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REVIEW

Progress in the Diagnosis and Management of Chorea-acanthocytosis

Yang Liu[1], Ziyuan Liu[1], Xinhua Wan[2], Yi Guo[1*]

[1]Department of Neurosurgery,
[2]Department of Neurology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100730, China

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Abstract Chorea-acanthocytosis (ChAc) is the most common subtype of neuroacanthocytosis syndrome, characterized by the presence of acanthocytes and neurological disorders. It is thought to be caused by *VPS13A* mutations. Characteristic movement disorders in ChAc is choreiform movements affecting both trunk and extremities and prominent orolingual dyskinesia is pathognomonic. Acanthocytosis in peripheral blood smear, elevated serum creatine kinase and atrophy of heads of caudate nuclei and dilation of the anterior horn of the lateral ventricles in magnetic resonance imaging could assist the diagnosis of ChAc. Botulinum toxin injection is a possible treatment for the typical orofacial dystonia. Deep brain stimulation is a novel surgical treatment modality. Most cases chose globus pallidus internus as target. Patients with dystonia as a major manifestation will benefit more from high-frequency stimulation and those with major findings of chorea and dysarthria are suitable for low-frequency stimulation. More evidence of long-term outcomes is warranted.

CHOREA-ACANTHOCYTOSIS (ChAc) is an autosomal recessive hereditary disorder caused by the mutation of gene *VPS13A*. It is the most common subtype of neuroacanthocytosis (NA) syndromes. NA syndromes refer to group of syndromes characterized by the presence of acanthocytes and neurological dysfunctions, which can be further classified into two major groups. First, the "core" NA syndromes present with basal ganglia degeneration, movement disorders, cognitive impairment and psychological symptoms. Based on various etiologies, there are four subtypes: ChAc, McLeod syndrome, Pantothenate kinase-associated neurodegeneration and Huntington's disease-like 2. The second major group of NA syndromes include abetalipoproteinemia (Bassen-Kornzweig syndrome) and familial hypobetalipoproteinemia, with peripheral neuropathy and sensory ataxia, but without movement disorders. In addition, several sporadic systemic diseases are also associated with acanthocytosis.[1] Despite that ChAc is the most common NA subtype, its prevalence is still

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*Corresponding author Tel: 86-10-61902918, E-mail: guoyi@pumch.cn

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exceedingly low, making comprehensive understanding of ChAc less feasible. Considering ChAc has a long clinical course with protean clinical manifestations, it is likely to be misdiagnosed at early phase. The management of ChAc, especially from a surgical perspective, has made substantial progress recently. This review focused on the epidemiology, clinical manifestations, diagnosis and treatment strategies of ChAc, aiming to improve physicians' understanding of this disorder.

ETIOLOGY AND PATHOGENESIS

The exact mechanism underlying ChAc remains elusive. Currently ChAc is thought to be caused by mutations on gene *VPS13A* (also called *CHAC*).[2-3] *VPS13A*, located on chromosome 9q21, has 73 exons throughout the whole length. Its protein product, vacuolar protein sorting-associated protein 13A (VPS13A, also called chorein), is a member of VPS13 protein family. *VPS13A* mutations can result in either complete absence of[4] or functionally-compromised[5] VPS13A. Mammalian VPS13 protein family consists of VPS13A-VPS13D, each playing specific roles, and VPS13B-VPS13D cannot compensate the absence of VPS13A.[6] Several researches have already unraveled some functions of VPS13A, while the exact pathophysiology of how VPS13A dysfunction can lead to the phenotype of ChAc remains unknown. A study of yeast VPS13p protein (homologue of mammalian VPS13) has demonstrated its role in maintaining normal mitochondrial function,[7] and another report showed that VPS13A was involved in polymerization of actin and in lipid synthesis.[8] Therefore, it was postulated that the abnormal spiky shape of erythrocytes in ChAc might be attributed to not only oxidative damage of membrane lipid secondary to mitochondrial dysfunction but also defected cell scaffold formation secondary to actin dysfunction. Besides, VPS13A was also involved in intracellular trafficking of vesicles.[9] However, how these dysfunctions could translate into phenotypes still remains to be clarified. Moreover, considering ChAc has high phenotypic variation, patients could have quite different symptoms even in one family, suggesting possible epigenetic or environmental influence to be unraveled.[10]

EPIDEMIOLOGY

ChAc was a rare disease with only scattered reports. Currently its actual prevalence was unknown. A relatively higher prevalence in Japan and some ethic groups (such as French-Canadians[11]) was reported, possibly due to founder effect.

CLINICAL FEATURES

ChAc generally has an onset in the age of twenties.[1] The key features of movement disorders in ChAc is choreiform movements affecting both trunk and extremities. Especially, prominent orolingual dyskinesia is thought to be pathognomonic in ChAc, which can cause self-mutilation such as lip- or tongue-biting.[12] Trunk instability with spasms (often called "rubber-man gait") can also be seen in patients with ChAc, while falls are uncommon (balance generally preserved).[13] Rarely, patients can develop Parkinsonism in the late stage, which may be related with involvement of nigrostriatal pathways as disease progresses.[14]

Besides, behavioral, cognitive and psychiatric disturbances can also be seen in patients with ChAc, such as depression,[15] schizophrenia-like behaviors[16] and compulsive behaviors.[17] Remarkably, psychiatric manifestations often precede movement disorders, leading to high risk of misdiagnosis sans thorough examination and continuous follow-up.

Finally, several clinical features are thought to be pathognomonic in ChAc. Seizures can present early in disease course, even before motor deficits.[18-19] Other findings, such as peripheral neuropathy,[20] cardiac involvements[21] (arrhythmia, cardiomyopathy), although more commonly seen in McLeod syndrome, can suggest a diagnosis of NA syndromes and be distinguished from other hyperkinetic disorders such as Huntington's disease.

ChAc is a highly disabling disease which slowly progresses for as long as 15 to 30 years. Orolingual dyskinesia and walking difficulty can be highly disturbing and debilitating. Swallowing problems can cause malnutrition and aspiration. Sudden death can result from choke, seizure attack or cardiac arrhythmia.

LABORATORY WORKUPS AND NEUROIMAGING

Several laboratory workups can assist the diagnosis of ChAc. Elevated serum creatine kinase can be seen in most patients with ChAc or McLeod syndrome.[22] Acanthocytosis in peripheral blood smear