was comprised of carriers of the p.His1069Gln mutation (in 17 examined from 8 families); less frequently (16.2%) - mutations c.2304insC (in 6 from 3 families); even less frequently (21.6%) - Glu1064Lys (in 4 from 2 families) and C3402del (in 4 others from 2 families) and single occurrences (5.4%) - Gly710Ser (in 2 from one family). Among the 16 patients in the first group (proband), there were: 8 with the p.His1069Gln mutation (50%); 2 with the Glu1064Lys mutation (12.5%); 2 others with the C3402del mutation (12.5%); 3 with the

c.2304insC mutation (18.8%); 1 with the Gly710Ser mutation (6.3%), which indicates the preservation of the same ratios in the frequency of mutation carriers in the *ATP7B* gene. (Figure 2, Table 2).

Table 1. The spectrum of mutations in the examined patients with hepatolenticular degeneration and their relatives.

Nature of mutation carriage	**Mutation**				
	p.His1069Gln	***Glu1064Lys***	***C3402del***	***c.2304insC***	***Gly710S***
	17 cases	**4 cases**	**4 cases**	**6 cases**	**2 cases**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Homozygous carriers n = 17 (45.9%)	11 (64.7%)	1 (25.0%)	2 (50.0%)	1 (16.6%)	2 (33.3%)
Compound-heterozygous carriers n = 12 (32.4%)	5 (29.4%)	2 (50.0%)	2 (50.0%)	3 (50.0%)	-
Heterozygous n = 4 (10.8%)	1 (5.8%)	1 (25.0%)	-	2 (33.3%)	-
In total, n = 37	17 (45.9%)	4 (10.9%)	4 (10.9%)	6 (16.2 %)	2 (5.4%)

Table 2. The spectrum of mutations in in the ATP7B gene in patients of the first group.

Nature of mutation carriage	**Mutation**				
	p.His1069Gln	***Glu1064Lys***	***C3402del***	***c.2304insC***	***Gly710Ser***
	8 cases	**2 cases**	**2 cases**	**3 cases**	**1 case**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Homozygous carriers n = 11 (68.75%)	7 (87.5%)	1 (50.0%)	1 (50.0%)	1 (33.3%)	1 (100.0%)
Compound-heterozygous carriers n = 5 (32.51%)	1 (12.5%)	1 (50.0%)	1 (50.0%)	2 (66.6%)	-
In total, n = 16 (100%)	8 (50.0%)	2 (12.5%)	2 (12.5%)	3 (18.8%)	1 (6.3%)

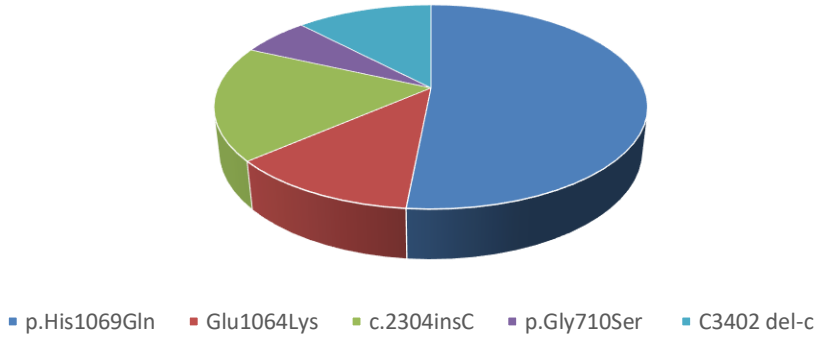


Figure 1. The spectrum of mutations in the examined patients with hepatolenticular degeneration and their relatives

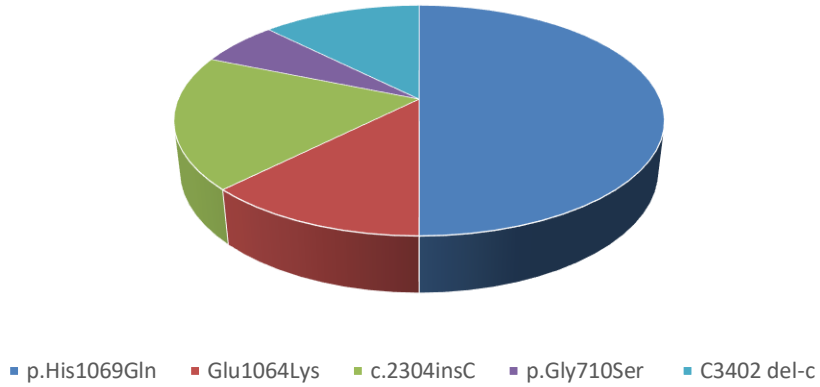


Figure 2. The spectrum of mutations in the *ATP7B* gene in patients of the first group.

The distribution of clinical manifestations of HLD in patients of the first group revealed a maximum (56.3% - in 9 examined) with the arrhythmia-hyperkinetic form. The proportion of tremulous and tremulous-rigid forms accounted for 31.3% (in 5 patients). Less frequently (in 12.5% - in 2 patients) the extrapyramidal-cortical form was recorded (Table 3).

Table 3. The frequency of different forms of hepatolenticular degeneration in patients of the first group.

Form of HLD	***p.His 1069Gln*** **8 cases** **n (%)**	***Glu 1064Lys*** **2 cases** **n (%)**	***C3402del*** **2 cases** **n (%)**	***c.2304insC*** **3 cases** **n (%)**	***Gly710Ser*** **1 case** **n (%)**	**In total,** **16 cases** **n (%)**
Arrhythmohyperkinetic	5 (62.5%)	1 (50.0%)	1 (50.0%)	1 (33.3%)	1 (100.0%)	9 (56.3%)
Extrapyramidal cortical	2 (25%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (12.5%)
Trembling	1 (12.5%)	1 (50.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)	3 (18.8%)
Tremor-rigid	0 (0.0%)	0 (0.0%)	1 (50.0%)	1 (33.3%)	0 (0.0%)	2 (12.5%)
In total, n = 16, abs. number (%)	8 (50.0%)	2 (12.5%)	2 (12.5%)	3 (18.8%)	1 (6.3%)	16 (100.0%)

The mean age of the probands at the time of examination exceeded 27 years, the delay in the diagnosis of HLD reached 22 years, and the severity of the pathology was classified as severe (25.0%) and moderate (75.0%). The frequency of detection of Kayser-Fleischer rings in them reached 75%, while specific HLD phenomena on brain MRI were found in 56.7%, changes in blood - 31.25%, and signs of internal organ damage on ultrasound – 100.0% (Table 4).

Table 4. Comparative characteristics of the frequency of registration of pathology manifestation indicators in representatives of both groups.

Indicators	**Frequency of registration**		**Significance of differences, p-value**
	First group 16 cases n (%)	**Second group 17 cases n (%)**	
Average age at time of examinatio	27.7	22.0	*> 0,05*
Average age at HLD onset	5.8	11.7	*> 0,05*
Duration of diagnostic delay	21.9	10.6	*> 0,05*
Jaundice	4 (25.0%)	5 (29.4%)	*< 0,01*
Changes in abdominal organs and kidneys	16 (100.0%)	15 (88.2%)	*> 0,05*
Specific changes on brain MRI	9 (56.3%)	5 (29.4%)	*> 0,05*
Presence of Kayser-Fleischer ring	12 (75.0%)	2 (11.8%)	*> 0,05*
Changes in blood (anemia, etc.)	5 (31.3%)	2 (11.8%)	*> 0,05*
Changes in biochemical tests (copper in 24h urine, CP in blood)	15 (93.8%)	13 (76.5%)	*> 0,05*
EEG changes	16 (100.0%)	11 (64.7%)	*> 0,05*
Degree of severity			
Severe	4 (25.0%)	1 (5.8%)	*> 0,05*
Moderate	12 (75.0%)	6(35.3%)	*> 0,05*
Mild	-	10 (58.8%)	*> 0,05*
Preclinical stage	-	-	*> 0,05*

From Table 4 it follows that in the second group the mean age at the time of examination lagged behind the age indicators of the probands by 7 years, and the delay in diagnosis decreased by 10 years or more. Among the 17 members of this group, there were: 10 (58.8%) with a preclinical diagnosis of HLD, 6 (35.3%) with mild clinical manifestations, and only one (5.8%) with a moderate degree of severity (Table 4).

Since the limited number of within-family observations hindered the conduct of large-scale studies with analysis of statistically significant differences in the features of clinical manifestations and the dynamics of the pathology among members of each family, it was conducted individually in each of them. Examples of these observations include the following cases:

Case Report No. 1: *The patient history of Sh.M.V., born on 14 November 2010, who has been under observation and treatment since age 3 (the duration of longitudinal follow-up is 11 years).*

The matrilineal lineage is burdened by chronic hepatitis, motor defects, and epilepsy: the grandfather had complex hyperkinesias (myoclonus, tics, choreiform jerks in the neck-shoulder region), died at age 24; the grandmother had chronic hepatitis and epilepsy with generalized seizures; the mother has tics and myoclonus in the facial muscles and shoulder girdle, and a speech impairment.

From the medical history, the child was from the first pregnancy and birth at 38 weeks. Birth weight 2540 g. Gross motor and speech development followed expected milestones (phrases formed by age 1.5 years).

At 1 year 8 months, after a viral infection, the child stopped articulating words, developed facial myoclonus and blepharoclonus, and sleep was disrupted (night awakenings with crying).

By age 3, articulation remained indistinct, choking while swallowing appeared, tremor of the hands developed, choreiform jerks in the neck-shoulder region with a dystonic phenomenon (neck turned to the side). Bruising and nasal bleeding began to occur intermittently.

By age 4, night awakenings with crying became daily, movement defects intensified, additional sounds appeared during meals, resembling "gurgling," as well as enuresis and encopresis.

During examination: EEG recorded paroxysmal activity (Figure 4).

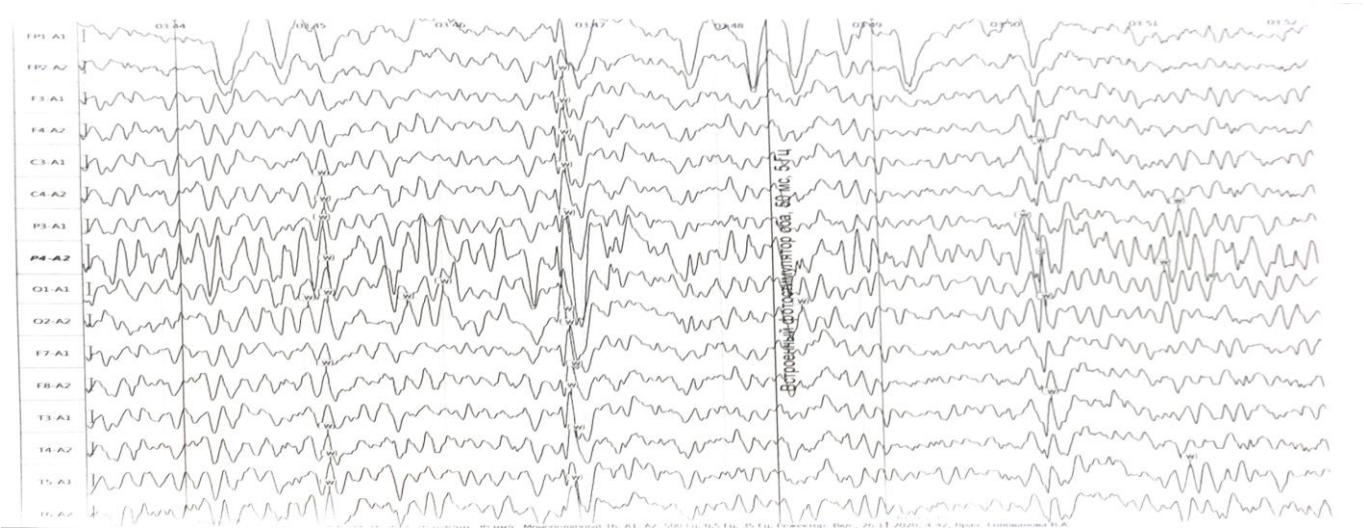


Figure 4. Paroxysmal activity on the EEG of the patient Sh.M.V.

Ultrasound of the abdominal organs detected hepatomegaly and a curved gallbladder. Microphthalmoscopy: Kayser-Fleischer ring in both eyes. Brain MRI: enlargement of subarachnoid spaces in the convexity regions. Biochemical tests: increased copper excretion in 24-hour urine up to 3.2 μmol/day (normal up to 1.2 μmol/day), decreased blood ceruloplasmin to 160 mg/L (normal 200--600 mg/L). Platelet count was elevated.

Diagnosed HLD, neurological stage, ataxic-hyperkinetic and extrapyramidal-cortical forms, hyperkinetic syndrome, generalized epileptic seizures. Therapy prescribed included anticonvulsants and chelation therapy (D-penicillamine with dose titration up to 750 mg/day). Condition improved: frequency of nocturnal awakenings reduced to 1--2 times per week, enuresis reduced to 3 times per week, articulation improved, bulbar syndrome regressed. EEG indicated positive evolution due to the disappearance of the characteristic epileptiform patterns (Figure 5).

Dynamics: during treatment:

By age 5, frequency of nocturnal awakenings decreased to 1--2 times per week, enuresis to 3 times per week, articulation improved, bulbar syndrome regressed. On EEG, there were no longer the specific epileptiform patterns (Figure 5).

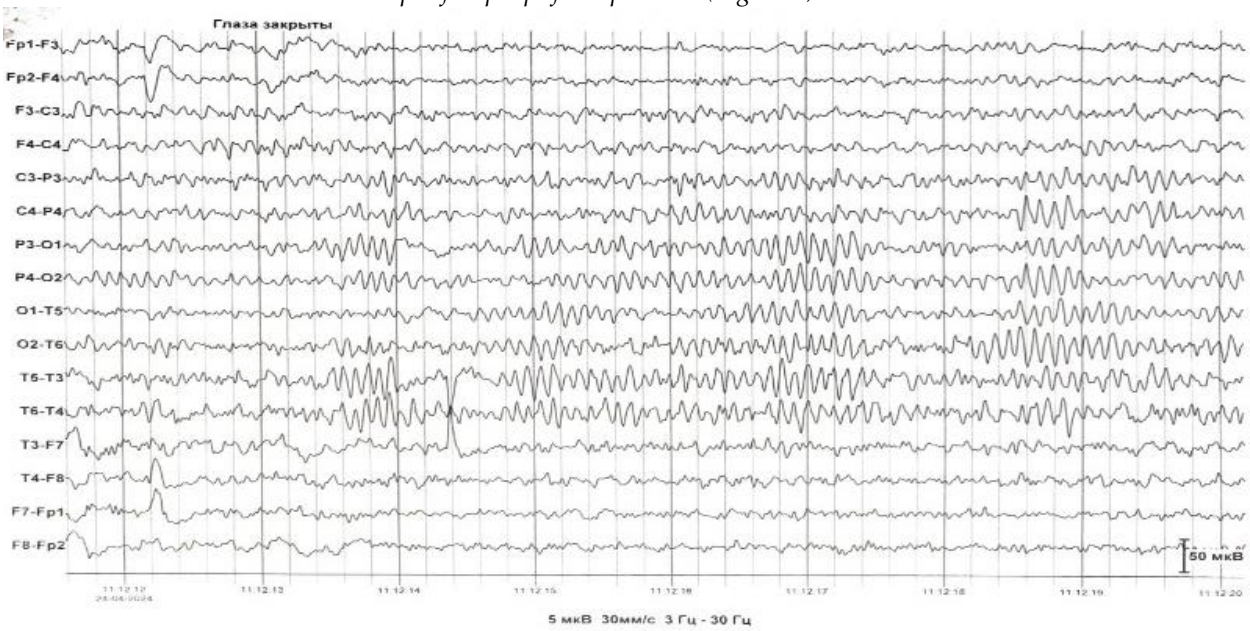


Figure 5. Positive dynamics on the EEG of the patient Sh.M.V. (the regression of paroxysmal activity).

From age 7, he has been studying in a regular school (education was challenging due to excessive motor activity, speech articulation problems, slowed thinking, and difficulties with oral counting and writing). However, he did not repeat grades.

At age 11, peripheral manifestations of chelation appeared: hematuria, weakness, bruising and contusions.

Diagnosed as tubulointerstitial nephritis with neurogenic bladder dysfunction.

During evaluation: in blood, lymphocytosis (53.4% with a normal up to 45%), neutropenia (36% with normal 46-66%), decreased alpha-amylase (22 U/L with normal 25-125), and creatinine (37 μmol/L with normal 40-72). In urine -- proteinuria and hematuria.

Dynamics of instrumental examination findings: Abdominal ultrasound: progression of hepatomegaly (protruding 1.5 cm below the right costal margin), diffuse changes of the pancreas, increased gas formation in the large intestine. Renal ultrasound and bladder: bilateral hydronephrosis due to hypotonia, dilation of the pelves on both sides, dilation of the calyces on the left, echogenic changes indicating sediment in the bladder.

Pathogenetic therapy was adjusted: the dose of Cuprenil (D-penicillamine) reduced to 250 mg/day, with the addition of Zincteral (zinc sulfate) and neuroprotectors. Transferred to a corrective class of a specialized school.

Clinical condition gradually normalized; EEG showed disappearance of paroxysmal patterns: significant reduction in motor deficits, improvement in articulation, memory, and counting.

Clinical-genetic examination of family members:

The mother has a neurologic stage of HLD, an arrhythmogenic-hyperkinetic form with onset at 17 years old (complex hyperkinesias with predominant myoclonus, tics, choreiform twitching in the muscles of the shoulder girdle, dystonia. Microophthalmoscopy: the Kayser-Fleischer ring. Abdominal ultrasound shows diffuse changes with areas of altered density. Brain MRI: a specific HLD phenomenon - "giant panda face" (Figure 6).

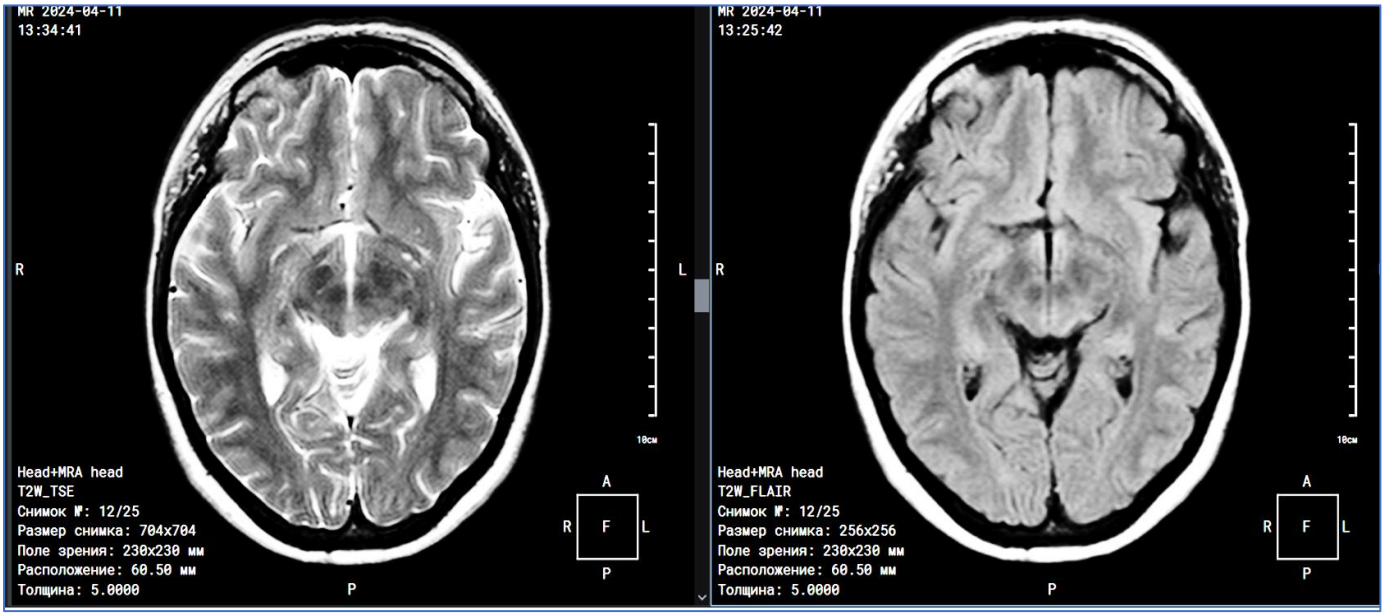


Figure 6. Brain MRI of the patient Sh.E.E. (42 years old): "giant panda face" phenomenon in the midbrain.

The younger sister, 5 years old - HLD with onset at 4 years (appearance of subcutaneous hematomas on the trunk, impaired pronunciation, detection of high copper content in daily urine, decreased level of ceruloplasmin in blood plasma, anemia, signs of thrombocytopathy).

Molecular genetic testing in all listed individuals revealed the p.His1069Gln mutation in the ATP7B gene in a homozygous state. The father is a carrier of the p.His1069Gln mutation in a heterozygous state, healthy.

This observation demonstrates the development of the same form of pathology (arrhythmohyperkinetic) and the same mutation in the ATP7B gene in first-line relatives within the same family, with good responsiveness to pathogenetic therapy. Differences are observed only in the timing of the onset of neurological manifestations and their severity.

Case Report No. 2: *History of patient R.L.R. 11 years old (born 05 October 2012). Under observation and treatment since 8 years of age.*

At initial presentation at 8 years: pale skin, bewildered gaze (does not understand tasks, although tries to focus on them). Excessive motor activity (cannot sit still for a minute, jumps up, walks around the office, aimlessly moves objects). Gait is "dancing" with widely spaced legs without control of movement direction. Clumsiness, awkwardness, hand trembling, which is periodically interrupted by instant throwing of one of the arms to the side (like a bird's wing flap). Eyelid twitching with rolling up of the eyeballs and instant freezing. Pronunciation is impaired (unclear sounding of both vowels and consonants), swallowing with additional sounds and "choking". Cannot read or count. Handwriting is altered (sometimes micrographia, sometimes macrographia). Muscle tone is low and very low reflexes in arms and legs.

From the history, it is known that the girl is from the second pregnancy, which proceeded without features. Born with a weight of 3100 g. From the first days of life: jaundice and renal dysfunction. Psychomotor development without features. Started walking at 12 months, phrasal speech formed by 1.5 years (clearly pronounced words and phrases).

At 2.5 years, vocabulary became impoverished, pronunciation impaired, movements became awkward, clumsy.

By 5 years, twitching in the facial muscles and instant, so-called, "blackouts" with rolling up of the eyeballs appeared (up to 8 -- 9 times a day). EEG recorded generalized epileptiform activity. Childhood absence epilepsy was diagnosed and anticonvulsant therapy (valproates) was prescribed.

From 7 years, studies in a comprehensive school. From the first days of schooling, unclear pronunciation, slowed thinking, writing impairment, inability to concentrate, remember simple words and perform elementary tasks were noted. Hand trembling intensified with movement, and every movement seemed mannered and uncoordinated, gait - "dancing".

By 9 years, involuntary additional sounds like screams appeared, swallowing problems intensified (had difficulty swallowing food and holding a cup). Cognitive deficit progressed. Nosebleeds, bruises on arms and trunk appeared. EEG recorded generalized epileptiform activity (Figure 7).

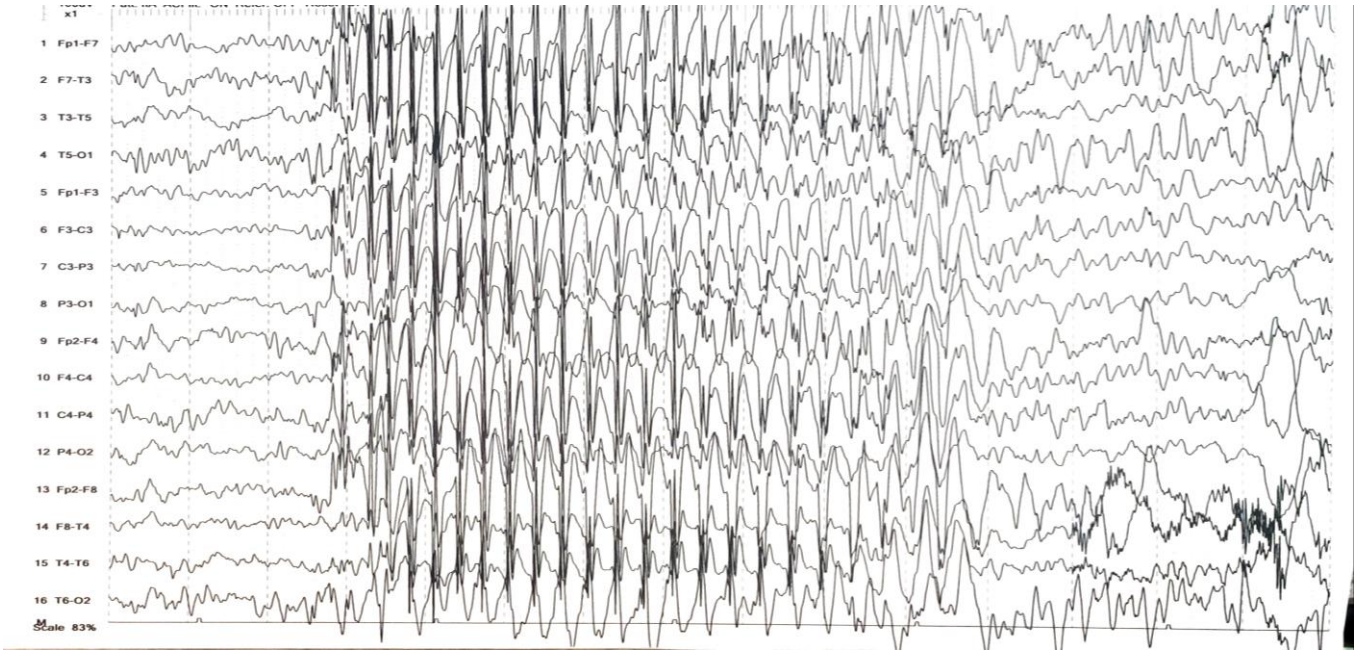


Figure 7. EEG of patient R.L.R. 9 years old. Against the background of delayed rhythm formation, generalized epileptiform activity is recorded (a burst of generalized spike-wave activity).

Examination data: In blood:

hypochromia (erythrocytes 3.56 million/μl), thrombocytopenia (platelets 122 thousand/μl), lymphocytosis (65% with normal up to 46%). ESR 13 mm/hour (normal -- less than 10mm/hour).

EEG (from 26.11, 28.12 2020 and 17.03 2023):

On EEG, against the background of delayed rhythm formation, generalized epileptiform activity is recorded.

Brain MRI (from 2021): platybasia and changes in the structure of nervous tissue in the midbrain.

Ultrasound of abdominal organs - hepatomegaly.

Copper level in daily urine 21 μg/day (Cuprenil test provoked an increase to 178 μg/day), ceruloplasmin (CP) level in blood 25.1 mg/dL.

Microophthalmoscopy detected copper deposition in the outer segments of the iris of both eyes.

Molecular genetic testing revealed the p.His1069Gln mutation in the ATP7B gene in a homozygous state.

Against the background of complex therapy: Cuprenil 375 mg/day increased to 500 mg/day in combination with Zincteral 248 mg/day and anticonvulsants, the condition significantly improved: motor activity normalized, trembling decreased, absences disappeared, began to perform school assignments, on EEG generalized epileptiform activity regressed, but signs of irritation in the frontal leads of the right hemisphere remained (Figure 8).

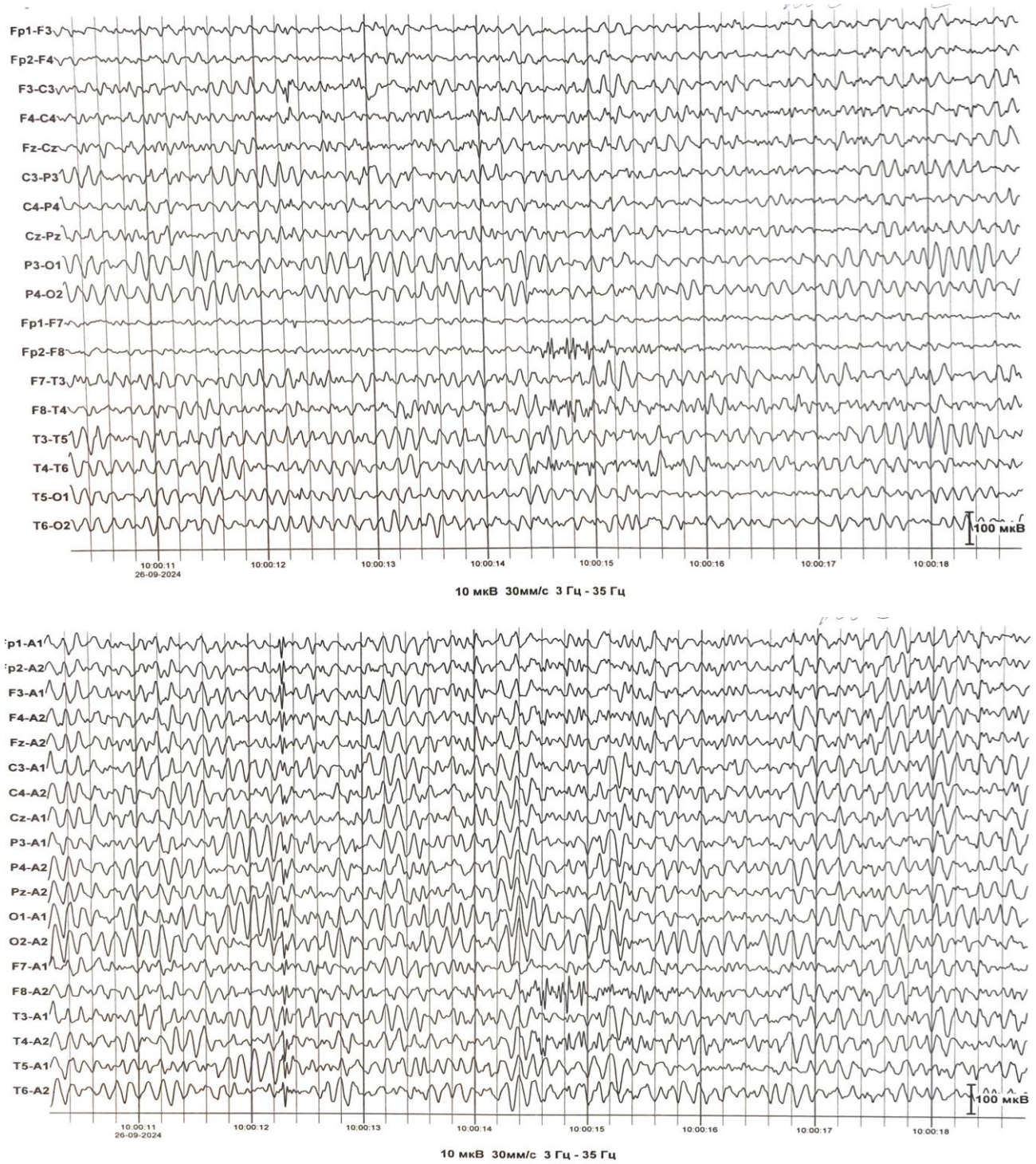


Figure 8. EEG of the patient R.L.R. (11 years old). Signs of irritation in the fronto-temporal leads of the right hemisphere persist and typical episodes of alternation of hypersynchronization with desynchronization for pathology of subcortical structures appear.

Results of examination of relatives:

In the father's niece (15-year-old cousin) HLD was diagnosed. The 12-year-old sister is healthy but is a carrier of the p.His1069Gln mutation in the ATP7B gene in a heterozygous state.

This observation demonstrates the early appearance of epileptic seizures, which regress rapidly as the cortex matures, giving way to a motor defect of extrapyramidal origin and other signs

indicating copper toxicity. However, the demonstrativeness of generalized epileptic seizures at the onset of HLD distracts clinicians' attention from the formation of motor defects.

***Case Report No. 3**: History of patient T.M.S. 20 years old. First referred for consultation by a hematologist at 17 years to exclude a metabolic defect. Heredity on the maternal side is burdened by hepatitis and blood pathology (grandmother and her sister were treated by hepatologists and hematologists with unspecified chronic hepatitis, hand trembling, numerous bruises on the trunk and limbs. They had pronounced cognitive impairments).*

At the patient's initial presentation, complaints included: hand trembling, painful tension of the back muscles with twisting of the trunk and psycho-vegetative episodes - attacks of dizziness with bright vegetative accompaniment (tachycardia, suffocation, chill-like trembling, occurrence of headache in the frontal area with a sensation of it "draining" onto the face and an obsessive irresistible desire for self-harm ("banging head against the wall", inflicting painful injury on oneself, etc.). Such episodes alternate with periods of general weakness, which is accompanied by decreased quick-wittedness, irritability with pains in various parts of the body, sore throat, rhinitis, lacrimation. Such states last for hours, changing in intensity over 2-3 weeks and hinder communication.

In the neurological status -- tremulous hyperkinesis of the hands and tonic tension of the long back muscles, leading to torsion of the trunk. Speech is slurred, thinking is difficult and slowed, cognitive deficit is pronounced.

From the history, it is known that the girl is from the first pregnancy, which proceeded with threatened termination. Born at term with low birth weight (2650 g). From the first days, prolonged jaundice and convulsive syndrome (from one month to 3 years, series and statuses of epileptic seizures. Treated with barbiturates until 3 years). Motor and speech development corresponded to age norm.

At 3 years, dystonic phenomena appeared in the form of periodic tension of the neck or back muscles with turning of the head or throwing it back. Convulsive seizures were replaced by frightening dreams with awakening and psychomotor agitation. Episodes of instant weakness with dropping objects from hands occurred. Did not receive anticonvulsant therapy.

At 5-6 years, bruises appeared on the body and nosebleeds began to occur periodically.

At 12 years - hand trembling and attacks of dizziness with vegetative accompaniment. Involuntary turns of the trunk became painful, gastrointestinal dysfunctions became constant, bleeding became more frequent (twice hospitalized in surgical departments with intestinal bleeding). Lymphocytic leukemoid reaction, thrombocytopathy and anemia were diagnosed (the patient was observed by hematologists).

Upon examination at 17 years old.

Initial copper level in daily urine 11 μg/day, but the Cuprenil test provoked a 40-fold increase to 414 μg/day. Ceruloplasmin level in blood -- 20 mg/dL (normal 20-60 mg/dL).

Brain MRI: foci of altered density in the basal ganglia of both hemispheres against the background of moderate mixed hydrocephalus.

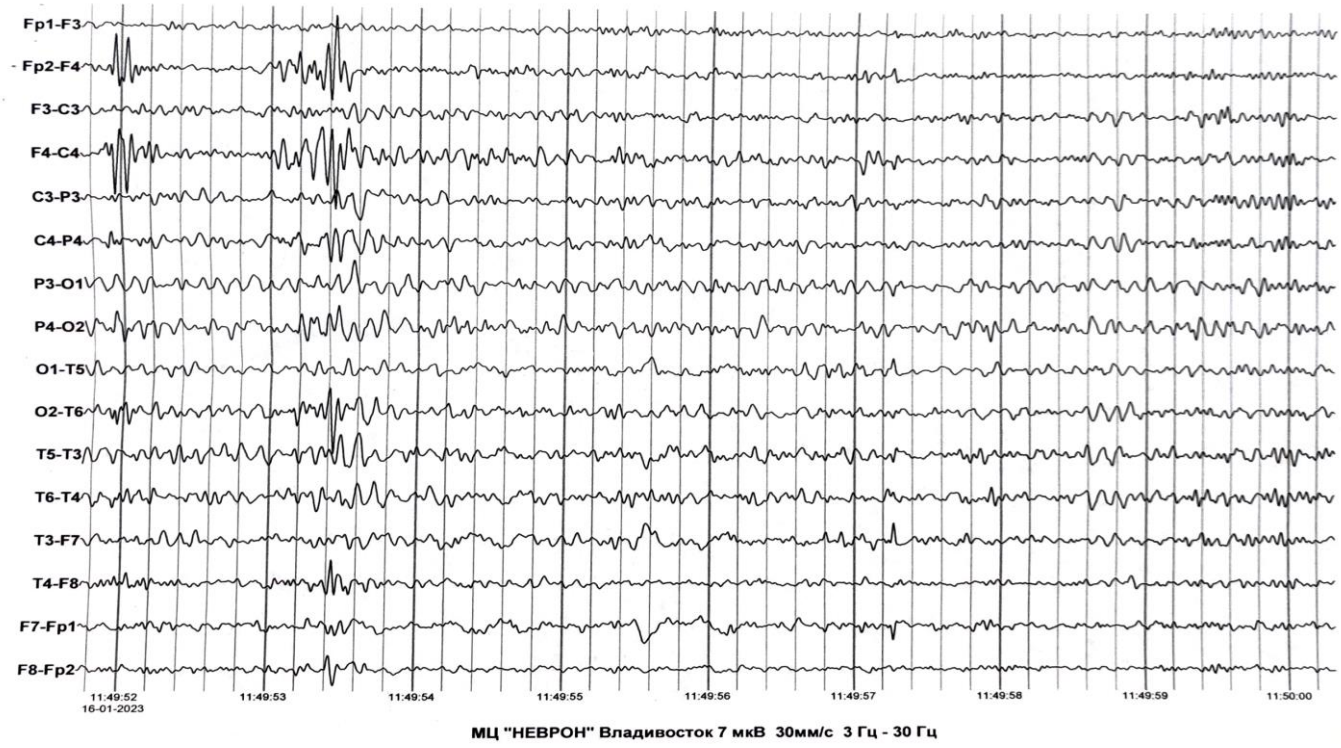
MR angiography of cerebral vessels: bilateral posterior trifurcation of the ICA.

Ultrasound of abdominal organs: diffuse changes and foci of increased echogenicity in liver tissue and in the gallbladder;

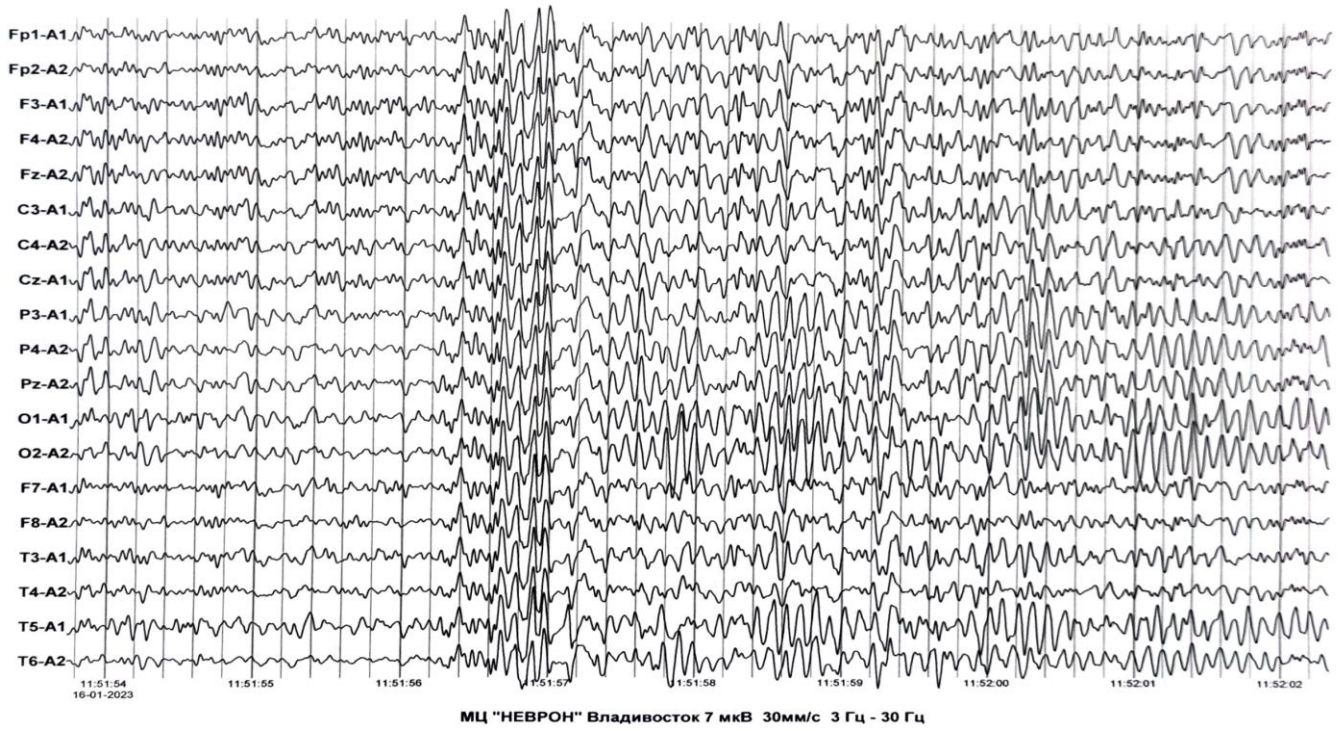
Renal ultrasound: nephroptosis and microlithiasis.

Microophthalmoscopy: Kayser-Fleischer ring in both eyes.

EEG: irritative manifestations and paroxysmal patterns with a source in the left hemisphere are recorded against the background of signs of delayed formation of the main rhythm (Figure 8a) and typical alternations of episodes of hypersynchronization with periods of desynchronization for HLD when recording with an indifferent electrode (Figure 9b).



(**a**)



(b)

Figure 9. EEG of the patient T.M.S. (20 years old). Paroxysmal patterns in the fronto-temporal leads of the left hemisphere are recorded (a) against the background of alternations of episodes of hypersynchronization with periods of desynchronization (b).

Molecular genetic testing revealed the p.His1069Gln mutation in the ATP7B gene in a homozygous state.

The patient was started on pathogenetic therapy (Cuprenil with dose increase to 500 mg/day) in combination with anticonvulsants, and minimal doses of Nakom (1/8 of 250 mg).

A positive effect was obtained, but psycho-vegetative attacks did not disappear.

Results of examination of relatives:

the mother has had anemia since childhood (under observation and treatment by hematologists), gastrointestinal (GI) tract dysfunctions, a high level of anxiety; from the age of 39, hand tremors and myoclonus in the oromandibular area were added. Instrumental examination: brain MRI revealed changes specific for HLD (the "giant panda face" phenomenon). Molecular genetic testing revealed the p.His1069Gln mutation in the ATP7B gene in a homozygous state.

This observation demonstrates the adverse consequences of late initiation of pathogenetic therapy, where even with correction of motor defects, it is not possible to achieve regression of mental disorders.

5. DISCUSSION

The analysis of the presented observations confirms the data from most publications devoted to studying the clinical presentation of neurological forms of HLD [1, 2, 8, 9, 10]. It indicates not only the uniformity of mutations in the ATP7B gene but also the similarity of clinical manifestations of the pathology in first-degree relatives within each of the examined families of patients with neurological forms of HLD, establishing differences only in the timing of the manifestation of neurological symptoms and their severity. This is consistent with the data of Liu Y. et al. (2015) [10]. It reveals the early manifestation of the neurological defect (in the first years and even months of life), which corresponds to the observations of Chetkina G.S. et al. (2011) [16].

It confirms the frequent development, at the disease onset, of signs indicating a copper metabolism defect against the background of disturbances in other metabolic processes, which themselves alter the functioning of various organs and systems, coinciding with the results of studies by Ribak N.V. et al. (2011) [17]. It indicates that in the early stages of HLD development, motor defects of extrapyramidal origin mask not only signs of damage to other systems but also the severity of neurotic (including epileptic) manifestations and behavioral disorders, which divert specialists' attention from motor defects, contributing to a long delay in diagnosis and, consequently, treatment. This aligns with the data of Proskokova T.N. et al. (2007), Litwin T. et al. (2016) [18, 19].

It reflects the "responsiveness" of patients to chelation therapy, which ensures not only the correction of the motor defect but also social adaptation for many years, corresponding to the observations of Członkowska A. et al. (2019), Ferenci P. et al. (2019), and Roberts E.A. et al. (2008) [1, 2, 20].

The study reveals the possibility of reducing the delay in HLD diagnosis by 10 years or more, allowing the detection of pathology in close relatives of patients with neurological forms of HLD already at the preclinical stage. This provides them with prevention of disability and guarantees social adaptation, which is consistent with the results of studies by Li H. et al. (2018) [9].

6. CONCLUSIONS

The similarity of clinical manifestations of the neurological defect and the uniformity of mutations in the *ATP7B* gene in close relatives within each family of a patient with the neurological form of HLD, combined with the possibility of reducing diagnostic delay by detecting it at the preclinical stage of the pathology, allows us to recommend that practical

healthcare conduct examinations of every first-degree relative to prevent severe HLD progression. In this case, molecular genetic testing can be limited to identifying only that specific mutation in the *ATP7B* gene which was found in the patient who first sought help (the proband).

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 Local Ethics Committee (protocol code No. EK-*И*26/23 20.04.2023).

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

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

REFERENCES

1. Akhan, O.; Akpinar, E.; Karcaaltincaba, M.; Haliloglu, M.; Akata, D.; Karaosmanoglu, A. D.; Ozmen, M. Imaging findings of liver involvement of Wilson's disease. *European Journal of Radiology*. **2009;** 69(1):147–155. https://doi.org/10.1016/j.ejrad.2007.09.029
2. Członkowska, A.; Dzieżyc-Jaworska, K.; Kłysz, B.; Roos, B. R.; Litwin, T. Difficulties in diagnosis and treatment of Wilson disease-a case series of five patients. *Annals of Translational Medicine.* **2019**; 7(Suppl 2):73. https://doi.org/10.21037/atm.2019.02.37
3. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Wilson's disease. *Journal of Hepatology.* **2012**; 56(3):671–685. https://doi.org/10.1016/j.jhep.2011.11.007
4. Ferenci, P. Diagnosis of Wilson disease. *Handbook of Clinical Neurology*. **2017**; 142:171–180. https://doi.org/10.1016/B978-0-444-63625-6.00014-8
5. Ferenci, P.; Stremmel, W.; Członkowska, A.; Szalay, F.; Viveiros, A.; Stättermayer, A. F.; Bruha, R.; Houwen, R.; Pop, T. L.; Stauber, R.; Gschwantler, M.; Pfeiffenberger, J.; Yurdaydin, C.; Aigner, E.; Steindl-Munda, P.; Dienes, H. P.; Zoller, H.; Weiss, K. H. Age and Sex but Not ATP7B Genotype Effectively Influence the Clinical Phenotype of Wilson Disease. *Hepatology.* **2019**; 69(4):1464–1476. https://doi.org/10.1002/hep.30280
6. Golubeva, V. V.; Mazurchik, N. V.; Garabova, N. I.; Nozdryukhina, N. V.; Strutsenko, A. A. Dva sluchaya bolezni Vil'sona-Konovalova. *Neurologiya, neiropsikhiatriya, psikhosomatika.* **2013**; (3):41-46.
7. Harada, M.; Sakisaka, S.; Terada, K. Role of ATPase in biliary copper excretion in a human hepatoma cell line and normal rat hepatocytes. *Gastroenterology.* **2000**; 118(4):A118.
8. Konovalov, N. V. Gepatocerebral'naya distrofiya. *Medgiz,* **1960**.
9. Li, H.; Liu, L.; Li, Y.; He, S.; Liu, Y.; Li, J.; Tao, R.; Li, W.; Shang, S. Familial screening of children with Wilson disease: Necessity of screening in previous generation and screening methods. *Medicine.* **2018**; 97(27):e11405. https://doi.org/10.1097/MD.0000000000011405
10. Litwin, T.; Dzieżyc, K.; Karliński, M.; Szafrański, T.; Członkowska, A. Psychiatric disturbances as a first clinical symptom of Wilson's disease - case report. *Psychiatria Polska.* **2016**; 50(2):337–344. https://doi.org/10.12740/PP/45218
11. Litwin, T.; Gromadzka, G.; Samochowiec, J.; Grzywacz, A.; Członkowski, A.; Członkowska, A. Association of dopamine receptor gene polymorphisms with the clinical course of Wilson disease. *JIMD Repo*rts. **2013**: 8:73–80. https://doi.org/10.1007/8904_2012_163
12. Liu, Y.; Zhou, H.; Guo, H.; Bai, Y. Genetic and Clinical Analysis in a Cohort of Patients with Wilson's Disease in Southwestern China. *Archives of Medical Research.* **2015**; 46(2):164–169. https://doi.org/10.1016/j.arcmed.2015.02.001
13. Proskokova, T. N.; Poleshchuk, V. V.; Illarioshkin, S. N.; Karyagina, M. V.; Avstyukhov, V. A. Partial epileptic seizures as the debut of the neurological stage of hepatolenticular degeneration. *Neurologicheskii Zhurnal.* **2007**; 12(2):22–25.
14. Ribak, N. V.; Kuzyk, Yu. I.; Pasnok, A. V. Hepatolenticular degeneration (Wilson's disease): clinical and pathomorphological analysis. *Medical Lyceum.* **2011**; (3):79.
15. Roberts, E. A.; Schilsky, M. L. Diagnosis and treatment of Wilson disease: An update. *Hepatology.* **2008**; 47(6):2089–2111. https://doi.org/10.1002/hep.22261
16. Sanger, F.; Coulson, A. R. A rapid method for determining sequences in DNA by primed synthesis with DNA polymerase. *Journal of Molecular Biology.* **1975;** 94(3):441–448. https://doi.org/10.1016/0022-2836(75)90213-2

17. Schumacher, G.; Platz, K. P.; Mueller, A. R.; Neuhaus, R.; Steinmüller, T.; Bechstein, W. O.; Becker, M.; Luck, W.; Schuelke, M.; Neuhaus, P. Liver transplantation: treatment of choice for hepatic and neurological manifestation of Wilson's disease. *Clinical Transplantation.* **1997**; 11(3):217–224.
18. Tsivkovskii, R.; Eisses, J. F.; Kaplan, J. H.; Lutsenko, S. Functional properties of the copper-transporting ATPase ATP7B (the Wilson's disease protein) expressed in insect cells. *Journal of Biological Chemistry.* **2002**; 277(2):976–983. https://doi.org/10.1074/jbc.M109368200
19. Chetkina, T. S.; Potapov, A. S.; Tsirulnikova, O. M.; Senyakovich, V. M.; Tumanova, E. L. Wilson's disease in children: variants of manifestation and difficulties of early diagnosis. *Voprosy diagnostiki v pediatrii.* **2011**; 3(1):41–47.
20. Xiao, H.; Deng, S.; Deng, X.; Gu, S.; Yang, Z.; Yin, H.; Deng, H. Mutation Analysis of the ATP7B Gene in Seven Chinese Families with Wilson's Disease. *Digestion.* **2019**; 99(4):319–326. https://doi.org/10.1159/000493314