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Name of Journal: *World Journal of Clinical Cases*

Manuscript NO: 80826

Manuscript Type: CASE REPORT

Rare adult neuronal ceroid lipofuscinosis associated with *CLN6* gene mutations: A case report

CLN6 gene mutation and *ANCL*

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sites are novel and contribute to the knowledge of mutations causing neuronal ceroid lipofuscinosis. Although there is no curative treatment for neuronal ceroid lipofuscinosis, early diagnosis and symptomatic treatment are possible.

INTRODUCTION

Neuronal ceroid lipofuscinosis (NCL) is a group of genetically heterogeneous neurodegenerative diseases. NCL is primarily caused by a genetic defect in the processing of proteases by lysosomes, resulting in intralysosomal storage of ceroid lipofuscin, which affects nerve function. The disease is more common in children and rare in adults. The age of onset is typically before 30 years. The incidence of the disease varies by region. In European and American countries, the incidence is 0.1-7.0/100000^[1]. However, NCL has not been reported in China previously.

The main clinical features of the disease are neurodegeneration, progressive motor dysfunction, seizures, cognitive decline, ataxia, vision loss and premature death^[2]. NCL is divided into four categories according to clinical manifestations and age of onset, as follows: ⁶infantile NCL (6-24-month-old); ⁶late infantile NCL (2-4-years-old); ⁶juvenile NCL (5-10-years-old); and ⁶adult NCL (ANCL) (over 18-years-old)^[3]. Thirteen different NCL subtypes have been found to be associated with mutations in 13 different genes (*CLN1-CLN8* and *CLN10-CLN14*)^[4]. Each gene mutation leads to a specific subtype of the disease, and ¹the protein products of these genes (*CLN1-CLN14*) differ in their function and intracellular localization. NCL-related ¹proteins are ¹localized to lysosomes (*CLN1, CLN2, CLN3, CLN5, CLN7, CLN10, CLN12, CLN13*), the endoplasmic reticulum (*CLN6, CLN8*) or the cytosol associated ¹with vesicle ³membranes (*CLN4, CLN14*). Some ³of the proteins are lysosomal soluble proteins [*e.g., CLN1*(palmitoyl protein thioesterase 1), *CLN2*(tripeptidyl peptidase 1), *CLN5, CLN10*(cathepsin D), *CLN13*(cathepsin F)], and others have been proposed as lysosomal transmembrane proteins (*e.g., CLN3, CLN7, CLN12*)^[5,6].

The *CLN6* subtype of ANCL is a primarily autosomal recessive neurodegenerative disorder. *CLN6* encodes an endoplasmic reticulum nonglycosylated transmembrane

protein involved in lysosomal acidification. Mutations in *CLN6* have been linked to late infantile NCL, juvenile NCL and ANCL (also known as Kufs disease)^[2]. Individuals affected by this disease have two identical (homozygous) or two different (compound heterozygous) *CLN6* mutant alleles. Due to the lack of information on the physiological role of *CLN6*, the pathogenesis of the disease is currently unclear^[7].

A rare form of ANCL is caused by variants in *CLN6*, with symptoms normally presenting in adulthood after the age of 30 years. The typical symptoms include ataxia, epilepsy and progressive cognitive function decline, and usually without vision loss. Adults with this disorder usually do not live more than 10 years after diagnosis^[2]. We present here the first case of *CLN6* subtype ANCL with novel mutations in *CLN6* in a Chinese patient.

CASE PRESENTATION

Chief complaints

A 37-year-old female was admitted to the hospital on May 12, 2021 due to limb weakness and walking instability for 3 years.

History of present illness

Three years prior to admission, the patient began to develop limb weakness and walking instability without obvious inducement. She reported an episode in which she became clouded in mind and fell to the ground, which was accompanied by limb stiffness, convulsions and upturned eyelid. The symptoms were alleviated after 3-5 min, and she did not experience dizziness, headache, nausea or vomiting. Atonic-clonic seizure was diagnosed.

Two years prior to admission, the limb weakness worsened. The patient reported slow movement, unstable walking, bedridden status, fear of the dark, paroxysmal chills and toothache. There was no memory loss or unconsciousness disorder. The family members were sent to another hospital for hospitalization. At that time, "brain atrophy" was considered.

One year prior to admission, the patient's symptoms again worsened, with obvious emaciation, chills, intermittent memory loss, speech disorder, and the inability to walk independently. Ataxia and involuntary limb shaking were present. She was admitted to another hospital, but her symptoms did not improve significantly by the time she was discharged.

Four days prior to admission, her symptoms worsened significantly (Figure 1). The patient reported numbness in the left lower limb below the knee and the right upper limb fingers and wrist joint, recurrent seizures, hand and foot pain, decreased appetite and a high temperature of 37.8°C. The patient did not experience nausea, vomiting or incontinence.

History of past illness

The patient denied having a history of hypertension, diabetes, heart disease, infectious disease and food and drug allergies. The patient's vaccination history was unknown.

Personal and family history

The patient was a life-long resident of the area and denied any long-term exposure to radioactivity, poisons or drugs. She was legally married and had a daughter. Both her husband and daughter were in good health. The patient and her family denied any disease-related family history. However, her sister had a similar history of walking instability, photophobia, seizures and poor memory.

Physical examination

The examination of the patient showed poor orientation to the surrounding environment, poor memory and a decline in comprehension capacity and numeracy. She had tremor of tongue and high limb muscle tension, and the limb muscle strength was level 4. Superficial sense hypoaesthesia of the left lower extremity below the knee and the right upper extremity finger and wrist joints and paresthesia of deep sensation and combined sensation accompanied by involuntary tremors in the extremities were

observed. We noted bilateral ankle clonus (+), detection of ataxia (+) and left side pathological sign (+).

Laboratory examinations

Routine blood work revealed white blood cell count of $8.09 \times 10^9/L$ (normal range: $3.5-9.5 \times 10^9/L$), neutrophil percentage of 76.8% (normal range: 50%-70%), hemoglobin of 144g/L (normal range: 113-151 g/L) and platelets of $221 \times 10^9/L$ (normal range: $100-300 \times 10^9/L$). No abnormalities were found for hypersensitive C-reactive protein, calcitonin, blood culture, bacteria, acid-fast bacilli, fungi and ink stain. No abnormalities were found in the routine stool and urine tests. Potassium levels were 3.34mmol/L (normal range: 3.5-5.3 mmol/L). Liver and kidney function, heart function and blood lipids were normal. Tumor indexes and immune indexes were not abnormal. No abnormality was found in thyroid function, rheumatism, tuberculosis antibody and the antinuclear antibody spectrum. The patient was negative for hepatitis B, hepatitis C, human immunodeficiency virus and syphilis. Blood coagulation function, trace elements, N-terminal brain natriuretic peptide and troponin were normal. The intracranial pressure was 110mmH₂O. Routine examination of cerebrospinal fluid was colorless and clear with normal cell counts and biochemistry.

Imaging examinations

Brain magnetic resonance imaging (MRI) and magnetic resonance angiography revealed leukoaraiosis and brain atrophy. No cerebral infarction was observed. Cerebral atherosclerosis was considered, and no obvious vascular stenosis was observed (Figure 2).

The basic rhythmic activity on electroencephalogram was the mid-potential 8-9c/s alpha wave and poor amplitude adjustment. Both sides were approximately equivalent. The visual response existed, and increased fast waves in both hemispheres were recorded without an obvious spike and slow wave (Figure 3).

Electromyography revealed normal nerve conduction in the extremities and abnormal F waves and sympathetic skin response in both lower extremities. Somatosensory evoked potential test revealed poor waveform differentiation and bilateral asymmetry as well as event-related evoked potential latency delay and potential instability. Abdominal ultrasound, cardiac ultrasound and neck vascular ultrasound showed no abnormalities.

MULTIDISCIPLINARY EXPERT CONSULTATION

After consultation with experts from the neurology, neuroelectrophysiology, pediatrics, imaging and oncology departments, genetic examination was arranged with the patient and her family to determine the genetic basis for the symptoms.

FINAL DIAGNOSIS

The final diagnosis was NCL, CLN6 type, based on the patient's clinical manifestations, imaging examination, genetic test and other examination results as well as the consultation of multidisciplinary experts.

TREATMENT

The patient received antiepileptic drugs for symptomatic relief and to improve her cognitive function.

OUTCOME AND FOLLOW-UP

The patient is currently under follow-up observation. At the last follow-up, the patient's condition had deteriorated. Unfortunately, she was unable to care for herself.

DISCUSSION

NCL occurs in the presence of two deleterious mutation alleles. All known genes are on autosomal chromosomes, and most are inherited in a recessive manner. Different gene mutations lead to different forms of NCL, and the mutation often determines the age of

onset, symptoms and the rate of disease progression, which is generally fatal^[8]. However, there are also individual NCL gene mutations that are autosomal dominant, such as ANCL due to mutations in *CLN4/DNAJC5*^[9]. The *CLN6* gene is located on chromosome 15q21-23, contains seven exons and encodes a protein with seven transmembrane domains, an N-terminal cytoplasmic domain and a lumen C-terminal. This protein is involved in endoplasmic reticulum-to-Golgi transfer of lysosomal enzymes, causing clinical symptoms^[10-13].

The first report of ANCL was in 1979, by Dom *et al*^[14]. The initial symptoms were more common in people in their 30s, but the age of onset ranged from teenage to over 50-years-old. Two phenotypes were reported: Kufstyp A and Kufstyp B. Kufstyp A presents with intractable epilepsy, dementia and myoclonus with no visual impairment. Kufstyp B presents as abnormal behavior, dyskinesia, dementia, ataxia, extrapyramidal symptoms and symptoms of brainstem involvement. Although the current clinical manifestations of ANCL do not include visual abnormalities and retinal atrophy, NCL-specific lipopigment^[14-16] may accumulate around the nucleus of retinal neurons.

Age of onset and disease duration in CLN6 type ANCL are associated with genetic variation across a broad phenotypic spectrum. More than 70 mutations in the *CLN6* have been linked with late infantile NCL, early juvenile NCL and ANCL (Kufstyp A)^[17,18]. The clinical manifestations of this reported case are consistent with the manifestations of Kufs type A. However, the patient had paresthesia of deep sensation, superficial sensation and combined sensation accompanied by depressive symptoms. These symptoms are particularities of this case.

The electroencephalogram of patients with NCL typically show paroxysmal diffuse spikes, polyspikes and multifocal spikes^[19]. MRI typically shows varying degrees of atrophy of the cerebrum, brainstem and cerebellum, with cerebellar atrophy being the most obvious. In the late stage of the disease, long T2 signal in the periventricular white matter, decreased T2 signal in the basal ganglia and cerebral cortex are observed^[20,21].

Although the epileptiform waves of our patient were not captured, the head MRI showed that the patient had obvious brain atrophy.

NCL histopathological findings suggest neuronal degeneration in the cerebral and cerebellar cortex and accumulation of autofluorescent ceroid lipochromes in nerves and peripheral tissues^[22,23]. Transmission electron microscopy ultrastructural examination reveals sparse storage deposits in lymphocytes, storage material coating, membrane-bound storage material as dense lipid pigments with fingerprints and amorphous materials. The ultrastructural analysis of skin biopsies reveals distinct storage inclusion in sweat gland epithelium, endothelial cells and smooth muscle cells. The inclusion body is a mixed type with curvilinear and fingerprint bodies. Different types of NCL have different sediment shapes, and mixed deposits may occur in atypical cases^[24,25]. Nevertheless, the pathological examination is still not completely clear.

There are currently three types of ANCL: CLN1; CLN2; and CLN10. The mechanism of action of these three enzymes and the relationship between the functions and clinical phenotype are unclear. At present, there are still 10%-20% of cases that cannot be correctly typed. The diagnosis can be assisted by methods such as serum enzyme detection or genomics detection^[26,27].

The diagnosis of NCL is primarily based on the age of onset, clinical manifestations, pathological examination results and genetic testing. Our patient was a 37-year-old female whose onset occurred 3 years before diagnosis. The initial symptoms were unsteady walking and seizures, with cognitive decline, paresthesia, depression and pyramidal tract sign (ankle clonus +). Before diagnosis, the patient also experienced cerebellar ataxia symptoms such as walking instability and shaking limbs. The patient's brain MRI showed brain atrophy and leukoariosis. Combined with the patient's clinical history and evidence of similar symptoms in the patient's sister, genetic testing confirmed CLN6 type NCL. Unfortunately, symptomatic treatment was the only available therapy. At the 1-year follow-up, the patient's symptoms progressed (bedridden, inability to walk, poorly controlled seizures, recurrent seizures and stiffness in extremities).

CONCLUSION

There is currently no effective treatment for NCL. However, enzyme replacement therapy, immunosuppressive therapy, gene carrier therapy, stem cell therapy and drug therapy^[28] have achieved promising results in animal models, clinical trials and various literature reports. Despite the lack of a cure for the disease, symptomatic treatment can slow the progression of the disease, stabilize organ function and increase lifespan.

ACKNOWLEDGEMENTS

Attending physician Xueqiang Wang sincerely thanks Prof. Yu Zhai, Director Chuanbi Chen and Wenjie Zhao for their insightful comments on the report.

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