Case Report / Olgu Sunumu

Considering Huntington's Disease and Neuroacanthocytosis in the Differential Diagnosis of Senile Chorea

Senil Kore Olgusu: Ayırıcı Tanıda Huntington Hastalığı ve Nöroakantositozun Yeri Nedir?

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Summary

Sporadic chorea that presents after the age of 50 years is called "senile chorea". Senile chorea is a rare entity with a wide differential diagnosis list. Causes of senile chorea include vascular and metabolic diseases, adverse events related to medications, hematologic and immune system diseases, genetic and sporadic neurodegenerative syndromes, and paraneoplastic disorders. Although the most common etiologies are vascular and metabolic disorders, neuroacanthocytosis, Wilson's and Huntington's disease are included in the differential diagnosis.

Herein, we discuss differential diagnosis and approach to late-onset chorea based on a patient whose clinical findings suggested chorea-acanthocytosis at first, but later revealed Huntington's disease after detailed laboratory studies.

Keywords: Chorea, senile chorea, Huntington's disease, chorea-acanthocytosis, neuroacanthocytosis

Öz

Elli yaş sonrasında ortaya çıkan sporadik kore "senil kore" adını almaktadır. Senil kore, nadir bir tablo olmasının yanı sıra geniş bir ayırıcı tanı yelpazesi içerir. Senil kore nedenleri arasında vasküler ve metabolik hastalıklar, ilaç yan etkileri, hematolojik ve immün sistem hastalıkları, genetik ve sporadik nörodejeneratif sendromlar ve paraneoplastik hastalıklar yer alır. Senil korenin en sık nedenleri vasküler ve metabolik hastalıklar olmakla birlikte, bu yaş grubunda nöroakantositoz, Wilson ve Huntington hastalıkları da ayırıcı tanıda mutlaka araştırılmalıdır. Bu yazıda, kliniğimize geç başlangıçlı kore ile başvurmuş, klinik özellikleri ilk olarak koreakantositozu düşündürmüş ancak ayırıcı tanı açısından yapılan ayrıntılı laboratuvar değerlendirmesinde Huntington hastalığı tanısı almış bir olgu temelinde ileri yaşta kore ayırıcı tanısı tartışılmaktadır.

Anahtar kelimeler: Kore, senil kore, Huntington hastalığı, kore-akantositoz, nöroakantositoz

Introduction

Chorea is frequently seen in childhood and puberty and adult onset is rare. Etiologic categorization depends on the age of onset. Sporadic chorea that presents after the age of 50 years is called "senile chorea" (1).

Causes of senile chorea include vascular and metabolic diseases, adverse events related to medications, hematologic diseases, immune system diseases, genetic and sporadic neurodegenerative syndromes, and paraneoplastic disorders (1,2). Although the most common etiologies are vascular and metabolic disorders, neuroacanthocytosis, Wilson's and Huntington's diseases are included in the differential diagnosis (3). Diagnosis of rare disorders in this age group requires specialized units and experience.

Herein, we discuss the differential diagnosis and approach to late-onset chorea based on a patient whose clinical findings suggested chorea-acanthocytosis at first, but later revealed Huntington's disease after detailed laboratory studies.

Case Report

A woman aged 65 years presented to our clinic with involuntary twisting movements that predominantly involved her face and perioral region, but also her arms and legs. It was learned that murmurs and lip smacking started five years ago and involuntary movements of right index finger were added, which then spread to her whole body. The patient was aware of these involuntary movements and was slightly uncomforable with them. There was no history of drug use, systemic disease, or infection prior to the starting of the involuntary movements. She had not taken any medication for the treatment of these movements.

The patients had no family history of movement disorders but it was learned that her mother and father died aged younger than 60 years of stomach cancer and Hodgkin's lymphoma, respectively. All members of the patient's extended family had died of stomach cancer or heart diseases, before reaching 60 years of age (Figure 1).

The neurologic examination showed impairment of orientation

Figure 1. Family tree of the patient; the pink spotted one represents the patient. It is shown that the patient's father and mother were cousins and many members of family died at early ages

in time; slowing of saccadic eye movements; difficulty in starting saccadic eye movements; hyperkinetic dysarthria with chorea; choreic movements of face, tongue, extremities, especially perioral region; involuntary vocalizations; increase in tendon reflexes; motor impersistence; orobuccal and vocal tics. The pyschiatric examination showed perseverations in thought content, obsession, and aggresion. The neuropsychologic test showed impairments of attention; sustained attention; registration process of verbal and visual memories; abstract thinking; inhibition of inappropriate answers and executive functions (failure to maintain a cognitive set, inefficient learning across stages of the test), which demonstrated severe cognitive deterioration. Her standardized mini-mental status examination score was 25/30. There were no findings of pathologic reflexes, paresis, apraxia, agnosia, or cerebellar dysfunction.

Neurodegenerative disorders including Huntington's disease; neuroacanthocytosis; Wilson's disease; and neurodegeneration with brain iron accumulation; tardive syndromes; and autoimmune, metabolic and paraneoplastic disorders were included in the differential diagnosis. Cranial magnetic resonance imaging (MRI) with contrast, peripheral blood smear, genetic testing for Huntington's disease, hemogram, biochemical measurements including lipid profile and creatinin kinase, ENA panel, hepatitis serology, VDRL-RPR, electroencephalography and eye examination were performed, and serum levels of tumour markers, antiphosfolipid antibodies, anti-HIV antibodies, anti-channel antibodies, anti-neuronal antibodies, vitamine B12 and heavy metals were measured.

All biochemical, microbiologic, neoplastic, autoimmune, and vasculitic serum markers were in normal ranges or negative.

There were no findings of Kayser-Fleischer ring and retinitis pigmentosa in the eye examination.

The electroencephalograph (EEG) recording showed moderate-high amplitude spike-multispike waves in the right frontal region, which tended to be generalized.

Cranial MRI showed global cerebral and cerebellar atrophy including nucleus caudatus. There was no sign of iron accumulation in the MRI (Figure 2).

Peripheral blood smears following standard EDTA blood and isotonic dilution showed acanthocytes. However, analysis of
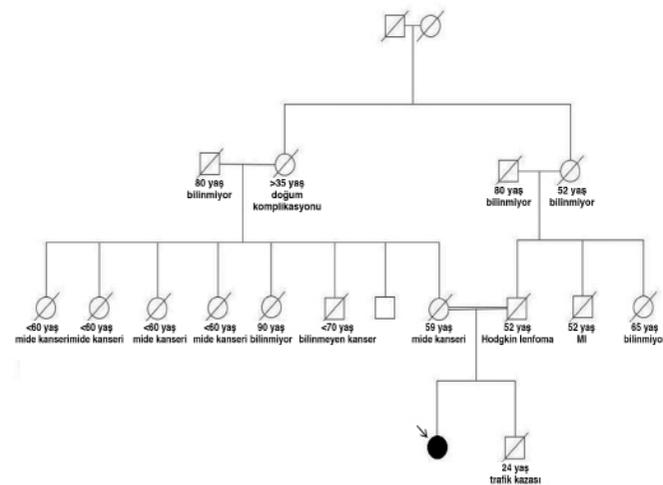
Table 1. Etiologic factors of focal and generalized chorea	
Senile Chorea	
Focal	**Generalized**
• Vascular • Metabolic • Drugs (antipsychotic drugs, metoclopramide) • Toxic • Infections (Lyme's disease, neurosyphyilis, viral encephalitis, cysticercosis, HIV infection and Creutzfeld-Jacob disease) • Neoplastic • Paraneoplastic (antibodies against CRMP5, ANNA-1, ANNA-2 and amphiphysin) • Autoimmune (SLE, AFAS, anti-NMDA) • Genetic (Huntington's disease, neuroacanthocytosis) • Degenerative	• Metabolic • Genetic (Huntington's disease, neuroacanthocytosis) • Degenerative • Paraneoplastic (antibodies against CRMP5, ANNA-1, ANNA-2 and amphiphysin) • Autoimmune (SLE, AFAS)

chorein protein in erythrocyte membranes was normal, which excluded the diagnosis of chorea acanthocytosis. The genetic test for Huntington's disease showed 44 repeated CAG trinucleotides in the Huntington gene. After the diagnosis of Huntington's disease was made, the peripheral blood smear was reevaluated and erytrocytes that had been previously reported as acanthocytes were reported as echinocytes (Figure 3).

Discussion

Although senile chorea is a rare disorder, there are many disorders in its differential diagnosis. Etiologic factors can be curable (vascular, infectious, and metabolic processes) and non-curable, such as neurodegenerative diseases (Table 1). We discuss the tests used for the differential diagnosis of senile chorea based on this patient.

In this patient age group, cerebrovascular diseases and metabolic disturbances are the most common causes of acute chorea. Chorea is typically focal in cerebrovascular diseases, especially in those that affect the lentiform nucleus and thalamus, which are the most common causes of hemichorea (4). Progression and generalization of chorea are not usually expected in cerebrovascular diseases. Our patient had progression of chorea over years and cranial MRI images revealed no vascular lesions.

Metabolic disturbances including hypo- and hyperglysemia and electrolyte disturbances can cause chorea. Non-ketotic hyperglycemia can be the first manifestation of diabetes mellitus, and can cause hemichorea and generalized chorea (5). Other metabolic disturbances that can cause chorea include hypernatremia, hyponatremia, hyperthyroidism, hypocalsemia,
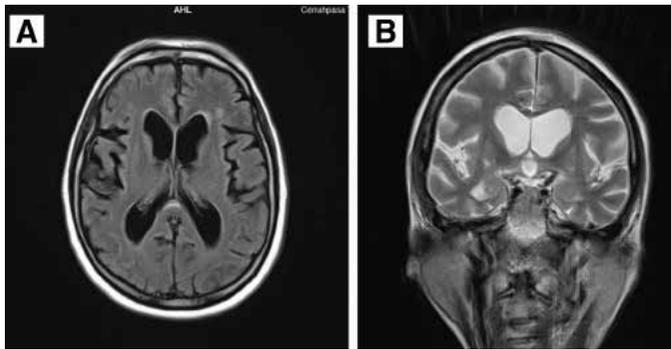

Figure 2. Global cerebral atrophy especially effecting the nucleus caudatus. A) Axial FLAIR magnetic resonance imaging (MRI) sequences, B) Coronal T2 magnetic resonance imaging sequences
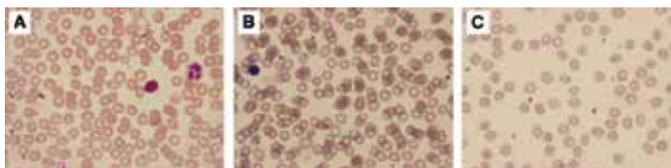

Figure 3. A) Standard blood smear, B) Provoked smear-basal, C) Provoked smear-after 30 minutes. Erythrocytes have normal morphologies in standard blood smear, whereasechinocytes cover the whole preparation in a provoked smearr

hypomagnesemia, hepatic encephalopathy, polycythemia vera, hyperparathyroidism, and hypoparathyroidism. After treatment of metabolic disturbances, chorea is expected to resolve. We found none of these metabolic disturbances in our patient.

One of the common causes of orobuccal dyskinesia in the elderly is drug use. Chorea commonly effects the orobuccal region but also chorea or other hypo- or hyperkinetic movement disorders can effect body and extremities with drug use (6,7). The most and second most common drugs that cause chorea are antipsychotic drugs and metoclopramide, respectively. Our patient did not use drugs and had no exposure to toxins that could cause chorea.

Infectious diseases including Lyme's disease, neurosyphylis, viral encephalitis, cycticercosis, HIV, and Creutzfeld-Jacob disease can also cause senile chorea (6). Our patient had no accompanying neurologic or systemic diseases. There were no biochemical and neuroimaging findings suggestive of infection. Although the patient had cognitive and phyciatric impairment, the relatively long duration of illness (5 years) and lack of cranial MRI and EEG disease findings made us exclude the diagnosis of prion diseases and thus we did not perform lumbar puncture.

Neoplastic diseases are also included in the differential diagnosis of chorea in this age. Primary brain tumours and brain metastases can cause chorea, which is usually focal. Chorea can also present as paraneoplastic effects of systemic cancers. Anti-CRMP5 antibodies, which are induced by small-cell lung cancer and tymoma, have been shown to cause chorea (8). Antibodies against ANNA-1, ANNA-2, amphiphysin, and other cancers including types of lung cancer, Hodgkin's and non-Hodgkin's lymphoma, chronic myeloid leukemia, colorectal adonecarcinoma, prostatic adenocarcinoma, tonsillar carcinoma, bladder cancer, breast cancer (adenocarcinoma type), pancreatic adenocarcinoma and gastric adenocarcinoma can cause chorea (9). Connective tissue diseases including systemic lupus erythematosus and antiphospholipid syndrome can cause chorea through distant autoimmune effects. Anti-NMDA receptor antibodies-induced autoimmune encephalitis can present with oro-facial-lingual dyskinesia (10). Long-duration disease, slow progress compared with neoplastic/autoimmune diseases, lack of accompanying neurologic, systemic, and laboratory findings made us exclude the diagnosis of these diseases. However, neoplastic diseases can present 5 years after the onset of chorea, hence research for cancer must be periodically performed in chorea with unknown cause, and in events of strong suspicion, positron emission tomography must be performed. We performed systemic and gynecologic examination, took radiologic images of the thorax, abdomen, and pelvis, and measurements of serum levels of paraneoplastic antibodies to exclude malignancy. All tests performed for malignancy in our patient were negative.

Genetic and degenerative disorders can also cause chorea in this age group. The lingual-facial-buccal dyskinesia, dysartria, vocalization, obsessive thought content, severe cognitive impairment, and EEG abnormalities in our patient suggested a diagnosis of chorea acanthocytosis and other neurodegenerative diseases. Existence of blood between patient's mother and father, family history, and acanthocytosis in the peripheral blood smear suggested diagnosis of autosomal recessive inherited chorea acanthocytosis in our patient.

Acanthocytes are contracted erytrocytes with thorny projections caused by defects in the cell membrane (Figure 4).

These defects cause impairment of membrane functions (anion transport and binding of membrane to the cytoskeleton) and clearance of old erythrocytes from the circulation, which results in acanthocytosis (11). It was first described as Bassen-Kornzweig sydrome (abetalipoproteinemia) in 1950, a lipoprotein metabolism disorder with neurologic symptoms (12). Critchley et al. (13) and Levine et al. (14) reported patients with neurologic symptoms whose serum lipoprotein levels were normal and this situation was then called "chorea acanthocytosis". Standard peripheral blood smears prepared with standard EDTA blood are easy to perform but can miss acanthocytes. A more sensitive and specific method the preparation of blood smears following isotonic dilution. In this method the blood sample is incubated in room temperature for 30-120 minutes following 1:1 dilution with 0.9% sodium chloride solution containing 10 units of heparin per one milliliter. Levomepromazine can be used for reversibility of acanthocyte formation. Dry blood smears prepared from these samples are investigated using a phase contrast microscope and can be combined with wet blood smears (15). Smears prepared with this method can induce echinocyte formation in normal erytrocytes but the degree of echinocyte formation differs from person to person. Hence, experienced physicians should evaluate blood smears to avoid false positivity. Negative results do not exclude diagnosis and repeat investigations are required.

Neuroacanthocytosis per se not a disease but a presentation of a heterogeneous group of diseases. This group includes chorea acanthocytosis, McLeod syndrome (MLS), Huntington's disease-like 2 syndrome (HDL-2), pantothenate kinase-associated neurodegeneration (PKAN), and diseases that result from disorders of lipid metabolism and other metabolic disorders (16,17,18). Heredodegenerative neuroacanthocytosis is in a rare group of diseases but it is possible that this condition is also frequently overlooked. It is thought that there are approximately a thousand patients with chorea acanthocytosis and a few hundred patients with MLS. PKAN is a relatively frequent condition, which has a prevelance of 3/1 000 000. To date, 50 families have been diagnosed with HDL-2 (18). Finding acanthocytes is important but not mandatory for diagnosis of neuroacanthocytosis. Acanthocytes may sometimes not be found at first but when disease progresses, it is expected to see acanthocytes. In typical cases, 10-30% of erytocytes become acanthocytes (3).

Acanthocytes can be seen with disorders of lipid metabolism including abetalipoproteinemia, familial hypobetalipoproteinemia, Anderson's disease, and Wolman's disease. Acanthocytes can also be seen with various diseases including severe malnutrition, cancers, thyroid diseases, liver diseases, after splenectomy, mitochondrial diseases, and psoriasis.

Echinocytes can be distinguished from acanthocytes by the shape of the projections, which are smaller and more numerous than in acanthocytes and are evenly spaced. Echinocytes also exhibit central pallor (Figure 4). Echinocytes are associated with severe anemia, uremia, defects of glycolytic enzymes, and malnutrition. The method used for preparation of smears or delay can cause echinocyte formation as an artefact, but in this scenario echinocytes cover the whole preparation (19). In our patient, as shown in Figure 3b, c, echinocytes cover the entire preparation. This finding can also be expected as a result of modification.

In our patient, age of presentation, sex of patient, and

normality of copper metabolism and lipid profile made us exclude the diagnosis of HDL-2, MLS, Wilson's disease, and disorders of lipoprotein metabolism, respectively.

Chorea acanthocytosis is an autosomal recessive disease caused by a mutation of VPS13A gene in chromosome 9 (20,21). Consanguinous marryiage is common in families of patients and disease may not be seen in past generations. Huntington's disease is an autosomal dominant disease, consequently a positive family history is common, but there is no family history of a neurophsyciatric disease in 12% of patients (22). In 30-50% of patients there is no family history of Huntington's disease (22,23,24), which is explained by adoption, loss of parents at early ages, number of CAG repeats and intermediate mutations, genetic heterogeneity, anticipation (from generation to generation, especially from father to child), and de novo mutations (24). In late-onset (≥60 years) Huntington's disease, 68% of patients have no family history of the disease, which is more common compared with patients with an expected age of onset (25). Usually these patients are the first to be diagnosed in their families. Furthermore, lying in hospital with pshyciatric symptoms and timidity can be seen in patients' families. According to these data, the negative family history of our patient can be explained by low CAG repeats and early deaths in the family.

As a result, senile chorea is a rare condition caused by vascular and metabolic diseases, adverse events related to medications, hematologic diseases, and diseases of the immune system, genetic and sporadic neurodegenerative syndromes, and paraneoplastic disorders (1,2). Diagnosis of this condition requires careful clinical and laboratory investigation, specialized units, and experience.

Relatively frequent diseases can present with typical presentations of rare diseases. In this context, Huntington's disease should be initially considered in the differential diagnosis of patients who present with chorea, despite an atypical clinical picture and negative family history.
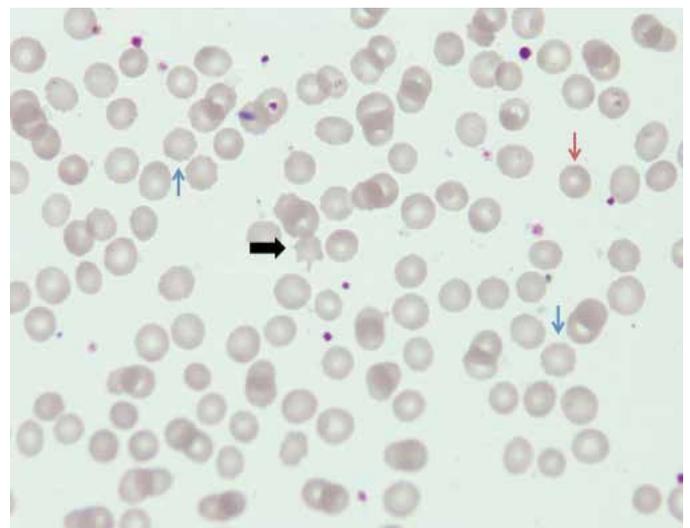

Figure 4. Erythrocytes with normal morphologies in blood smear (red and thin arrow), echinocytes (blue and thin arrow) and acanthocytes (black and thick arrow) are shown. (From archives of Prof. Zafer Başlar)

Informed Consent: Consent form was filled out by all participants. **Concept:** Fatoş Sibel Ertan, Ayşegül Gündüz, **Design:** Fatoş Sibel Ertan, Ayşegül Gündüz, **Data Collection or Processing:** Ayşe Deniz Elmalı, Ayşegül Gündüz, **Analysis or Interpretation:** Ayşegül Gündüz, Fatoş Sibel Ertan, Zafer Başlar, **Literature Search:** Ayşe Deniz Elmalı, Ayşegül Gündüz, Fatoş Sibel Ertan, Zafer Başlar, **Writing:** Ayşe Deniz Elmalı, Ayşegül Gündüz, Fatoş Sibel Ertan, Zafer Başlar, **Peer-review:** External and internal peer-reviewed. **Conflict of Interest:** No conflict of interest was declared by the authors. **Financial Disclosure:** The authors declared that this study has received no financial support.

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