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Diseases of the Neuroacanthocytosis Group: A Systematic Review of Clinical Cases and Difficulties in their Diagnosis

Anna Spesivtseva*, Natalya Gvarzhdets, Kazbek Autlev, Evgeny Kruchinin, Ivan Kuznetsov

Abstract

This systematic review examines diseases within the neuroacanthocytosis group, including chorea-acanthocytosis (ChAc), McLeod syndrome (MLS), Huntington's-like type 2 disease (HDL2), and other neurodegenerative disorders. The objective of this review is to provide a comprehensive overview of the clinical manifestations, diagnostic challenges, and current understanding of these rare hereditary diseases. Each nosological unit from this group is caused by various genetic mutations and has a different type of inheritance, pathogenetic changes, and clinical picture. Due to the rarity and relatively little knowledge of the pathogenetic foundations of these diseases, their diagnosis is a difficult task, and their treatment, as a rule, is only symptomatic.

Introduction

The term "neuroacanthocytosis" refers to a group of hereditary disorders manifested by a combination of changes in the shape of erythrocytes (acanthocytosis) and progressive degenerative changes in the brain [1-3]. The clinical picture can vary widely depending on the form of pathology. The most common symptoms include motor disorders, neuropathy, epileptic seizures, as well as mental and neurocognitive disorders [4,5]. The first reports of a combination of acanthocytosis with motor disorders appeared in the middle of the 20th century, but only in the 1970s they were described as an independent pathology called Levin-Critchley syndrome after its researchers [6].

Japanese doctors introduced the term "neuroacanthocytosis" in 1982, which subsequently became widespread [7]. However, the new name has led to taxonomic confusion, mainly due to the lack of identification of the genetic component underlying the pathogenesis. For some time, various syndromes were designated by one single term, until 1994 and 2001, the genetic correlates of chorea-acanthocytosis (ChAc) and McLeod syndrome (MLS) were discovered and studied. Currently, the classification proposed in 2011 is used [8,9]. According to it, pathologies are grouped as follows. ChAc and MLS are combined into the first group as the main neuroacanthocytosis syndromes. Pantothenate kinase-associated neurodegeneration (PKAN), Huntington's-like type 2 disease (HDL2), and aceruloplasminemia belong to the second group and are degenerative diseases in which sometimes acanthocytosis is observed. The third group consists of abetalipoproteinemia (ABL) and hypobetalipoproteinemia – diseases characterized by a reduced content of lipoproteins in the blood and acanthocytosis. ChAc and MLS are the most typical diseases in the presented classification, in which each pathology is extremely rare [10]. For example, PKAN is most often diagnosed in limited foci in the Netherlands and the Dominican Republic and has a prevalence lower than 1-3 per 1 million population, and only about 250 cases of MLS and about 1,000 cases of ChAc have been detected worldwide [11,12].

Methods

Criteria for the Search and Selection of Literature

This systematic review was conducted following the provisions of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Search strategy

We carried out a systematic search in electronic databases, including Scopus, Web of Science, and PubMed/Medline, using keywords selected from the Medical Subject Headers (MeSH). The search was conducted using the following keywords: chorea syndromes, chorea-acanthocytosis, neurodegenerative disorder, neuroacanthocytosis syndrome, and McLeod syndrome.

Following the search, literature was selected and analyzed. Fifty research articles were selected for review.

Discussion

Chorea-acanthocytosis

ChAc is understood as an autosomal recessive disease, usually caused by mutations in a large gene on chromosome 9 (VPS13A; 73 exons), which encodes the protein chorein and manifests itself in degenerative changes, acanthocytes, and progressive motor disorders [13].

Motor disorders include pronounced dystonic syndromes, in particular, oromandibular and orofacial, damage to the lower extremities with the drop foot (foot drop), damage directly to chorea, the so-called "rubber man appearance", characterized by sudden spasms of the body during flexion and extension, which can lead to gait instability and falling. Manifestations of parkinsonism, epilepsy, and obsessive-compulsive spectrum disorders are also observed [14,15].

Currently, the physiological function of the chorein protein encoded by the VPS13A gene of the same name is poorly understood at the molecular level. Mutations in the VPS13 family can lead to certain neurological pathologies, for example, Cohen syndrome (VPS13B), Parkinson's disease (VPS13C, as one of the genes), and spinocerebellar ataxia (VPS13D). The pathogenetic links of ChAc remain completely unexplored [16]. Several disorders at the cellular level are assumed, including dysfunction of autophagy processes, deformation of the structure of cell membranes, and disturbance of ion flow. From the perspective of regulating cellular signals, the most important aspects in understanding the pathophysiology of the disease may be the increased activity of tyrosine protein kinase Lyn and changes in the PI3K-Akt signaling pathway [15,17].

In one study, it was demonstrated that mice with overexpression of the Lyn protein developed hemolytic anemia with acanthocytic erythrocytes [18]. Promising results were also obtained by German scholars led by K. Peikert demonstrating that striatum neurons obtained from patients with ChAc (using the hiPSC technique) were characterized by increased excitability and cell death, which was offset by the use of a selective PP2 kinase inhibitor [18]. Another mechanism of signaling PI3K implies activation of the universal transcription factor NF-kB, followed by the effect on the subunits of the calcium channel ORAI1 and its associated SOCE, the so-called depot of Ca2+ entry into cells, which plays

an important role in regulating the basal calcium level, its intracellular replenishment, and several associated specialized processes (apoptosis, exocytosis, enzyme control, etc.). According to the results by Peikert et al., suppression of SOCE promotes increased susceptibility to apoptosis, while lithium can activate ORAI1 and, as a result, has a stimulating effect on SOCE, which can be used to suppress cell death [18-20].

Another leading ChAC syndrome, in addition to neurological, is a change in the metabolism of lipoproteins: ABL and hypobetalipoproteinemia, often leading to malabsorption of vitamin E with clinical manifestations of peripheral neuropathy and sensory ataxia due to degenerative disorders of the dorsal spine [13,21,22]. Laboratory parameters at ChAc are not subject to strong changes [23]. The determination of acanthocytosis in peripheral blood smears can often be negative and have a variable character, which, however, is not a criterion for excluding the diagnosis [24,25]. Usually, there is a large number of hyperchromic erythrocytes, and a more specific marker is an increased level of creatine phosphokinase. Confirmatory DNA analysis of the VPS13A gene is difficult due to the high heterogeneity of mutations and is available only in one commercial laboratory [11,18].

Of the instrumental methods, EMG and EEG are often used, according to which, sensorimotor axonal neuropathy and neuromyopathic changes are noted, respectively [14,20]. According to instrumental imaging data, as a rule, ChAc is characterized by bilateral atrophy of the predominantly caudate nucleus, a decrease in its volume, to a lesser extent damage to the putamen (shell), and involvement of the thalamus with substantia nigra. The disease usually progresses slowly over 15-30 years and leads to death [5,10]. Etiotropic therapy has not been developed and the main treatment is carried out symptomatically [21,23]. Selective kinase inhibitors and lithium preparations are currently promising directions, but the clinical experience of their use in ChAc remains limited [13, 19]. The use of deep brain stimulation (DBS) in this pathology is considered experimental and should be adapted to a specific patient. Physiotherapeutic and psychotherapeutic techniques aimed at improving the patient's quality of life make a special contribution to the treatment of the disease [12,15].

McLeod syndrome

MLS is a progressive neurodegenerative disease with predominant damage to the basal ganglia, primarily the caudate nucleus and shell, and the presence of acanthocytes in the blood [24,26]. The syndrome is caused by nucleotide deletions in the XK gene, localized in the p21.1 region of the X chromosome and responsible for encoding the XK protein. The disease may be part of a deletion syndrome in which deletion of nucleotides occurs not only in the XK gene but also at adjacent loci, which leads to the development of Duchenne muscular dystrophy, chronic granulomatous disease, and retinitis pigmentosa [25].

XK is a transmembrane protein that forms a heterodimer with Kell glycoprotein on the erythrocyte membrane through a disulfide bond. The XK-Kell dimer is part of a membrane multiprotein complex, which also includes the Band3 glycoprotein, glycophorin C, Rh protein/Rh-associated glycoprotein, and Duffy protein [8,26].

The functions of this transmembrane complex include maintaining the disc-shaped shape of erythrocytes and controlling deformability and transmembrane exchange of ions and metabolites. The absence of the XK-Kell multiprotein complex in the membrane leads to a violation of the homeostasis of bivalent cations, which may explain the premature hemolysis of erythrocytes in patients with MLS due to disruption of Ca2+-activated K+ channels [27]. In the absence of XK protein in erythrocytes, phosphatidylserine deficiency is observed in the inner part of the bilipid layer, which leads to the narrowing and deformation of the cell membrane, as well as disruption of transmembrane transport. Only the XK protein is expressed in the nervous system, and the formation of the XK-Kell complex does not occur there. XK protein plays a role in organogenesis, the exchange of nutrients and electrolytes, and the maintenance of cellular structure [21,28]. This is due to the multi-system nature of damage in MLS.

The clinical picture is characterized by high variability of symptoms, which is explained by at least 56 allelic variants of the XK gene identified at the moment. MLS manifests on average at the age of 40 (from 25 to 60), almost exclusively in males. The clinical picture depends on the phenotype and may include neurological, neuromuscular, mental, and cardiological manifestations [29]. The most common neurological symptoms are chorea, dystonia, vocal tics, parkinsonism, and cognitive deficits with the subsequent development of dementia. Mental disorders such as depression, bipolar affective disorder, obsessive-compulsive disorder, and pathological personality changes are often detected in patients [27,30,31]. Neuromuscular manifestations include areflexia, atrophy, and muscle weakness. Patients are most often diagnosed with atrial fibrillation, other benign arrhythmias, and dilated cardiomyopathy among the cardiac symptoms [24,32]. Sometimes generalized epileptic seizures are observed with MLS. Diagnosis of MLS is a complex task and requires the exclusion of Huntington's disease, Wilson's disease,

ChAc, and c9orf72-associated disorders [33,34]. The diagnosis is based on the identification of the most typical clinical manifestations, the gender of patients (almost exclusively male), and laboratory, instrumental, and genetic data. Typical laboratory changes include increased serum creatine kinase levels (300-3000 U/L), absence of Kx antigen (detected several years before the onset of the disease), decreased level and activity of Kell antigens, acanthocytosis, and compensated hemolysis (in almost all patients). Atrophy of the caudate nucleus and shell is visualized on CT and MRI in patients with MLS [12,35,36]. It is often possible to detect fatty degeneration of the muscles of the lower extremities. Genetic testing (Xp21.1, deletion of the XK gene, or multigenic testing) is performed to confirm the diagnosis of patients. The treatment of MLS consists of the control and relief of symptoms and constant monitoring of the condition of patients [37-39]. Tetrabenazine, which is an inhibitor of the vesicular monoamine transporter VMAT2, is used in therapy to relieve motor disorders (mainly chorea) [40]. As a result, the transport of monoamines from the cytosol to synaptic vesicles is disrupted, which leads to premature degradation of dopamine, norepinephrine, serotonin, and histamine. Treatment of other clinical manifestations, as in ChAc, is symptomatic and depends on the phenotype of the disease [41]. Some patients require a transfusion of blood components. There are particular difficulties with compatibility since transfusion of blood positive for Kx antigen should be avoided [42,43]. The literature describes a case of successful transplantation of allogeneic stem cells to a 14-year-old patient with MLS and chronic granulomatous disease. However, at the moment, there is no evidence of whether this can prevent the late onset of neurological, neuromuscular, or cardiac complications [44]. Promising areas of treatment also include the use of CRISPR/Cas9 technology for the repair of damaged DNA and gene therapy using viral vectors [45,46].

Huntington's-like type 2 disease (HDL2)

Huntington's-like type 2 disease (HDL2) typically presents in midlife with a relentless progressive triad of movement, emotional, and cognitive abnormalities, leading to death within 10 to 20 years [47]. The clinical characteristics of HDL2 closely resemble those of Huntington's disease, making it difficult to differentiate the two conditions based on clinical features alone. Neurologic abnormalities observed in HDL2 include chorea (involuntary movements), hypokinesia (rigidity and bradykinesia), dysarthria, and hyperreflexia, with the latter being more prominent in the later stages of the disease [48]. The duration of the disease correlates strongly with the progression of motor and cognitive impairments.

The diagnosis of HDL2 relies on a positive family history, characteristic clinical findings, and the detection of an expansion of 40 or more CTG trinucleotide repeats in the JPH3 gene. The presence of these genetic mutations confirms the diagnosis and helps differentiate HDL2 from other conditions with similar clinical presentations. However, it is important to note that HDL2 resulting from a de novo pathogenic variant has not been reported but is theoretically possible.

Currently, there is no cure for HDL2, and management focuses on symptomatic treatment to address specific manifestations and improve the individual's quality of life. Pharmacologic agents such as tetrabenazine and its derivatives, as well as low-dose neuroleptic agents like fluphenazine and haloperidol, may be used to suppress abnormal movements. Psychiatric symptoms can be managed with antidepressants, antipsychotics, mood stabilizers (e.g., lithium, valproic acid, carbamazepine, and lamotrigine), and occasionally stimulants[49]. Education about the disease's progression and environmental interventions, such as regular schedules and memory aids, can be helpful. Measures to ensure safety, such as removing hazards from the home and minimizing the need for stairs, are important in preventing falls and injuries. Additionally, surveillance should be implemented to monitor nutrition and swallowing, gait and fall prevention, mood and irritability, and driving ability.

Genetic counseling is an integral part of HDL2 management, as the disorder follows an autosomal dominant inheritance pattern. Children of an individual with HDL2 have a 50% chance of inheriting the disease-causing allele [50]. Predictive testing for asymptomatic adults at risk is available but requires careful consideration and genetic counseling due to the lack of a cure for the disorder. Prenatal testing and preimplantation genetic testing can be offered when an HDL2-causing expansion has been identified in an affected family member.

While the search for disease-modifying therapies continues, the current focus remains on symptom management and support for individuals and families affected by HDL2. Ongoing research efforts aim to deepen our understanding of the underlying mechanisms of HDL2 and explore potential avenues for future treatments.

Conclusion

Neuroacanthocytosis encompasses a group of rare and genetically heterogeneous neurodegenerative diseases,

including HDL2, McLeod syndrome, and Chorea-acanthocytosis. The prevalence rates for these conditions are challenging to determine precisely due to their rarity, but the reported cases worldwide are relatively low. McLeod syndrome, caused by nucleotide deletions in the XK gene, has been documented in a small number of individuals, while Chorea-acanthocytosis, primarily caused by mutations in the VPS13A gene, has only been detected in approximately 1,000 and 250 cases worldwide, respectively. HDL2, although less prevalent than Huntington's disease, is still rare, with reported rates ranging from 0.1 to 1 case per 100,000 individuals.

These disorders pose significant challenges in diagnosis and management due to their limited number of cases and the scarcity of available information. Medical professionals encountering these conditions in their clinical practice are often faced with limited references and research studies. As a result, a close interdisciplinary approach is crucial, including genetic counseling, to ensure that important clinical information is updated and to accurately assess the likelihood of disease manifestation in relatives or children.

Currently, treatment options for the neuroacanthocytosis group of diseases remain limited, emphasizing the need for further research and advancements in the understanding of their pathogenesis. The rarity and complexity of these disorders make them challenging to study and develop effective therapies. However, with continued efforts in research, increased awareness, and collaboration among healthcare professionals, it is hoped that progress will be made in improving the diagnosis, management, and treatment of these rare neurodegenerative diseases.

Competing Interest

The authors declare that there is no conflict of interest.

Author Contributions

All authors contributed equally to the study and manuscript.

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