Two Case Reports of Chorea-acanthocytosis and Review of Literature

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Case report

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Abstract

Background: Chorea-acanthocytosis (ChAc), as the most common subtype of neuroacanthocytosis syndrome, is characterized by the presence of acanthocytes and neurological symptoms. It is thought to be caused by the VPS13A (vacuolar protein sorting-associated protein 13A) mutations. This article reports two confirmed cases of ChAc and summarizes some suggestive features, which provide direction for the diagnosis and treatment of acanthocytosis in the future.

Case presentation: Here, we present two cases of ChAc diagnosed based on typical clinical symptoms, neuroimaging features, genetic findings of VPS13A, and response to the symptomatic treatment.

Conclusions: Chorea-acanthocytosis is a rare neurodegenerative disease with various early clinical manifestations. The final diagnosis of the ChAc can be established by either genetic analysis or protein expression by Western blotting. Supportive treatments and nursing are helpful to improve the quality of the patient's life. Nevertheless, it is imperative to investigate the impact of neuroimaging and neuropathological diagnosis in a larger group of ChAc in future studies.

Background

Chorea-acanthocytosis (ChAc) is a rare genetic disease caused by loss-of-function-mutation of the vacuolar protein sorting-associated protein 13A (*VPS13A*) which is an encoding gene of the protein chorein(1, 2). The ChAc mainly occurs in adulthood with an average age of about 35 years, and rarely occurs before the age of 20 years or after the age of 50 years (3). Clinical manifestations of ChAc include progressive chorea, orofacial lingual dyskinesia, seizures, cognitive impairment, psychiatric symptoms, and neuromuscular manifestations with elevated serum biochemical indicators and increased acanthocytes in peripheral blood (1, 4, 5). Neuroimaging showed atrophy of the caudate nucleus and decreased glucose uptake in the corpus striatum in the basal ganglia of the brain (6).

The diagnosis of ChAc is mainly based on clinical manifestations and laboratory findings of increased acanthocytes in peripheral blood, as well as the exclusion of other diseases that present similar clinical features. In recent years, molecular neuroimaging and genetic testing have played an increasingly important role in the diagnosis of ChAc. 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 conditions caused by infection, immunization, drugs, etc. Currently, the treatment of ChAc is limited, mainly drugs and deep brain stimulation (DBS) are used to relieve its symptoms.

The incidence of ChAc is very low and the current knowledge about the disease is mainly based on the small number of case reports. There is no systematic review exploring the pathogenesis, clinical manifestations, imaging characteristics, and management of ChAc in the literature to the best of our knowledge. To improve the understanding of this unique congenital disease, this paper reports two cases

of ChAc and discusses its clinical manifestations and the pattern of the genetic cause by analyzing laboratory findings, imaging reports, and relevant literature.

Case Presentation

Case 1

A 45-year-old female has been suffering from abnormal limb-face movement, uncontrolled frequent nictation, and lip biting during the last four months. These symptoms worsened during stress and disappeared during sleep. The patient had a history of induced abortion 4 months ago. The patient had frequent oral ulcers when she was overworked, which healed in a few days without any systematic treatment. The subject was born to non-consanguineous parents. The family history did not show similar conditions, and there was no history of drug exposure that would have caused extrapyramidal dysfunction symptoms.

A neurological physical examination showed chorea, head drops, tongue-lip biting, orofaciolingual dyskinesias, slurred speech with vague words, 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 were observed. The muscle strength of the extremities was normal, and the muscle tension was reduced. Tendon reflexes were reduced, and sensory response and autonomic nerve function were normal. There was no Kayser-Fleischer (K-F) ring in both corneas. The advanced cognitive function was hardly impaired, and a mini-mental state examination (MMSE) score was 28/30.

On blood, urine, and stool examinations, liver function, renal function, humoral immune function, tumor markers, lupus anticoagulant, erythrocyte sedimentation rate, coagulation function, rheumatoid factor, glycosylated hemoglobin, serum B12 levels, folic acid levels, serum copper, ceruloplasmin, and autoantibody were normal. Electrocardiography, echocardiography, abdominal ultrasonography, and chest radiograph were normal. Abnormal cell findings were as follows: spinous red blood cells accounted for 15.0%; Blood biochemistries were as follows: 61.11 g/L total protein (normal: 65-85 g/L), 36.51 g/L albumin (normal: 40-55 g/L), 280 U/L creatine kinase (normal: 40-200 U/L), 917 mg/L lipoprotein (normal: 0-300 mg/L), 10.96 g/L apolipoprotein A (normal: 1-1.6g/L), and 1.16 g / L apolipoprotein B (normal: 0.6-1.1 g/L). Brain magnetic resonance imaging (MRI) scans showed moderate anterior horn dilation of the lateral ventricles and bilateral atrophy of the caudate nucleus in the brain (Fig. 1A-C). EEG revealed mild abnormal electroencephalogram recording (Fig. 2). On genetic testing, a hemizygotic mutation was found in the exon 13-44 of the *VPS13A* gene: c.4063C > T (cytosine > thymine) (Fig. 3A); a heterozygous deletion variant in the exons 13-44 of the *VPS13A* gene (Fig 5).

The patient was prescribed idebenone, tiapride, clonazepam, mecobalamin, vitamin E, and vitamin B1. Later, based on the patient's medical history, clinical manifestations, neurological examinations, cranial MRI, and genetic test, the patient was diagnosed with ChAc and took clonazepam regularly. During the follow-up period, her condition gradually improved. The frequency and amplitude of involuntary movements of limbs were alleviated compared with the initial manifestation. Tongue biting

movements and slurred speech dramatically improved than before and no support was required to sit up normally.

Case 2

The patient was a 33 year old female who developed drooling after fatigue three years ago. Two years ago, her symptoms worsened and consisted of involuntary movements of the tongue and limbs, writing jitters, and clumsy fine movements. Dysphagia and lower limb weakness occurred 2 months ago, however, which did not affect her daily life. It was self-reported that taking tiapride, clonazepam, sertraline did not improve the symptoms. There was no family history of this neurological disorder and the patient was not exposed to drugs causing extrapyramidal dysfunction symptoms.

A neurological examination showed systemic chorea characterized by involuntary movement of limbs and tongue. There were sporadic ulcers on the buccal mucosa and several cracks on the lips. The muscle strength of the extremities was normal, and the muscle tension was reduced. Tendon reflexes were not elicited. Coordination function, sensory response, and autonomic nerve function were all normal. There was no K-F ring in both corneas of the eyes. The advanced cognitive function was almost unimpaired, and an MMSE score was 27/30.

There was no abnormal cell finding. Biochemical findings: 488 μmol/L uric acid (normal: 149-368 μmol/L), 1015 U/L creatine kinase (normal: 40-200 U/L), and 283 U/L lactate dehydrogenase (normal: 120-250 U/L). MRI of the brain showed moderate anterior horn dilation of the lateral ventricles and bilateral atrophy of the caudate nucleus (fig.1 D-F). EEG: Mild abnormal electroencephalogram recording (Fig. 4). Genetic testing: Two heterozygous mutations were found in the exon region of the *VPS13A*: c.4321_4322insA and C.2833A > T (adenine > thymine) (Fig. 3 B, C). The results of the remaining auxiliary examination items were similar to those of the previous subject and were normal.

Based on the patient's medical history, clinical manifestations, neurological examination, cranial MRI findings, and genetic testing results, the diagnosis was confirmed as ChAc. She was prescribed clonazepam, thiamine, mecobalamin, and vitamin B1. After a year and a half of follow-up, she was aware of her condition that gradually improved, especially the symptoms of drooling and involuntary shaking.

Discussion And Conclusions

In this study, we present two cases of ChAc diagnosed based on clinical symptoms, neuroimaging features, genetic findings of *VPS13A*, and response to the symptomatic treatment.

Genetic features

The ChAc is a rare autosomal recessive inherited neurological disorder (7) caused by *VPS13A* mutation (3, 8). The total length of the gene is about 250kb, which is composed of 73 exons (8-10). *VPS13A* is precisely located in two laboratories (2, 11), and the encoded protein is named "chorein". The types of *VPS13A* mutations include missense, nonsense, frameshift, splice site, replication, and deletion

mutations (10, 12). These mutations have been reported to eliminate or severely alter chorein expression (13). The chorein is expressed in several tissues (14), especially in the brain tissue and red blood cells, but the expression is absent or severely down-regulated in the tissues of ChAc patients (13). The absence of chorein or significant reduction of chorein protein level can be shown using Western blots (13). The DNA analysis of the *VPS13A* gene is difficult due to the size of the *VPS13A* gene and the heterogeneity of mutation sites (15), and therefore, chorein protein detection may be the only promising option to detect the altered gene expression. The morphology of erythrocytes is maintained by membrane lipids, proteins, and spectrin-actin cytoskeleton. Chorein protein involves in the intracellular transport by many transmembrane proteins and affects actin polymerization (16). Further, VPS13A participates in regulating the level of PtdIns phosphorylation on the plasma membrane of the erythrocytes (17). The level of PtdIns (4)P regulates the interaction between the plasma membrane and cytoskeleton, and the altered expression of VPS13A results in the destruction of the cell membrane and abnormal morphology of red blood cells (18).

These patients presented in this report were two sporadic cases with no family history of this neurological condition and likely had an autosomal recessive inheritance pattern. In this study, a heterozygous mutation, and a heterozygous deletion variant in exons 13-44 of the *VPS13A* gene were found in patient 1 (c.4063C >T), while two heterozygous mutations in the exon region were found in patient 2 (c.4321-4322insA and c.2833A>T). In general, the mutations in these patients may probably give rise to premature translation termination, nonsense-mediated mRNA decay (NMD) pathway induced *VPS13A*-mRNA degradation (19), abnormal spliceosome formation, and production of aberrant chorein, which can genetically contribute to the pathogenesis of ChAc. The deletion of exon 13-44 of the *VPS13A* gene has not been reported. If the mutation c.4063c > T and deletion mutation are pathogenic, it will theoretically explain the pathogenesis of ChAc in patient 1. Since patient 1 had a history of induced abortion before the onset of the disease, we can conclude that the conditions such as exertion, agitation, stringent state (e.g., childbirth and miscarriage), and malnutrition can accelerate the progression. Parents did not have a genetic test because of the expenses and the absence of the genetic result is the limitation of this study.

Clinical features

The clinical manifestations of ChAc are diverse, and there is no common diagnostic standard. Progression of clinical symptoms such as chorea, orofaciolingual dyskinesias (involuntary movements of eyes, mouth, tongue including vocalization), limb or facial dystonia, and sometimes parkinsonism is the main clinical characteristic (15). Perioral chorea, head drops, and writing jitter were the concrete manifestations of the hyperkinetic movements in both patients. Several reports have shown that tongue and lip biting is suggestive indicators of ChAc (3, 20).

Seizure, neuropathy, cognitive-mental disorder, and dilated cardiomyopathy are also relatively common manifestations of ChAc (15). In some patients, the disorder begins with the above atypical symptoms, and it challenges making a definitive early diagnosis (21). It has been speculated that about 42% of

patients have at least one seizure attack in the middle stage or the late stage of the disease (1). Most of the seizures are antiepileptic drugs (AEDs)-sensitive generalized tonic-clonic seizures (GTCS), which mainly result from the abnormal discharges in the temporal lobe (22). Connolly et al. (23)found that there was a significant loss of parvalbumin-positive intermediate neurons in the cerebral cortex and striatum in the ChAc patients experiencing epilepsy. Cognitive-mental disorders are mainly characterized by emotional instability, apathy, anxiety, depression, and mania. About half of the patients have mild to moderate mental disorders. The cognitive function of both patients evaluated by the MMSE scale was still normal, and the patients may have been in the early clinical course.

Elevated serum creatine kinase is also a useful diagnostic marker, which may be used as a sign of subclinical myopathy before the onset of clinical neurological symptoms (15, 24). Muscle atrophy was common. Electromyography showed neurogenic atrophy of the muscles. Biopsy showed inclusion bodies in myocytes. Rhabdomyolysis is seldom seen. Elevated serum CK levels occur mostly in cases of ChAc (15). The acanthocyte in a peripheral blood smear is higher than 3%, usually 5-50% in ChAc (5), which has a definite diagnostic significance, but negative spinous cells can’t be ruled out (15, 25). The scanning electron microscope is the most reliable tool for finding morphological features of acanthocytes, but it is not frequently used at present. We have successfully identified acanthocytes in peripheral blood smears in patient 1.

MRI of the brain showed atrophy of the caudate nucleus and decreased glucose absorption in the striatum (26), which indicates that advanced MRI technology may become a promising diagnostic tool for clinical management in the future. Neuropathological examination showed neuron loss and glial hyperplasia in the putamen, globus pallidus, and substantia nigra, and these changes were more obvious in the caudate nucleus (27). The MRI of both patients showed dilated anterior horn of the lateral ventricle and atrophy of the caudate nucleus.

Case management

Currently, there is no effective primary treatment for the ChAc and symptomatic supportive treatments are adopted. Involuntary movement can be treated with dopamine antagonists or consumptive agents such as thiacloprid and clozapine. L-dopa can alleviate dystonia (28), and focal botulinum toxin injection is one treatment modality for the typical orofacial dystonia of ChAc patients (29). The use of surgical interventions in ChAc has made substantial progress in recent decades. Deep brain stimulation is gradually adopted as a potential treatment, many of which have reported globus pallidus internus (GPi) as the surgical target. The DBS is more effective for patients with drug-refractory involuntary movement (30). Epilepsy can be treated with valproate and levetiracetam (31). The treatment of epilepsy in patients with chuck is a challenge because the symptoms of epilepsy in these patients are difficult to control. Besides, some antiepileptic drugs can aggravate chorea. A large dose of vitamin E can change the fluidity of the erythrocyte membrane and lessen the symptoms. It is also necessary to manage patients' self-mutilation behaviors, such as pulling out teeth or biting sticks, towels, and other items. According to relevant literature reports (32), the course of ChAc is 12~20 years, and the longest survival period is 40

years. Generally, the prognosis of this disease is poor, and most of the patients died of aspiration pneumonia and severe malnutrition.

In conclusion, Chorea-acanthocytosis is a rare neurodegenerative disease with various early clinical manifestations. When the triad of orofacial dyskinesia, epileptic seizures, and elevated creatine kinase, neuro-physicians should be alerted to the diagnosis of ChAc. The final diagnosis of the ChAc can be established by either genetic analysis or protein expression by Western blotting. Supportive treatments and nursing are helpful to improve the quality of the patient's life. Nevertheless, it is imperative to investigate the impact of neuroimaging and neuropathological diagnosis in a larger group of ChAc in future studies.

List Of Abbreviations

Erythrocyte Sedimentation Rate: ESR

Electrocardiograph: EEG

Magnetic Resonance Imaging: MRI

Generalized Tonic-Clonic Seizure: GTCS

Antiepileptic Drugs: AEDs

Mini-mental State Examination: MMSE

Kayser-Fleischer: K-F

Declarations

Competing interests

There are no conflicts of interest or financial ties to disclose.

Authors' contributions

SFH and JLZ followed the patient clinically and were responsible for initial manuscript writing. MLT, YDL, and LYX reviewed the literature. ZGL was responsible for the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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Availability of data and materials

The datasets for this article are not publicly available due to concerns regarding participant/patient anonymity. Requests to access the datasets should be directed to the corresponding author.

Ethics approval and consent to participate: All clinical diagnoses and treatments in this article were in accordance with China's national guidelines for diagnosis and treatment and in compliance with the requirements of the Hospital Ethics Committee.

Consent for publication: The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

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Figures

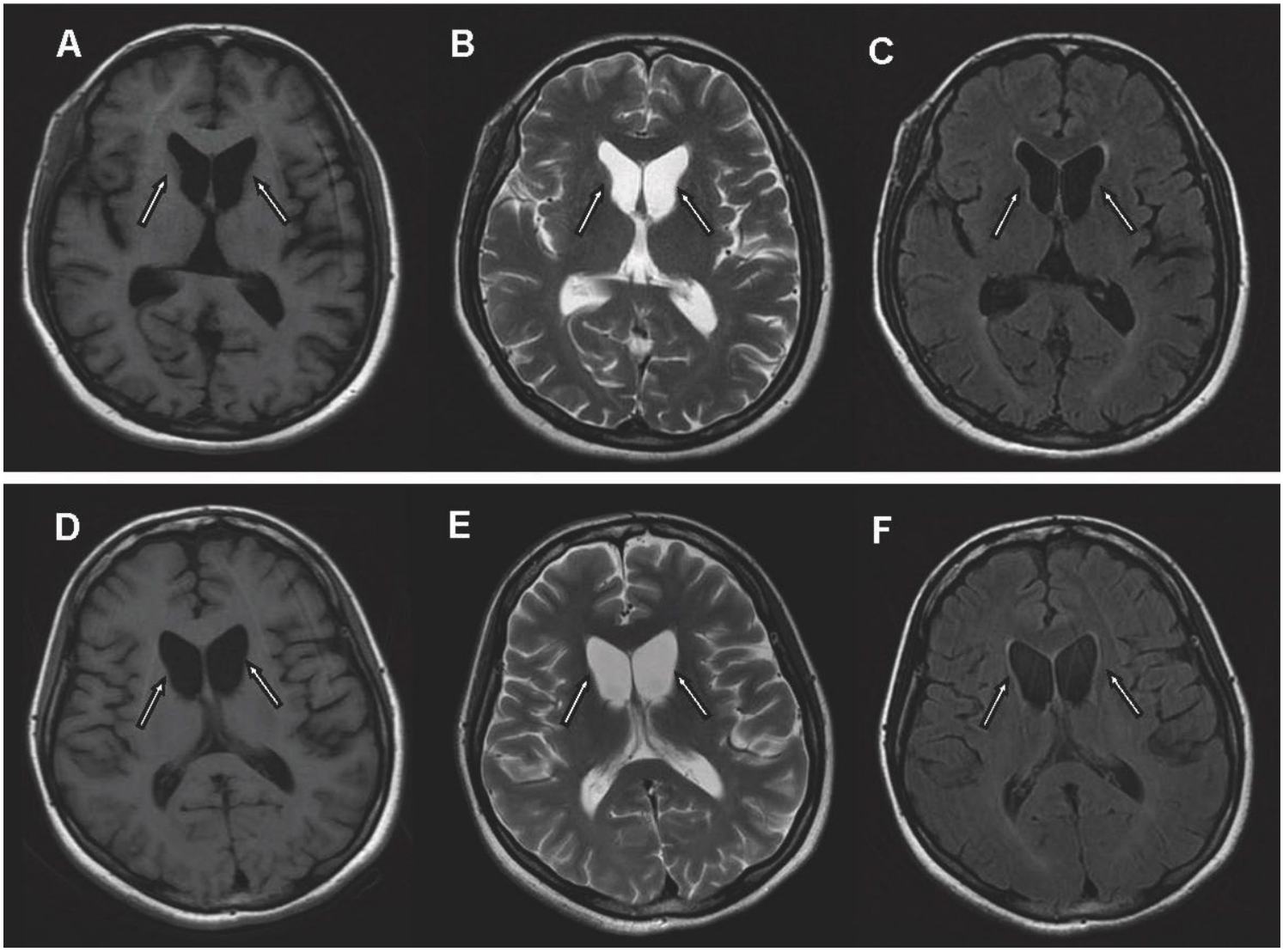

Figure 1

Magnetic resonance images show bilateral atrophy of the head of the caudate nucleus and anterior horn dilation of lateral ventricles (arrows). (A and D: T1 weighted image, B and E: T2 weighted image, C and F: Fluid attenuated inversion recovery image, A, B and C of patient 1, D, E and F of patient 2)

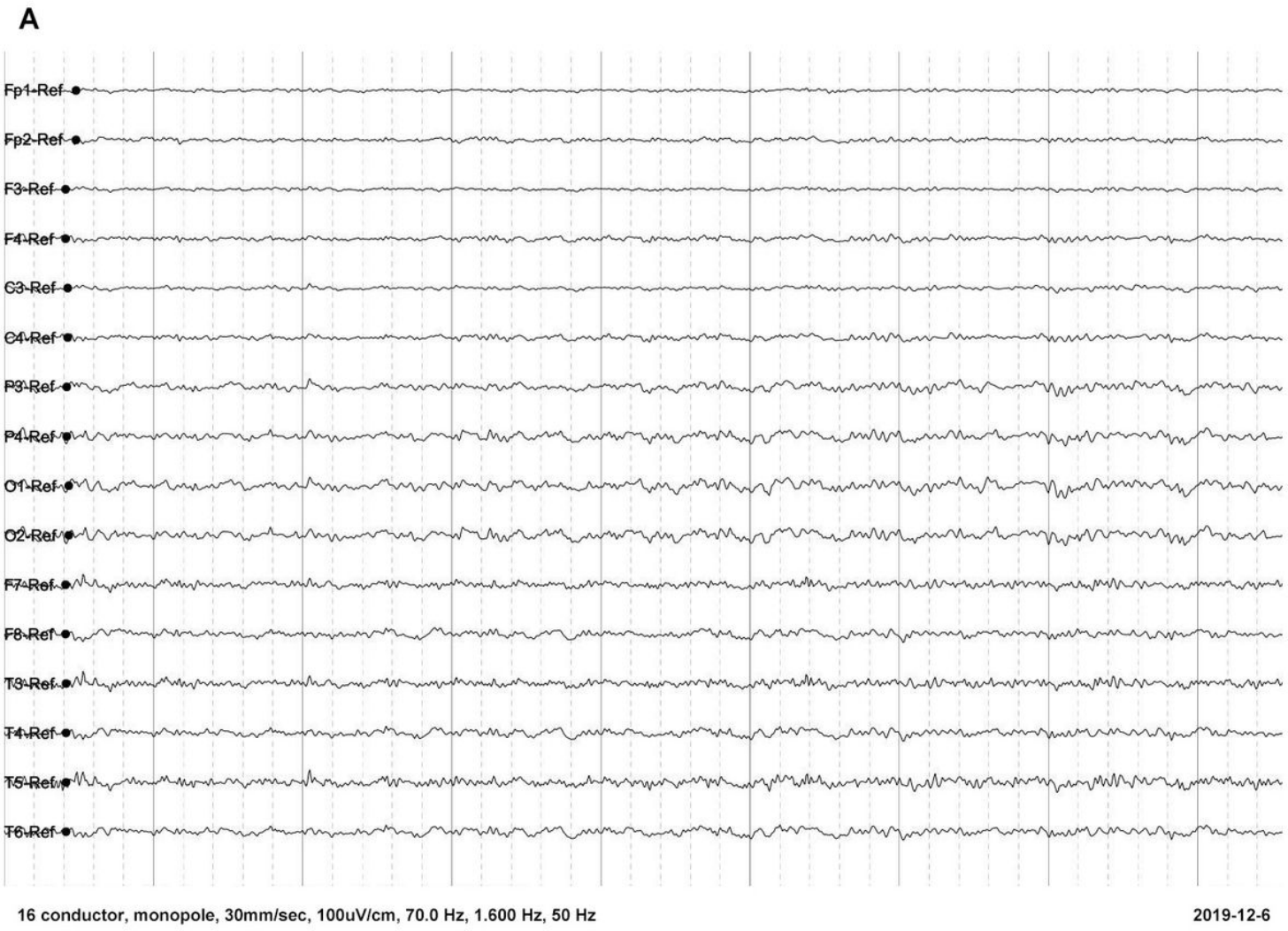

Figure 2

Electroencephalogram of the patient 1.

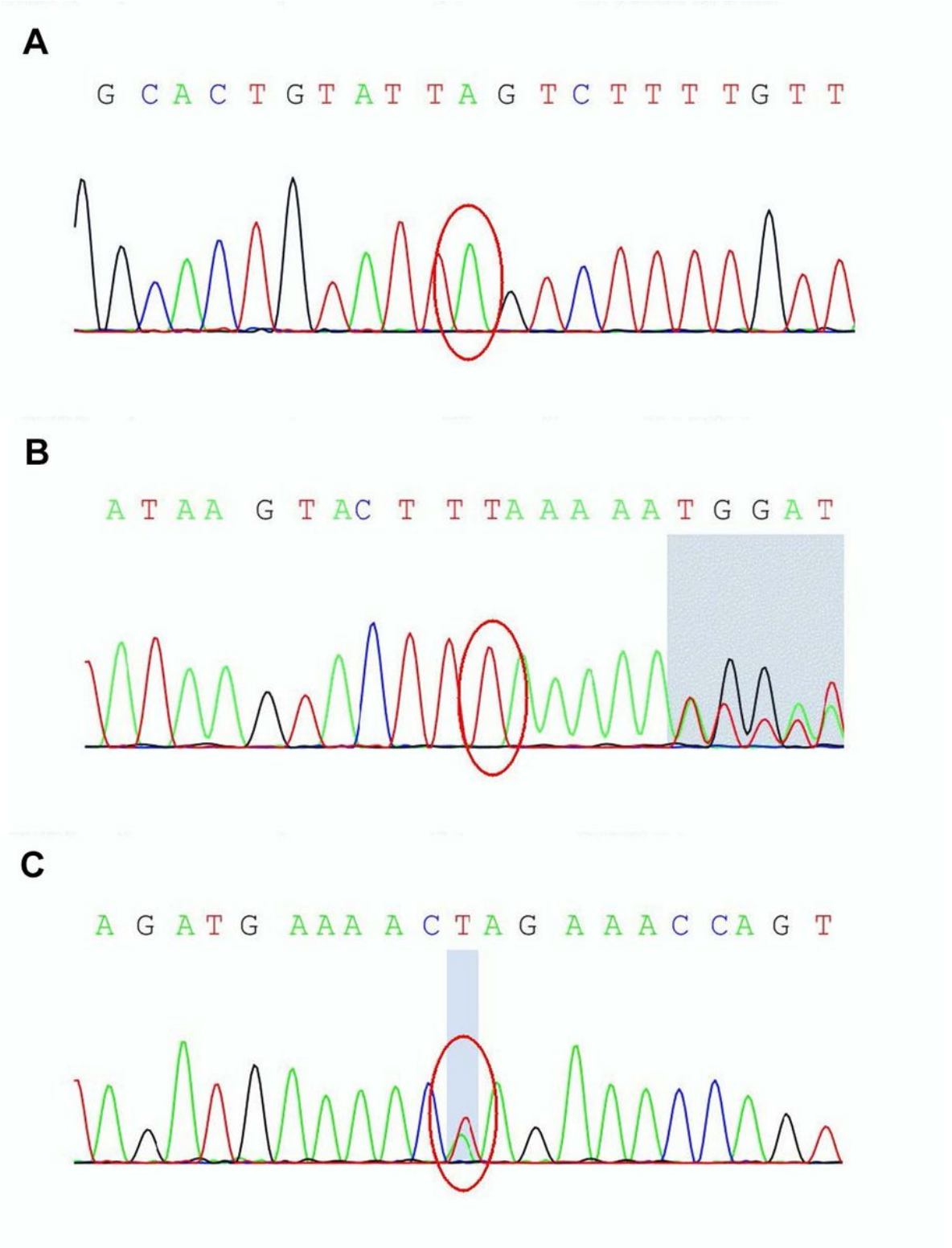

Figure 3

VPS13A gene sequence: (A) The genetic test found a hemizygotic mutation (antisense chain) of c. 4063C > T in Chr9:79922963 in patient 1. (B and C) Two heterozygous mutations were found in patient 2: c. 2833A > T in Chr9:79895083 and c.4321_4322insA in Chr9:79929484.

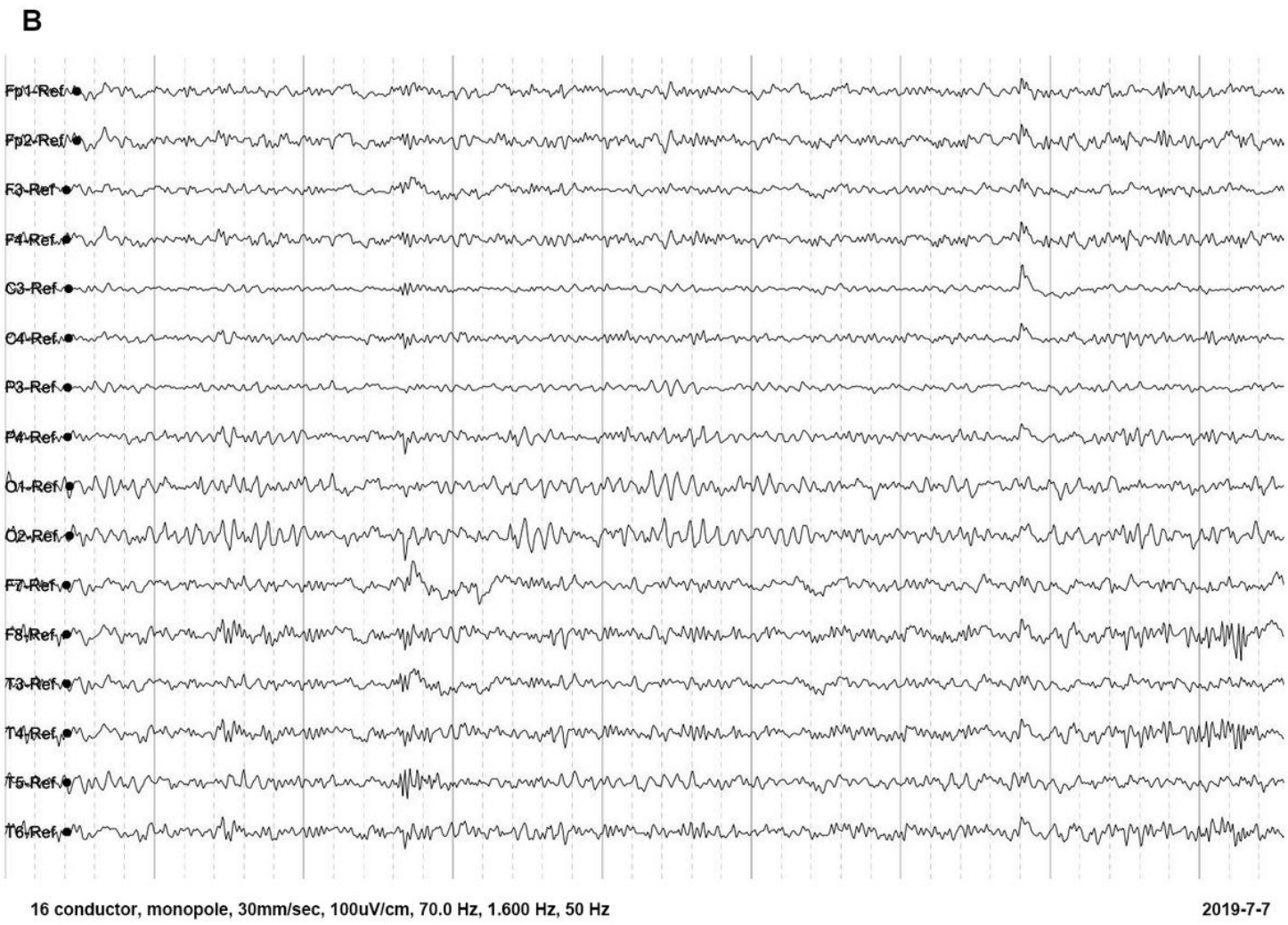

Figure 4

Electroencephalogram of the patient 2.

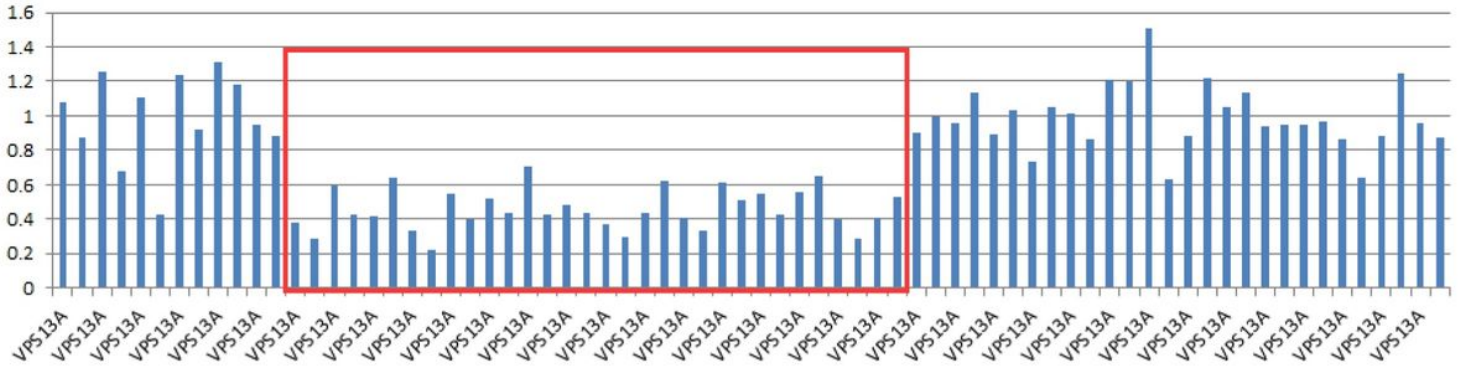

Figure 5

VPS13A gene sequence: the genetic test found a heterozygous deletion variant in exons 13-44 of the VPS13A gene in patient 1.

Supplementary Files

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- CAREchecklistEnglish2013.pdf