Chorea-acanthocytosis: report of one case

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Introduction

Chorea-acanthocytosis (ChAc) is a rare neurodegenerative autosomal recessive hereditary disease. Its clinical manifestations include progressive nerve degeneration, progressive involuntary movement of the mouth and the tongue, self-mutilative bite of lips and tongue, choreatic movements, dysarthria, epilepsy, peripheral neuropathy and acanthocytosis [1, 2]. We hereby present a patient with mutations of the VPS13A gene encoding for chorein.

Case report and methods

A 23-year-old unmarried Chinese woman was referred to the Neurology Department of Guangzhou Hospital of Traditional Chinese Medicine. The reason the patient was hospitalized was because of the following: progressive involuntary mouth closing, choreatic movements of the tongue, unstable gait more than 2 years. She had two episodes of limbs twitch in November 27, 2014.
About 2 years ago (July 2012) the patient was admitted to the hospital on account of involuntary mouth closure, choreatic movements of the tongue, odaxesmus. The patient presented with the following symptoms: tongue ulcer, aphthous ulcer, saliva and water swallowing difficulty, choking after eating and drinking, drooling, pronunciation difficulty, and poor nutrition due to swallowing difficulty. The symptoms worsens when she is under stress but disappears when she sleeps. She had neither dizziness nor headache. She sought medical attention late because her parent taught her condition was as a result of her bad lifestyle.

In October 2013, she had lower limbs muscle weakness, gait instability, side walking and choreiform movements (someone told that she had a dance like gait). The patient sometimes had involuntary tic-like sensation of the lower limbs. There is no specific pattern or uniform fluctuation of the symptoms. The severity of the symptom is not affected by the time of the day. The following are some additional symptoms presented by the patient: limbs tic, mouth foaming, eyes rolled back. In December 2013 and November 2014 she became unconscious for about 2-5 minutes. However there were no fever, chills, cough and abdominal pain. Her stool and urine was normal. In addition she had normal sleep.

Her past medical history were as follows: No history of hepatitis, tuberculosis, trauma, surgery, blood transfusion. Had no drugs and food allergies. Did not smoke, or drink alcohol. Had normal menstruation.

The marriage between her parents was not consanguineous. There is no history of similar disease in her family. Her elder sister who is now 26 year old was diagnosed of simple eye muscle type myasthenia gravis when she was at the age of 4. She took pyridostigmine bromide tablets 60 mg qd to control the symptom.

She was well oriented in place time and space and able to communicate well. Not malnourished. On examination she had several bite marks on the tongue and secondary ulcer. She has green bean size ulcer on the left oropharyngeal wall near the second molar teeth. There was no hyperemia on the pharyngeal wall. Tonsil was not swollen. Examination of the circulatory, respiratory, gastrointestinal systems, spine and limbs reveal no abnormality.

Neurological examination reveals the following: Patient was conscious and alert, normal intelligence (MMSE29 points), speech was not audible, dysartrhia, and choreatic movements of the tongue. The patient placed a towel in the mouth in order to limit choreatic movements of the tongue and to avoid biting the tongue. Bilateral eye movement was normal. The diameter of each pupil was 3 mm, light reflex was present, no shaking of eyes, no diplopia. The nasolabial

Figure 1. Acanthocytosis in peripheral blood. The smear shows frequent acanthocytes, representing 50% of all red blood cells in patient (A), 30% in patient's father (B), 25% in patient's mother (C), 2% in patient's sister (D).
groove on both sides was symmetrical. Her tongue was stuck out and the uvula was in its normal position. There was bilateral soft palate weakness, gag reflex decreased significantly. Muscle strength of limbs was grade V -. There was reduced tone in all the limbs, tendon reflex was decreased significantly, Hoffmann sign (-), Babinski sign (-), has poor coordination when walking, meningeal stimulation (-), Romberg sign (-).

Laboratory investigation revealed blood routine examination: WBC 10.49×10⁹/L, NEU 7.40×10⁹/L, RBC 4.36×10¹²/L, HGB 128.40g/l, HCT 0.38L/L, PLT 265.00×10⁹/L. Urine routine, stool routine were normal. Her blood group profile was: K⁺, Na⁺, Cl⁻, Ca²⁺, Mg²⁺, P⁵⁺, GLU, UA, BUN, CR, HCO³⁻, CysC, CHOL, TRIG, HDL-C, LDL-C, r-GGT, ALP, TP, ALB, GLB, TBIL, DBIL, ILI, APOA₁, Lpa were normal. APOB 0.43g/L (normal values 0.8-1.1), ALT 48 U/L (normal values 0-40), AST 80U/L (normal values 0-40), LDH 459U/L (normal values 109-245), CK 2806U/L (normal values 38-174), CK-MB 47U/L (normal values 0-24), a-HBDH 393U/L (normal values 72-182), TNT-HS was normal, MYO 72.49ng/ml (normal values <58), NT-proBNP 246.70 pg/ml (normal values <125). Erythrocyte osmotic fragility incubation test (-). ESR, ASO, RF, CRP, IgG, IgA, IgM, C3, C4 were normal. Leptospira IgG (-). Anti-MPO (-). Anti-PR3 (-). TB-DOT (-). Liver parasite test (-). Angiostrongylus cantonensis antibody (-). Schistosoma japonicum IgG (-). Anti-HCV (-). HIV-Ag/Ab (-). RPR(-). TPPA (-). FT₃, FT₄, h-TSH, Anti-TPO, Anti-TG were normal. FSH (follicle stimulating hormone), LH (luteinizing hormone), E₂ (estradiol), T (testosterone) were normal. PRL (Prolactin) 38.35ng/ml (normal values 3.4-24.1). AFP, CEA, CA125, CA199, CA153 were normal. HAV-IgM, HBV-IgM, HCV-IgG, HDV-IgM, HEV-IgM, HEV-IgG, HGV-IgG were negative. Umbar puncture cerebrospinal fluid pressure was 155 mmH₂O, colorless and transparent. CSF-RBC 40×10⁹/L (puncture wounds), CSF-WBC 0, CSF-GLU 3.56mmol/L, CSF-LDH 14U/L, CSF-Pro 90mg/dl, CSF-ADA 0.10U/L, CSF cryptococcus neoformans smear (-), CSF tuberculosis bacterium smear (-), CSF cultures no bacterial growth and fungal growth. Chest X-ray, ECG, EEG, TCD, digestive B ultrasound, urinary tract B ultrasound and gynaecology B ultrasound were normal. EMG showed multiple peripheral nerve damage. There was not corneal K-F ring under the eye slit lamp check. For the patient, acanthocyte in peripheral blood smear were seen accounted for 50% of the red blood cell count under the high magnification microscope (Fig.1. A), and the second time accounted for 25%. For the patient's father (male, 50 years old), acanthocyte in peripheral blood smear were seen accounted for 30% of the red blood cell count (Fig.1. B). For the patient's mother (female, 48 years old), about 25% (Fig.1. C). For the patient's sister (female, 27 years old), about 2% (Fig.1. D). Cranial MRI showed bilateral cauda head atrophy (Fig.2.).

Peripheral blood was used in the detection of the gene and gene sequence analysis related to ChAc was done. We extracted DNA from peripheral blood through the application column method, and sequence analysis of exon coding areas of the MTTP, VPS13A, XK gene was done through sequencing technology, compared with the reference sequence, so as to find possible genetic mutation. As a result, we detected a hybrid pathogenic mutation, gene mutation was VPS 13A c.9403C>T p.(Arg3135 *)hybrid pathogenic mutation (Fig.3.).

Results

Summarize the characteristics of this case. A. The patient was a young woman, onset of symptoms slow which gradually became progressive. B. The patient had progressive choreatic movements of the mouth and the tongue, spitted tongue, tongue ulcer, aphthous ulcer, drooling from the mouth, glossolalia, unstable gait, generalized tonic-clonic seizures, reduced gag reflex, decreased muscle tone, hyporeflexia. C.
Her parents' marriage was not consanguineous, no history of similar disease in her family. Family pedigree of the patient's father (Fig.4. A) and family pedigree of the patient's mother (Fig.4. B) conforms to the characteristics of autosomal recessive heredity. D. LDH, CK, PRL were increased, EMG showed multiple peripheral nerve damage. E. Checked lots of acanthocyte in peripheral blood smear of the patient and the patient's parent. F. Cranial MRI showed bilateral caudate head atrophy. G. Detected mutation in VPS 13A.

This disease is one kind of genetic disease of the nervous system and so far there is no known specific therapy for it. Clinical management is only for the symptoms relief. After admission to the hospital, the patient was given haloperidol, from 1 mg bid increased to 2 mg tid gradually, vitamin E 100mg tid, vitamin B complex 2 tablets tid, butylphthalide 2 tablets tid, inosine 0.4g tid, ATP 20 mg tid, coenzyme Q10 10mg tid, oral care tid, psychological counseling given, swallowing exercise, the tongue function exercise. After 18 days treatment, choreatic movements of the mouth and the tongue reduced significantly, drooling and unstable gait got better, but still had some swallowing difficulty, choking on water, tongue ulcer, aphthous ulcer. There is a scheduled follow-up visit with the patient.

Discussion

Chorea-acanthocytosis (ChAc) is clinical rare, and it is a subtype of the neuroacanthocytosis (NA) syndromes. ChAc is an autosomal recessive disease due to the mutations of the VPS 13A gene encoding forchorein [3], belong to a rare genetic disease of the nervous system. It is a later understood disease. Described by by Levine in 1960 and also first reported by Critchley [4, 5], NA mainly affects children and young adults. According to characteristics of gene mutation, NA at least include five subtypes genetic clearly [6, 7]: A. Bassen-Kornzweig syndrome (ABL), mutation in MTP. B. Choreacanthocytosis (ChAc), mutation in VPS 13A. C. McLeod syndrome (MLS), mutation in the XK; D. Huntington's Disease-like 2 type (HDL2), mutations in JPH3. E. Pantothenate kinase-associated neurodegeneration (PKAN), mutation in PANK2.

ChAc clinical features include extrapyramidal symptom, hematology changes and neuroimaging changes [8-10]: A. The onset age is 8-62, the average age is 32, more prevalent in male than female. B. Involuntary movement of tongue and masticatory muscle, eating dystonia, often accompany limbs or trunk choreatic movements, self-mutilative biting of lips and tongue. C. Epilepsy, cognitive impairment and mental disorder. D. Decreased muscle tone, diminished or disappeared tendon reflex, electromyography shows peripheral nerve damage. E. Involve multiple systems. F. Variable acanthocytosis of red blood cell in peripheral blood (5% - 50%, except to liver disease, splenectomy and hemolytic anemia). G. The serum creatine kinase increased. H. Cranial CT and MRI usually reveal that the disease is accompanied by atrophy of the caudate nuclei with dilatation of the anterior horns of the lateral ventricles.

Although there are lots of acanthocyte in peripheral blood of this patient, there was no anemia, no hypoxemia, no clotting mechanism obstacle, no lipid metabolism disorder.
The blood prolactin is increased in this case which is rare in ChAc. It is therefore ok to speculate that this is due to the damage of the hormone regulating function of the hypothalamus pituitary dopaminergic system.

Genetic basis in ChAc is complex. The susceptible gene is significant, mutations are diverse, there are no clear lesions of exons. This case is investigated through the gene mutation sequencing of ChAc to find mutation in the gene of VPS 13A c.9403C>T p. (Arg3135 *) hybrid pathogenic mutation. The mutation is a nonsense mutation (that is expected to make coding protein of the 3135th amino acid from Arg to terminate codon). Hence make protein translation due to early termination, which is a pathogenic mutation. There are reports which detects that mutation in ChAc patients is linked with hypertrophic cardiomypathy/dilated cardiomypathy [11, 12]. It conforms to the common mutation type of the ChAc detected in the genetic mutation in this case.

There is no specific treatment for ChAc and generally the choice of drug is for symptomatic treatment [13]. Treatment favors long-term efficacy and relative safety of the bilateral GPi-DBS for severe, drug-resistant hyperkinetic movement disorders in ChAc [1]. In nursing the patient it is important to do the following: Pay attention to oral care, use clean handkerchief in the mouth and change regularly. Feed the patient with high protein, high vitamin, warm and digestible food. Take meals little at a time but enough to be satisfactory. If there is difficulty in feeding patient should be fed through nasogastric tubes to improve nutritional status. It is important that let the patient do swallowing exercises to improve the function of swallowing. Comprehensive rehabilitation must be given. In addition patient must go through psychological counseling to alleviate depression and anxiety and to build up confidence.

Conflicting interests

The authors have declared that no conflict of interests exist.

Author contributions

Chengyin Wang, Jie Liang, Jianhong Liu, and Jianhong Huang made the diagnosis and treatment for the patient. Limei Zhou did peripheral blood smear under the high magnification microscope. Xin Bi made the genetic analysis. Samir Misbah checked and edited language.

References