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Case Report

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Irregular Case of Neuroacanthocytosis Presenting with Late Onset Attention Deficit Hyperactivity Disorder: A Case Report

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Abstract

Neuroacanthocytosis (NA) syndromes are characterized by various neurological abnormalities accompanied by abnormal red blood cells called acanthocytes. Neuroacanthocytosis syndromes may be divided into 4 main subgroups. These subgroups are named as; Core NA syndromes, Degenerative disorders where acanthocytosis is occasionally seen, Paroxysmal dyskinetic disorders and Disorders with reduced blood lipoproteins and acanthocytosis. This report focuses on a patient with Chorea-acanthocytosis who presented with motor signs in the 3rd decade of life. In the later course of disease, the patient developed attention deficit hyperactivity disorder and various tic disorders. We wanted to emphasize the importance of multidisciplinary care in the management of chorea-acanthocytosis.

Keywords: Neuroacanthocytosis • Attention deficit disorder with hyperactivity • VPS13A protein • Dyskinesias

Introduction

Neuroacanthocytosis (NA) syndromes are characterized by various neurological abnormalities accompanied by abnormal red blood cells called acanthocytes [1]. These disorders were originally named as "Levine-Citchley syndrome" because they were originally thought to have homogenous etiology [2]. After the identification of the responsible genes, it is recognized that neuroacanthocytosis syndromes may be divided into 4 main subgroups. These subgroups are named as; Core NA syndromes, Degenerative disorders where acanthocytosis is occasionally seen, Paroxysmal dyskinetic disorders and Disorders with reduced blood lipoproteins and acanthocytosis [3]. Our case report focuses on Chorea-acanthocytosis, which is one of the two core NA syndromes along with McLeod syndrome.

Chorea-acanthocytosis is an autosomal recessive disorder [4]. It is a very rare disorder that is estimated to affect one thousand people worldwide [5]. It is evenly distributed among males and females and appears to be more prevalent in Japan and French-Canadian population [6]. Initial symptoms usually present in 20s and progresses slowly over 15-30 years [5].

Initial presentation of Chorea-acanthocytosis may be misleading. Often patients develop cognitive or psychiatric symptoms before the neurologic manifestations [2]. Manifestations may vary widely. Most bizarre and characteristic feature of this syndrome is orolingual dystonia that involves the lower face and tongue [7]. This presentation may also occur in other disorders but the severity is highly significant in chorea-athetosis. Feeding dystonia is also part of this syndrome and it occurs with eating. As soon as the tongue touches the food bolus, it pushes the food out of the mouth [8]. Additionally, self-mutilating lip or tongue biting may be seen, which resembles Lesch-Nyhan syndrome [4]. Another associated disorder that may cause self-harm is a sum of symptoms called as rubber-man appearance, described as sudden head and trunk flexion and extensions that may cause violent head banging or dangerous falls [9, 2]. Parkinsonism may also develop and sometimes be the initial presentation. Accompanying bradykinesia characteristically develops later in the process [10]. As emphasized later in this paper, psychiatric component of the disease may also be very dominant and early presenting. These include tics that resemble Tourette syndrome especially if they were present before the neurological symptoms [11]. Also, even a decade earlier than the neurological signs, patients may present with apathy, poor judgement, obsessive-compulsive disorder and schizophrenia like psychosis [3].

Despite the name of the syndrome suggests, acanthocytes are not always seen in peripheral blood smears of these patients. Acanthocytes levels tend to change during the course of the disease and these levels don't correlate with the severity of disease [12]. Serum Creatinine Kinase (CK) levels are a much more useful parameter regarding its moderate or evident elevation is a frequent finding among patients. Also, elevated liver enzymes are seen in nearly 50% of the patients. As a confirmatory test, Western blot assay of the Chorein protein, product of VPS13A gene, may be performed [1]. Additionally, electroneurography may demonstrate sensorimotor axonal neuropathy. On magnetic resonance imaging (MRI), specific involvement of the head of caudate nucleus is seen [13]. Putamen and Globus Pallidus are also predominantly affected [14].

In this case report, we present a rare case of chorea-acanthocytosis with attention deficit hyperactivity disorder (ADHD).

Case Presentation

6A thirty-three-year-old female presented to neurology outpatient clinic with choreiform movements in both her upper and lower extremities and difficulty with fine motor movements. She reported that these complaints have been going on for 12 years. In the last 4 years, she has also developed forgetfulness, attention deficit, orofacial dyskinesia and tic disorder that affects her eyes.

Physical examination was insignificant except for decreased deep tendon reflexes in her four extremities. Echocardiography of the patient and cranial imaging with MRI yielded no abnormalities. Upon clinical suspicion,

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hematology referral was made, and peripheral blood smear was obtained. Smear revealed 15% acanthocyte formation.

To further investigate, EMG was performed and showed sensory axonal peripheral neuropathy which is expected in chorea-acanthocytosis. In addition to these, creatine kinase levels were highly elevated.

A psychiatry referral was made to evaluate the relatively newer symptoms of the patient. Psychiatry department performed DIVA scoring system and diagnosed the patient with ADHD [15]. The patient was enrolled with routine psychiatric follow up for adult onset ADHD.

Upon diagnosing the patient with chorea-acanthocytosis, treatment with clonazepam was initiated as recommended in the literature (Figure 1) [10].

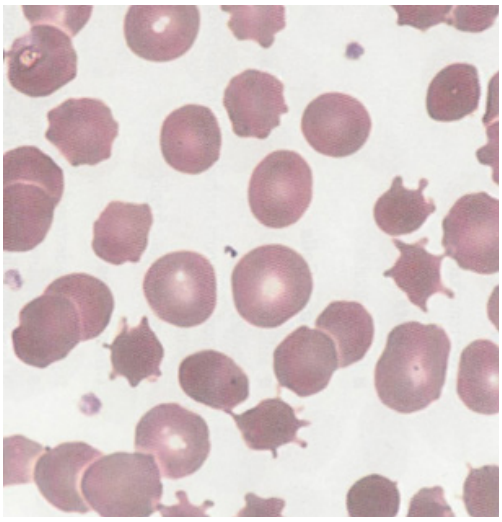

Figure 1. Acanthocytes detected under microscopy-peripheral blood smear of the patient.

Results and Discussion

Neuroacanthocytosis is a general term that is used for a group of diseases that present with abnormal erythrocyte morphology and multi-system neurologic manifestations [1]. This group of diseases include pantothenate kinase associated neurodegeneration (PKAN), Huntington's disease like 2 (HDL-2), McLeod syndrome (MLS) and Chorea-acanthocytosis. The latter two are also called as core syndromes of the group [3].

Chorea-acanthocytosis is a rare autosomal recessive disease caused by mutations in the 73-exon long VPS13A gene that encodes the protein Chorein. The mutations in this gene may result in complete absence of the protein or functional impairment [8]. It's role in mitochondrial maintenance, actin polymerization, intracellular trafficking of the vesicles and lipid synthesis have been previously demonstrated [12]. Also, for ADHD symptoms, involvement of frontostriatal network is suggested to play an important role. This suggestion was further supported by various data from neuroimaging, neuropsychology, genetics and neurochemical studies [16]. However, the exact pathogenesis of chorea-acanthocytosis remains elusive.

Initially, patients may present with cognitive or psychiatric symptoms years before the neurological manifestations develop. These symptoms include depression, schizophrenia-like behaviors and compulsive disorders [3]. This usually leads to misdiagnosis and confounds the neurological manifestations [14]. Impaired memory or executive functions may be present. Personality changes, Tourettism and trichotillomania may also be seen [11].

For one third of the patients, the initial symptom is a seizure, typically generalized type 14. Mostly, the dominant movement disorder is chorea. Feeding dystoniais a bizarre and characteristic symptom of the disease [2]. This symptom occurs while eating. Contact of food and patient's tongue triggers spasm of the tongue and pushes the food out, as a result weight loss may be seen in patients [8,10]. Orfacial dystonia is also a common manifestation and may present as grimacing, involuntary vocalization and dysarthria as well as self-mutilating tongue and lip biting [2]. Another important presentation is 'Rubber man appearance'. This refers to truncal instability and sudden trunk spasms which may result in head banging and self-harm [9]. Rarely, Parkinsonism may be encountered in these patients [17].

Diagnosis of chorea-acanthocytosis is very challenging. Its early psychiatric symptoms generally leads physicians to wrong diagnosis and confound the neurological manifestations that develop later in the disease course [5]. Laboratory workups and imaging techniques may be helpful in the diagnosis. Serum Creatine Kinase levels are usually elevated in these patients [13]. Presence of acanthocytosis in peripheral blood smear may be a helpful diagnostic clue; however, presence or number of acanthocytes do not correlate with disease progression [18]. Thus, peripheral smear has very low sensitivity for the diagnosis. It is important to note that, non-existence of acanthocytes cannot rule out the disease [4]. In neuroimaging, caudate head atrophy and dilation of anterior horns of the lateral ventricles are seen with MRI13. Fluorodeoxyglucose -positron emission tomography (FDG-PET/CT) scan shows impaired glucose metabolism within the basal ganglia [17]. To confirm the diagnosis, western blot may be performed [8].

Our patient first presented with motor symptoms (choreiform movements) in her early 20s. Later in the course of disease, she developed forgetfulness, attention deficiency, orofacial dyskinesia and a tic disorder that is affecting her eyes. In psychiatric evaluation, she was diagnosed with ADHD.

Evaluation of this patient was complex and very demanding. Despite being a neurological disease, the initial symptoms may vary widely, and these patients may be evaluated in different departments even for years. Unrevealing the underlying disease may not be possible if the physician is not aware of the neuroacanthocytosis or includes it in the differential. To evaluate our patient properly, we needed a team including psychiatrist, hematologist and a neurologist. Patients, depending on their symptoms and severity, may present to any of these three specialties for initial evaluation. For this reason, multidisciplinary approach is very important to rule out other pathologies and include the neuroacanthocytosis in the differential diagnosis.

Conclusion

In this case report, we presented a rare case of acanthocytosis that presents with ADHD in the later stages of disease. We wanted to emphasize the importance of multidisciplinary care in the management of chorea-acanthocytosis.

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