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Classification and Clinical Heterogeneity of Hepatolenticular Degeneration

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Abstract: Hepatolenticular degeneration (HLD) or Wilson-Konovalov disease (OMIM277900) is a hereditary monogenic autosomal recessive degenerative disease related to metabolic diseases - a category of storage diseases. HLD has been studied for more than 130 years. During this time, more classifications of this disease were proposed. In this review, we systematized all the proposed classifications of HLD. And we noticed, they are based on the following criteria: 1) clinical signs of the disease; 2) the sequence of their appearance as the pathology progresses (with the primary appearance of signs of liver or brain damage); 3) severity of the disease. This review also systematizes data on the clinical picture of HLD.

Keywords: *hepatolenticular degeneration Wilson-Konovalov disease; ATP7B gene; classifications; clinical symptoms*

Introduction

Hepatolenticular degeneration (HLD) or Wilson-Konovalov disease (OMIM277900) is a hereditary monogenic autosomal recessive degenerative disease related to metabolic diseases - a category of storage diseases. The cause of the development of HLD is a violation of the copper excretion in the urine due to excessive accumulation of the metal with its toxic effect on various organs and systems (mainly on the brain and liver) [1]. Among storage diseases, there is no other etiology that is differ by such polymorphism of clinical manifestations and the difficulty of selecting diagnostic criteria. Over the 130-year period of its study, attempts have been made to systematize individual manifestations of the disease and create valid clinical classifications. However, none of the known classifications has been able to fully reflect the clinical diversity of the disease and the ability to use their systematization as a sensitive and specific marker for diagnosing HLD. At the same time, significant changes have occurred in the assessment of the clinical reflection of pathology and the indicators of laboratory tests for diagnosis. The *ATP7B* gene (OMIM 606882) is responsible for the molecular defect of HLD. It is responsible for the synthesis of P type ATPase, which binds a copper molecule to apoceruloplasmin and converts it into ceruloplasmin. After the discovery of this gene, there was hope to obtain the main criterion for diagnosing this pathology in terms of molecular genetic research. And, based on clinical and genetic data, it became possible to

develop classifications that will help diagnose HLD in the early stages of its development. However, a wide range of causal mutations in the *ATP7B* gene (genetic polymorphism) and the complexity of population genetic screening to identify asymptomatic and low-symptomatic patients have not led to the expected success yet [2].

Objective

The purpose of this lecture is to update the knowledge of neurologists and doctors of related specialties (pediatricians, general practitioners, internists, gastroenterologists, laboratory diagnostic doctors, etc.) about approaches to the use of classifications and clinical criteria for HLD in real clinical practice.

Results

Classifications of hepatolenticular degeneration

Throughout the entire 130-year period of studying HLD, numerous proposals to systematize the clinical pattern of the disease have appeared one after another. National and international classifications have been developed and updated. The most famous ones are presented in Table 1.

It follows from the table that the classifications of HLD is based on the following criteria: 1) clinical signs of the disease; 2) the sequence of their appearance as the pathology progresses (with the primary appearance of signs of liver or brain damage); 3) severity of the disease.

From a historical point of view, the first classification is considered to be the proposal of Wilson [14], who identified the phenotype of HLD, combining extrapyramidal disorders and liver damage, named it "progressive lenticular degeneration". Then, Hall H.C. combined the known phenotypes of HLD into a single classification, highlighting the classic form with an unfavorable prognosis; torsion spasms; and the trembling form described by Westphal (1883) and Strumpell (1898) [3]. Bearn [4] proposed to distinguish two phenotypes of HLD: the Wilson's variant (progressive lenticular degeneration) and the Westphal-Strumpell's variant (pseudosclerosis). This classification of HLD phenotypes underwent minor changes at the end of the 20th century [6,7,9,11,12,15,16]. Thus, Brown (1964) proposed calling progressive lenticular degeneration a juvenile phenotype, and the Westphal-Strumpell variant a pseudosclerotic phenotype [6]. Cox [7] identified three phenotypes of the disease: two typical and an atypical phenotype with a low content of cerulloplasmin in the blood. Walshe & Yealland M. [9] identified four phenotypes (latent or asymptomatic, abdominal, cerebral and mixed). He paid attention to such variants as parkinsonian, pseudosclerotic, dystonic and choreiform. Oder [15] classified the disease into three phenotypes (dyskinetic with dyskinesia, dysarthria, organic personality syndrome, focal lesions of the putamen and globus pallidus; pseudoparkinsonian with rigidity, bradykinesia, altered consciousness and dilatation of the third ventricle according to magnetic resonance imaging; pseudosclerotic with ataxia, tremor and focal lesions of the thalamus according to magnetic resonance imaging. Kim [16] identified only two phenotypes (hepatic and neurological); Sukhareva [11] - six phenotypes of GLD with varying degrees of liver damage (hepatic, endocrine, neurological, psycho-emotional, hemolytic and renal); as later by Taly A.V. [12] - six other phenotypes (hepatic, hepatoneurological, neurological, psychiatric, osteomuscular and presymptomatic). Over the past decade, Voloshin-Gaponov I.K. [13] identified three neurological phenotypes of HLD: extrapyramidal, cerebellar and mental.

Table 1. Classifications of hepatolenticular degeneration.

Author of the classification (year of publication)	Phenotypes
Hall H.C. (1921) [3]	Classical Trembling Torsion spasms
Bearn A.G. (1953) [4]	Wilson's variant (progressive lenticular degeneration) Westphal-Strumpel's variant (pseudosclerosis)
Konovalov N.V. (1948, 1960) [5]	Abdominal Arrhythmo-hyperkinetic Trembling-rigid Trembling Extrapyramidal-cortical
Brown D. (1964) [6]	Juvenile (progressive lenticular degeneration) Pseudosclerotic
Cox D.W. (1972) [7]	Typical "juvenile" Typical "slavic" Atypical
Lössner J., Bachmann H. et al. (1980, 1988) [8]	Pseudoparkinsonian (trembling-rigid form) Pseudosclerotic (trembling form) Mixed
Walshe J.M. & Yealland M. (1992) [9]	Latent (asymptomatic) Abdominal Cerebral (parkinsonian, pseudosclerotic, dystonic and choreiform) Mixed
Cuthbert J. A. (1998) [10]	Pseudoparkinsonian (trembling-rigid form) Pseudosclerotic (trembling form) Dystonic Choreiform Mixed
Sukharev G.V. (2005) [11]	Hepatic Endocrine Neurological Psycho-emotional Hemolytic Renal
Taly A.B. et al. (2007, 2009) [12]	Hepatic Hepatic-neurological Neurological Psychiatric Osteomuscular Presymptomatic (latent)
Voloshin-Gaponov I.K. et al. (2014) [13]	Extrapyramidal Cerebellar Mental

All researchers paid special attention to the dynamics of the clinical pattern of the disease as it progresses. However, there is no consensus on this issue. Some authors propose to distinguish several stages, reflecting the degree of accumulation of free toxic copper in the body of a patient with HLD [13]. Other authors pointed out the advisability of taking into account only two stages based on the formation of leading phenotypes: visceral (preneurological) and neurological [13].

In Russia, the Konovalov [5] classification is recommended for use. A meticulous long-term study of the clinical picture and morphology of this disease made it possible to show that pathological changes in the brain in patients with HLD are not limited to the lenticular

nuclei, but are diffuse in nature, and to create an original classification of the disease (1948, 1960), which is still relevant today. A long-term study of more than 500 patients with HLD not only allowed to identify the most typical symptoms characteristic of each phenotype and different types of disease. Also, it helped to identify signs that make it possible to suspect HLD even before the development of a typical clinical picture of the disease. In addition, Konovalov N.V. was the first who proposed isolating a mixed form without a clear definition of the predominant clinical picture in the brain or liver. According to his classification [17], it is recommended to distinguish five main phenotypes of the disease: abdominal, arrhythmic hyperkinetic, characterized by arrhythmic hyperkinesis with various dystonic phenomena; trembling-rigid with the early appearance of rigidity and akinesia, which is accompanied by irregular trembling; trembling with predominant non-rhythmic tremors; extrapyramidal-cortical, characterized by various types of epileptic seizures.

Lössner J. and Bachmann N. [8], trying to modify the classification of Konovalov N.V., proposed to divide neurological phenotypes into pseudoparkinsonian (trembling-rigid form), pseudosclerotic (trembling form) and mixed forms. Later, Cuthbert [10] proposed to additionally distinguish dystonic and choreiform forms from mixed phenotypes.

A large number of transitional phenotypes, dissociation in the clinical manifestations of individual signs and an ambiguous response to the drugs used, became an obstacle to the systematization of the clinical phenotypes of the disease and continued to cause discussions, interfering with the choice of criteria for the clinical diagnosis of HLD. The number of works reflecting the choice of criteria for the differential diagnosis of HLD from similar diseases (phenocopies) have increased [18]. Unfortunately, none of the known classifications has been able to fully reflect the heterogeneity of clinical phenotypes in the early stages of development of HLD and at the stage of disease manifestation to date. There is no consensus on the age of onset of the disease and the reasons for the late manifestation of HLD yet, which may be a cause of its genetic heterogeneity (the nature of the causal mutation in the *ATP7B* gene). Therefore, World Health Organization (WHO) proposed to use the International Classification of Diseases, 10th revision (ICD X, 1994), which recommends distinguishing two phases during the course of the disease: latent (when there are no clinical symptoms, and signs of the disease are detected only for laboratory examination); phase of development of clinical manifestations (hepatic, neurological) with the stage of negative copper balance (in cases when assessing the effectiveness of treatment, regression of clinical and laboratory manifestations of the disease is observed after achieving and long-term maintenance of a negative copper balance) [19]. At the same time, it is recommended to take into account three phenotypes of HLD: with predominant liver damage; with predominant damage to the nervous system; mixed phenotype. ICD 11th revision (ICD XI, 2016) proposes to divide disorders of copper metabolism into "5C44.00 Wilson-Konovalov disease", "5C44.0Y Other specified disorders of copper metabolism", "5C44.0Z Disorders of copper metabolism, unspecified" [20].

The discovery of the *ATP7B* gene [21] and its causal mutations [22] changed approaches to systematizing disease phenotypes. Traditional clinical classifications have been replaced by new ones, which are based on taking into account the heterogeneity of causal mutations in the *ATP7B* gene, the allelic frequency of which can vary over a wide range in different ethnic and racial groups [23-35].

This explains the variable prevalence and clinical heterogeneity of HLD phenotypes in populations around the world. In this connection, it has been proposed to distinguish three phenotypes of the disease depending on the ethnic group and the most common causal mutations in the *ATP7B* gene: "Slavic" (more common in Russia, Belarus, Poland, Slovakia); "Western" (mainly registered in France, Germany, England, Italy, as well as China and Central Asia); "atypical", which occurs without clinical signs of the disease, but is manifested only by a decrease in the level of ceruloplasmin [36-37].

In the 21st century, interest in studying the relationship between the phenotype and genotype of HLD is growing, which influences changes in terminology. For example, terms have been proposed that reflect the molecular genetic basis of the disease. However, the problem remains in the selection of key criteria for early diagnosis and differential diagnosis of HLD and its phenocopies [38]. Nowadays none of the available domestic and foreign studies have demonstrated a significant correlation between phenotype and genotype in HLD, formed new clinical and genetic classifications, or indicated the place of the results of molecular genetic research in the set of criteria for diagnosing HLD.

Clinical symptoms of hepatolenticular degeneration

The first descriptions of the clinical picture of the HLD belong to Westphal [39] and Strumpell [40], who discovered a peculiar irregular trembling in young people (similar to trembling in patients with multiple sclerosis), provided a detailed description of the movement defect and called the disease "pseudosclerosis". The first attempt to systematize the clinical manifestations of HLD belongs to Wilson. In 1912, he published a work in which he provided a pathological picture of the new disease, pointed out combined liver and brain damage in patients with HLD and described the characteristic clinical symptoms, especially emphasizing the further progression leading to death in patients over the next 5-6 years [14]. For a long time, the disease was classified as rarely detected and absolutely fatal. Discovery by Cumings et al. [41] a defect in copper metabolism in the origin of the pathology made it possible to classify it as a storage disease. The clinical picture of HLD is distinguished not only by the heterogeneity of neurological and somatic manifestations, but also by a change in the clinical pattern of the disease as free copper accumulates in various tissues and organs. Although it was noted that HLD may have an asymptomatic course even with an increase in copper levels in biochemical samples (blood and urine) [42].

At the same time, no consensus has been formed neither about its clinical manifestations at the stage of manifestation, nor about the timing of the appearance of each of the signs of damage to a particular system, nor about the reasons for the formation of various clinical phenotypes [43-44].

Cases are described when damage to the central nervous system is the first and its diagnosis is delayed for several years [33]. Therefore, neurological phenotypes of HLD may predominate by the age of 10-20 years of a patient's life, and clinical cases with hepatic phenotypes are generally less common. By the age of 30, neurological phenotypes account for about 70% of clinical cases of HLD, while the hepatic phenotypes are about 15% [45].

The neurological phenotypes of HLD are characterized by a variety of defects caused by damage to extrapyramidal motor neurons and neuronal pathways: irregular tremor, dystonia, myoclonus, choreiform and athetoid phenomena. The frequency of these symptoms varies widely in different populations. Thus, various forms of dystonia, which lead to dysarthria and impaired swallowing, are described in 11 to 69% of patients with HLD [45-46]. In the absence of treatment, there is a tendency for dystonia to spread and generalize, which impairs the movement of patients up to their immobilization. These hyperkinesis change facial expression spreading to the facial muscles. When hyperkinesis passes to the limbs, it acquires an explosive character. The spectrum of hyperkinesis in HLD is so wide, and their combinations are so diverse that it is often impossible to separate them by nature.

Choreioform and athetoid hyperkinesis occur with a frequency of 6 to 30% of cases [47].

Akinetic-rigid syndrome occurs in 12-58% of cases and can be combined with tremor, which has various characteristics. Unlike Parkinson's disease, resting tremor in HLD is rarely described (4% of cases) and is characterized by an earlier onset [48]. However, in

recent years, the term parkinsonism has been used more often, the frequency of which in HLD varies from 19 to 62% of cases [49,50].

On the other hand, tremor (except for resting tremor) can also be the leading clinical symptom of HLD with an incidence of up to 55% of cases at the onset of neurological phenotypes of the disease and up to 90% at clinically advanced stages. Tremor in patients with HLD can be mixed, combining several characteristics, without clearly identifying any specifics [17,48]. As the disease progresses, the nature of the tremor may change, flow into another characteristic, and spread to other parts of the body (head, lower limbs, torso) [45].

Epileptic seizures are observed in 6–28% of cases and can be focal with preservation of awareness, focal with impaired awareness, bilateral, generalized [46,48].

Cerebellar disorders include cerebellar ataxia, scanned speech, intention tremor, and dysdiadochokinesis. They occur in 30% of cases of HLD, are not isolated, but are combined with other neurological symptoms of the disease [45].

Table 2. Clinical pattern of hepatolenticular degeneration.

Disorders	Symptom	General characteristics
Extrapyramidal	Tremor	Involuntary rhythmic oscillatory movements of complementary antagonistic muscle groups, usually involving the hands, head, face, vocal cords, torso, legs
	Rest tremor	Violent rhythmic involuntary movements of an oscillatory nature involving any part of the body, occurring in the absence of purposeful motor activity
	Postural tremor	Violent rhythmic involuntary movements of an oscillatory nature involving any part of the body that occur when holding a pose
	Dystonia	Persistent involuntary muscle contractions of antagonistic muscle groups in one area of the body, resulting in persistent abnormal body posture or sharp, intermittent twisting spasms that may resemble tremors, athetosis, or choreoathetosis
	Orofacial dyskinesia	Grimaces, lockjaw, forced opening of the mouth, forced sideways movements of the lower jaw
	Dystonic dysarthria	Loss of the ability to correctly articulate words due to persistent involuntary muscle contractions of the muscles of the mouth, tongue, larynx, and oropharynx
	Akinetic-rigid syndrome	Movement disorders manifested by poverty and slowing of active movements (bradykinesia) and increased muscle tone of the plastic type (rigidity)
	Oropharyngeal dysphagia	Choking when taking liquid and solid food, impaired swallowing of saliva and secondary drooling
	Cerebellar ataxia	Coordination motor disorder, including gait disorder, disproportionality and asynergy of movements, dysdiadochokinesis, changes in handwriting (macrography)
	Choreiform hyperkinesis	Fast, intense, sweeping, non-rhythmic involuntary movements in various muscle groups: involuntary frowning of the eyebrows, forehead, squinting of the eyes, sticking out the tongue, smacking, sniffing, impetuous and erratic movements of the limbs
	Tic hyperkinesis	A fast, stereotypical short-term involuntary elementary movement, externally resembling a reflex or purposeful one
	Crumpy	Short-term involuntary painful contractions of muscles or muscle groups
Epileptic	Focal, bilateral and generalized epileptic seizures	Motor (usually myoclonic), psychomotor, tonic-clonic, clonic
Mental	Cognitive disorders	Decrease in memory, mental performance and other cognitive functions compared to the initial level (individual norm)
	Behavioral disorders	Mental disorders in which social norms and rules are violated
	Intellectual disorders	A state of delayed or incomplete mental development
	Psychotic mental disorders	Disorders accompanied by disturbances in thinking, behavior and emotional state

The incidence of specific clinical symptoms may depend on the ethnic group of patients, which is likely associated with various causal mutations that are the "culprits" of different HLD phenotypes. In a study of newly diagnosed patients, the most common symptoms were tremor and ataxia (62.3%), dystonia (15.1%) and parkinsonism (11.3%) [51] unclassified features of neurological phenotypes of HLD were diagnosed in only 11.3% of patients, further illustrating the significant clinical heterogeneity of the disease [51].

HLD may begin with non-psychotic mental disorders, including cognitive impairment and decreased intelligence, emotional or behavioral disorders [51-53]. Sometimes cognitive deficits progress rapidly and lead to the development of dementia [54]. In some patients, psychotic mental disorders are registered, which lead in the clinical picture of the disease and can complicate timely diagnosis since the patient can be observed by a psychiatrist for a long time without conducting the necessary laboratory diagnostic tests for differential diagnosis of schizophrenia spectrum disorders and HLD [55].

With all phenotypes of HLD, somatic manifestations are possible. About 10% of patients may have the onset of the disease with hemolytic anemia, leukopenia and thrombocytopenia [48], as well as with cardiovascular diseases [56]. In a number of patients, due to copper deposition in the proximal renal tubules, signs of kidney damage come to the fore, which leads to erroneous diagnosis of diseases such as pyelonephritis, glomerulonephritis, "salt" cystitis, and urolithiasis [57]. Other patients are diagnosed with various endocrine disorders, including decreased function of the thyroid and parathyroid glands [58].

It is a possible damage of the musculoskeletal system. Often, the accumulation of copper in the joints leads to osteoarthritis and chronic joint pain syndrome [59-60] (Table 2).

Conclusions

The information presented in the lecture demonstrates that to date, none of the known classifications fully reflects the relationship between the heterogeneity of phenotypes and genotypes of HLD, which is especially important for diagnosing the disease at the stage of its debut, since it can ensure the timely prescription of pathogenetic therapy (copper-eliminating medicines).

Diagnosis of the severity of HLD phenotypes (primarily neurological) is still based on the assessment of clinical signs, including: neurological manifestations (tremor, torsion, parkinsonism, dysarthria and others), abdominal disorders (hepatitis, cirrhosis, acute fulminant cirrhosis), mental disorders (anxiety-phobic syndromes, somatoform disorders). However, the rapid development of modern genetic technologies, which makes it possible to diagnose causal mutations in the *ATP7B* gene in both asymptomatic (little symptomatic) and symptomatic patients, prompts a revision of approaches to the classification and early clinical diagnosis of HLD.

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