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Short Communication

Neuroacanthocytosis: a case report of chorea-acanthocytosis

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Neuroacanthocytosis is a rare progressive neurodegenerative disease, including chorea-acanthocytosis, McLeod syndrome, Huntington's disease-like 2, and pantothenate kinase-associated neurodegeneration, where chorea-acanthocytosis occupies the main entity of this disease group. Here, a classic case of chorea-acanthocytosis is reported that exhibited gradually deteriorating abnormal movements of limbs and face, swallowing difficulty, and lip and cheek biting for the past two years. Peripheral blood smears revealed that 35% of the red blood cells were acanthocytes and electron microcopy scans clearly showed the morphology of acanthocytes. VPS13A gene sequencing found a heterozygous novel VPS13A gene mutation (c.80dupT). Brain magnetic resonance imaging scans showed moderate anterior horn dilation of lateral ventricles and bilateral atrophy of the head of caudate nucleus. Several suggestive features are summarized to provide diagnostic clues for chorea-acanthocytosis and facilitate future diagnosis and treatment.

Keywords

Neuroacanthocytosis; chorea-acanthocytosis; neurology; VPS13A gene mutations.

1. Introduction

Chorea-acanthocytosis (ChAc) is a rare, relentlessly progressive multisystem neurodegenerative disorder characterized by the presence of acanthocytes in peripheral blood smear, neurodegeneration of the basal ganglia (Walker et al., 2011) and marked by phenotypic heterogeneity (Ueno et al., 2001). Clinical manifestations of ChAc include progressive chorea, orofacial lingual dyskinesia, seizures, cognitive impairment, psychiatric symptoms, neuromuscular manifestation, elevated serum biochemical indicators and increased acanthocytes in peripheral blood (Govert and Schneider, 2013; Jung et al., 2011; Rampoldi et al., 2002).

ChAc occurs mainly in early adulthood between 20 to 40 years old, and rarely before age 20 or after age 50 (Walker et al., 2007). It is associated with vacuolar protein sorting 13 homolog A (VPS13A) gene mutations encoding the protein chorein (Rampoldi et al., 2002; Ueno et al., 2001). The differential diagnosis of ChAc includes McLeod syndrome (MLS), pantothenate kinase-associated neurodegeneration (PKAN), Huntington's disease-like 2 (HDL2), other forms of inherited chorea (such as Huntington's disease), other forms of Huntington-like disorders, other syndromes of neurodegeneration with brain iron accumulation (NBIAs), Wilson disease and acquired causes such as infection, immunization, drugs, etc. should also be considered. ChAc is rare, and current research is mainly from case reports and small case series. The number of published ChAc reports from China is relatively small but it is speculated that the incidence of ChAc in China may be underestimated (Liu et al., 2014; Shen et al., 2017). Here experience with a case of ChAc is reported, the importance of identifying such rare entities in light of the relevant literature is discussed and the neuroimaging, laboratory, genetic and protein features are discussed to facilitate future diagnosis and treatment.

2. Case history

The patient was a 28-year-old male with gradually deteriorating abnormal limb and face movement, swallowing difficulty due to uncontrolled tongue protrusion and lip and cheek biting for the previous two years. Some solid food was pushed into his throat with his fingers or chopsticks. The patient continuously held a roll of cloth in his mouth to absorb saliva and reduce the risk of lip and cheek biting. These symptoms became worse when tense and disappeared during sleep. The subject was born to nonconsanguineous parents and the father died of lung cancer. Further family history revealed no similar symptoms. Any long history of drug exposure, known to cause extrapyramidal dysfunction, was denied.

On neurological examination, the patient presented with generalized chorea, intermittent head drops with ballistic flexion of the neck, vague words, involuntary vocalizations, frequent suck-mimicking activities, and mild drooling. There were sporadic ulcers on the buccal mucosa and several cracks on the lips. When sitting unsupported, sudden involuntary forward flexions of the trunk and sudden loss of tone while walking could be observed.

The fundus was normal and there was diminished power (4/5) and reduced muscle tone in all four limbs. Tendon reflexes were

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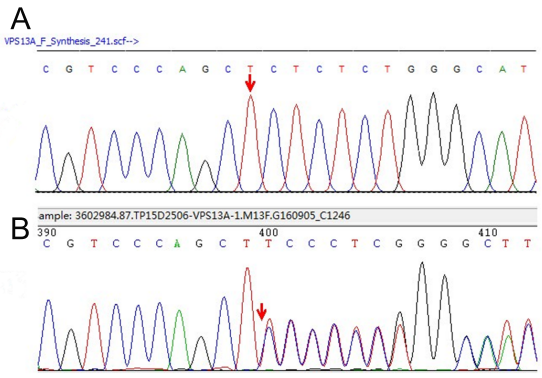

Figure 1. VPS13A gene sequence: (A) Reference sequence showed no abnormality in the VPS13A gene of c.80T locus, (B) while the genetic test found patient to be heterozygous for a novel VPS13A gene mutation (c.80dupT, arrow)

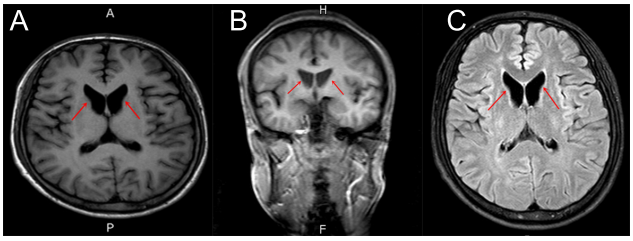

Figure 2. Magnetic resonance images showed bilateral atrophy of the head of caudate nucleus and anterior horn dilation of lateral ventricles (arrows). (A and B: T1 weighted image, C: Fluid attenuated inversion recovery image.)

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reduced in the arms and absent in the legs. Coordination and sensory examination were normal. Kayser–Fleischer (K-F) ring and autonomic dysfunction were absent. Memory function was mainly preserved and a Mini Mental State Examination score was 27/30.

The complete blood count, thyroid assessment, blood biochemistry and liver and renal function tests, HIV, hepatitis B antigen, hepatitis C, serum copper, ceruloplasmin, urine for organic acids, erythrocyte sedimentation rate, serum B12 levels, antinuclear antibody, double stranded DNA, tumor markers, coagulation function, cerebrospinal fluid tests, EEG, ECG, echocardiography, abdominal ultrasonography and chest radiograph were all within normal limits.

Total cholesterol was 2.78 mmol/L (normal: 3.6–6.2 mmol/L) and HDL-C and LDL-C were within normal range. Serum creatine kinase (CK), l-lactate dehydrogenase (LDH) and alpha hydroxybutyrate dehydrogenase (HBDH) levels were respectively increased to 453 U/L (normal: 50–310 U/L), 291.40 U/L (normal: 120–250 U/L) and 229.60 U/L (normal: 90–220 U/L). Electromyogra-phy showed multiple peripheral nerve injuries (motor and sensory fibers all damaged, mainly axonal injury).

Based on the available medical history, clinical features, neurological findings and laboratory biomedical findings, a diagnosis of ChAc was proposed. Peripheral blood smears with standard settings (Storch et al., 2005) were then performed, revealing that 35% of red blood cells were acanthocytes. Electron microcopy scans showed the shape of acanthocytes more clearly. Mutations of the VPS13A gene were sequenced using previously reported techniques (Dobson-Stone et al., 2002) and this procedure further confirmed the diagnosis. The patient was found to be heterozygous for a novel VPS13A gene mutation (c.80dupT, Fig. 1). Additionally, genetic testing was negative for Huntington's disease, dentatorubral-pallidoluysian atrophy (DRPLA) and spinocerebellar ataxia type 17 (SCA17).

Brain magnetic resonance imaging (MRI) scans showed moderate anterior horn dilation of the lateral ventricles and bilateral atrophy of the head of caudate nucleus (Fig. 2).

In conclusion, the patient was diagnosed with ChAc based on the clinical, laboratory, neuroimaging and especially the genetic findings. He was prescribed haloperidol (2 mg three times a day) and clonazepam (2 mg three times a day) with no side effects other than some daytime sleepiness. However, he responded poorly to these drugs and orofacial dyskinesia and feeding dystonia was unimproved with the exception of partial relief of chorea. Subsequently, other medications was tried, but with limited results. During a two-year follow-up his condition gradually deteriorated.

3. Discussion

3.1 Neuroimaging and neuropathological features

The imaging findings of ChAc strongly resemble those of Huntington's disease and other neurodegenerative choreas (Walker et al., 2007; Walker, 2015). Neuroimaging includes bilateral caudate nucleus atrophy with or without T2 hyperintensity in the putamen (Katsube et al., 2009), while the head of the caudate nucleus is the most vulnerable region (Ishida et al., 2009; Walterfang et al., 2008). Cortical atrophy has also been reported, but to a much lower degree (Walker et al., 2007; Walker, 2015), while cerebellar atrophy has been very rarely described (Katsube et al., 2009; Sharma et al., 2014). Other observations, such as iron deposits in the striatum and globus pallidus, have occasionally been reported (Kaul et al., 2013; Lee et al., 2011), but their significance is unclear.

Given the importance of the caudate nucleus in ChAc, several neuroimaging studies have been conducted. By means of voxel-based morphometry two studies have confirmed volume reduction in caudate nucleus and putamen (Henkel et al., 2006; Huppertz et al., 2008). Subsequently, with the help of a non-parametric spherical harmonic technique, Walterfang et al. (2011) confirmed morphometric changes, especially of the caudate nucleus but also in the putamen.

Significant hypometabolism in bilateral caudate nuclei and putamen has been shown by ^{18}F-FDG PET brain scans (Cui et al., 2015; Selcuk et al., 2010), even prior to evident structural change (Lopez-Mora et al., 2018). Such results indicate that these advanced MRI techniques could be promising diagnostic indicators in future clinical applications.

Regrettably, some patients only complete structural imaging studies. Multimodal image studies should be applied in the future to analyze structural and functional changes in ChAc. Even diffusion tensor imaging could be applied to perform non-invasive detection of white matter changes in ChAc patients, as investigators have in models of Huntington's disease (Gatto et al., 2019).

On neuropathologic examination, there is often significant neu-

ronal loss and gliosis, especially in the caudate nucleus and to a lesser extent in the putamen, globus pallidus and substantia nigra (Ishida et al., 2009; Miki et al., 2010; Rinne et al., 1994).

3.2 Laboratory tests

Serum biochemical studies have shown that most patients with ChAc have elevated CK, LDH and HBDH and may present with signs of subclinical myopathy preceding the onset of neurological symptoms (Lossos et al., 2005; Walker, 2015). Elevated serum CK levels occur mostly in cases of ChAc and MLS (Danek et al., 2005; Walker et al., 2007; Walker, 2015), but not in HDL2, PKAN and Huntington's disease, thus making CK a specific diagnostic indicator (Liu et al., 2014).

Acanthocyte detection in peripheral blood smear has been shown to be helpful for diagnosis of neuroacanthocytosis (NA) syndromes, especially ChAc and MLS, but findings are sometimes inconsistent (Sorrentino et al., 1999). The number of acanthocytes in the blood of ChAc and MLS individuals is variable, usually ranging from 5–50% of red blood cells in ChAc, and from 8-30% in MLS (Jung et al., 2011). Acanthocytes may only appear late in the disease course (Sorrentino et al., 1999) and may occasionally be detected in other diseases, such as mitochondrial diseases and metabolic disorders. Therefore, their presence should not be relied upon to diagnose ChAc or MLS. Additionally, the diagnosis of NA syndromes cannot be ruled out merely by absence of acanthocyte (Bayreuther et al., 2010) as there are also cases where no acanthocytes may be detected (Bayreuther et al., 2010; Danek et al., 2001; Sorrentino et al., 1999; Walker, 2015). The efficiency of acanthocyte detection depends to a large extent on several specific endogenous factors and blood sample processing methods, thus conducting a study in a standard manner (Storch et al., 2005) and repeating a test several times in highly suspicious cases may improve the positive rate of detection. Scanning electron microscopy is the most reliable morphological diagnostic method for acanthocytes, but it is not yet popular. Fortunately, we have successfully detected acanthocytes in peripheral blood smears and observed their morphological changes by scanning electron microscopy.

3.3 Genetic and protein discoveries

VPS13A, located on chromosome 9q21 and composed of 73 exons (Danek and Walker, 2005; Velayos-Baeza et al., 2004; Walker et al., 2012) is currently the only known pathogenic gene associated with ChAc (Walker et al., 2007, 2012). It was simultaneously identified in two laboratories (Ueno et al., 2001; Rampoldi et al., 2001), and the encoded protein was named "chorein" (Ueno et al., 2001).

According to previous reports, the inheritance patterns of ChAc include autosomal recessive (predominant pattern (Danek et al., 2012)) and autosomal dominant and X-linked recessive inheritance patterns (Dobson-Stone et al., 2002; Ueno et al., 2001), with different degree of penetrance in different patients or families (Saiki et al., 2003; Walker et al., 2007). According to the literature, there is no clear genotype-phenotype correlation and there may be significant differences in the clinical manifestations of affected family members (Bohlega et al., 2003; Karkheiran et al., 2012; Lossos et al., 2005; Ruiz-Sandoval et al., 2007).

Reported VPS13A mutation patterns include missense, nonsense, frameshift, splice site, duplication and deletion mutations (Dobson-Stone et al., 2002; Velayos-Baeza et al., 2004). These mutations have been reported to eliminate or severely degrade chorein expression (Dobson-Stone et al., 2004).

Chorein is widely expressed (Kurano et al., 2007), mainly in the brain and red blood cells, but it is absent or significantly reduced in tissues of ChAc patients (Dobson-Stone et al., 2004). It is involved in the intracellular trafficking of many transmembrane proteins seems to be involved in the polymerization of actin, so its dysfunction may lead to cell membrane rupture and abnormal red blood cell shapes (Foller et al., 2012; Shiokawa et al., 2013).

Confirmatory DNA analysis of the VPS13A gene is challenging because of the large size of the gene and the heterogeneity of mutation sites (Allen et al., 1961; Jung et al., 2011; Marsh et al., 1981; Walker, 2015). However, deletion or remarkable reduction of chorein in erythrocytes can be demonstrated in Western blots (Dobson-Stone et al., 2004; Velayos-Baeza et al., 2004). Detection of chorein can be an alternative to genetic tests (Dobson-Stone et al., 2004; Velayos-Baeza et al., 2004; Walker et al., 2007).

The patient described here was a sporadic case with no family history and likely had an autosomal recessive inheritance pattern. However, he was found to only be a heterozygote of the novel VPS13A gene mutation (c.80dupT). It was unclear whether there were any abnormalities such as small fragment deletions that had not been detected in another chromosome. His father was dead and the genetic testing of his mother was not ever completed. Additionally, testing for chorein was not available, which could be a limitation of this study. However, Walker (2015) concluded that clinical and inheritance features may permit a reasonable accuracy in making a diagnosis in the absence of definitive testing. Here, close step by step differential diagnoses ruled out other diagnoses to leave MLS as the disease most needing to be differentiated. Clinically, the patient reported here was adult-onset with the presence of orofacial dyskinesia, feeding dystonia with tongue protrusion, self-mutilation with lip and cheek biting, absence of predominant cardiovascular manifestation and presence of 35% erythrocytes as acanthocytes on peripheral blood smears, which together preferentially supported a diagnosis of ChAc, rather than MLS, although mutations of the XK gene or Kell antigen expression were not checked.

3.4 Treatment and prognosis

Currently, there are no curative or disease-modifying treatments for ChAc and all therapeutic approaches are purely symptomatic due to the heterogeneous phenotype and ambiguous pathophysiology of the disease. It has been reported that levodopa can reduce dystonia (Kobal et al., 2014), and botulinum toxin may be helpful for orofacial dystonia (Miquel et al., 2013; Schneider et al., 2006). Deep brain stimulation has increasingly been adopted as a potential treatment and the globus pallidus internus has been reported the most common surgical target, especially for hyperkinetic movement difficult to treat with medication (Fernandez-Pajarin et al., 2016; Liu et al., 2018; Wang et al., 2019).

Timely identification of treatable complications such as seizure and swallowing are especially important. Epilepsy usually responds well to conventional anticonvulsants, however, drug-refractory epilepsy is also present. It has been reported that levetiracetam can reduce truncal tics (Lin et al. , 2006).

The treatment of psychiatric symptoms is often very challeng-

ing. Dopamine antagonists or depleters such as clozapine or tetrabenazine may be helpful.

The management of self-mutilation can be very challenging. Some patients have all of their teeth removed, while others learn to use mechanical devices such as sticks or towels to reduce biting.

4. Conclusions

Several suggestive features and clues for diagnosis of ChAc are summarized, ranging over clinical features, neuroimaging characteristics, laboratory tests and genetic (or protein) discoveries: (1) clinical features: self-mutilation and feeding dystonia, (2) neuroimaging characteristics: caudate nucleus head atrophy and anterior horn dilation of lateral ventricles, (3) laboratory tests: elevation of serum CK and detection of acanthocytes, (4) genetic discoveries: VPS13A gene mutations and (5) protein discoveries: absence or marked reduction of chorein in erythrocytes.

Authors' Contributions

YYX and JWW designed the research study, consulted the literature and wrote the manuscript. SL collected clinical data of the patient. XHL, JFL, QJS, YC and YFD reviewed and edited the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Shandong Provincial Hospital Affiliated to Shandong University. A written informed consent for publication of case details and pictures was obtained from the patient and his mother prior to the study.

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Conflict of Interest

The authors declare no competing interests.

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