ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2023 May 26; 11(15): 3369-3663

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

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ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Gulali Aktas, MD, Professor, Department of Internal Medicine, Abant Izzet Baysal University Hospital, Bolu 14030, Turkey. draliaktas@yahoo.com

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RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

PUBLICATION DATE
May 26, 2023

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 26; 11(15): 3533-3541

DOI: 10.12998/wjcc.v11.i15.3533

ISSN 2307-8960 (online)

CASE REPORT

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

Xue-Qiang Wang, Chuan-Bi Chen, Wen-Jie Zhao, Guang-Bin Fu, Yu Zhai

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Pitton Rissardo J, Brazil; Sotelo J, Mexico

Received: October 13, 2022
Peer-review started: October 13, 2022
First decision: January 30, 2023
Revised: March 6, 2023
Accepted: April 13, 2023
Article in press: April 13, 2023
Published online: May 26, 2023

Xue-Qiang Wang, Department of Neurology, Sanya People's Hospital, West China (Sanya) Hospital, Sichuan University, Sanya 572000, Hainan Province, China

Chuan-Bi Chen, Department of Pediatrics, Sanya Women and Children's Hospital Managed by Shanghai Children's Medical Center, Sanya 572000, Hainan Province, China

Wen-Jie Zhao, Department of Neurology, The First Affiliated Hospital of Hainan Medical College, Haikou 570100, Hainan Province, China

Guang-Bin Fu, Yu Zhai, Department of Neurology, Hainan Western Central Hospital, Danzhou 571799, Hainan Province, China

Corresponding author: Yu Zhai, MD, Chief Physician, Department of Neurology, Hainan Western Central Hospital, No. 2 Fubo East Road, Danzhou 571799, Hainan Province, China. diyumail@163.com

Abstract

BACKGROUND

Adult neuronal ceroid lipofuscinosis (ANCL) can be caused by compound heterozygous recessive mutations in *CLN6*. The main clinical features of the disease are neurodegeneration, progressive motor dysfunction, seizures, cognitive decline, ataxia, vision loss and premature death.

CASE SUMMARY

A 37-year-old female presented to our clinic with a 3-year history of limb weakness and gradually experiencing unstable walking. The patient was diagnosed with CLN6 type ANCL after the identification of mutations in the *CLN6* gene. The patient was treated with antiepileptic drugs. The patient is under ongoing follow-up. Unfortunately, the patient's condition has deteriorated, and she is currently unable to care for herself.

CONCLUSION

There is presently no effective treatment for ANCL. However, early diagnosis and symptomatic treatment are possible.

Key Words: *CLN6*; Neuronal ceroid lipofuscinosis; Genetic testing; Epilepsy; Ataxia; Case report

Core Tip: Adult neuronal ceroid lipofuscinosis (NCL) is a rare neurodegenerative disease that can be caused by mutations in the *CLN6* gene. Our patient experienced limb weakness and unstable walking. Whole exome sequencing and Sanger sequencing revealed that the patient had a recessive compound heterozygous mutation in *CLN6*. The mutation sites are novel and contribute to the knowledge of mutations causing NCL. Although there is no curative treatment for NCL, early diagnosis and symptomatic treatment are possible.

Citation: Wang XQ, Chen CB, Zhao WJ, Fu GB, Zhai Y. Rare adult neuronal ceroid lipofuscinosis associated with *CLN6* gene mutations: A case report. *World J Clin Cases* 2023; 11(15): 3533-3541
URL: https://www.wjgnet.com/2307-8960/full/v11/i15/3533.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i15.3533

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].

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: Infantile NCL (6-24 months old); late infantile NCL (2-4-years-old); juvenile NCL (5-10-year-old); and adult 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 the protein products of these genes (CLN1-CLN14) differ in their function and intracellular localization. NCL-related proteins are localized to lysosomes (CLN1, CLN2, CLN3, CLN5, CLN7, CLN10, CLN12, CLN13), the endoplasmic reticulum (CLN6, CLN8) or the cytosol associated with vesicle membranes (CLN4, CLN14). Some of 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 lysosomaltransmembrane 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 hospit-

alization. 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 had 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

Physical 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 hypoesthesia 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 × 10^9/L (normal range: 3.5-9.5 × 10^9/L), neutrophil percentage of 76.8% (normal range: 50%-70%), hemoglobin of 144 g/L (normal range: 113-151 g/L) and platelets of 221 × 10^9/L (normal range: 100-300 × 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 3.34 mmol/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 110 mmH_2O. Routine examination of cerebrospinal fluid showed it to be 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).

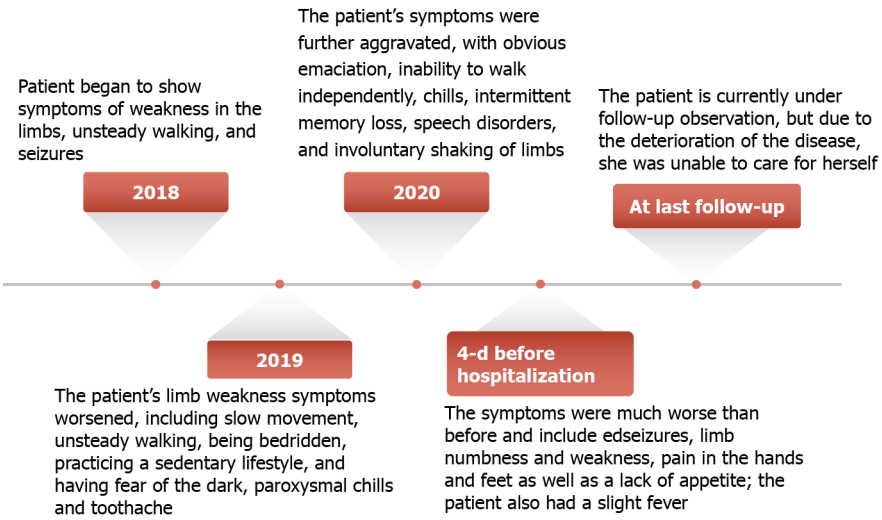
The basic rhythmic activity on electroencephalogram was the mid-potential 8-9c/s alpha wave and poor amplitude adjustment. Both sides were approximately equivalent. The visual response existed, and increased fast waves in both hemispheres were recorded without an obvious spike and slow wave (Figure 3).

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.

Genetic testing

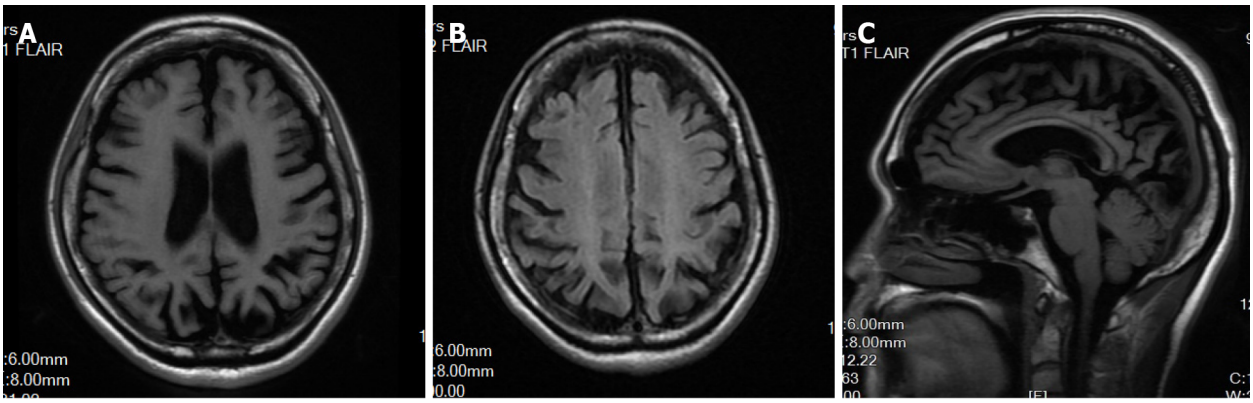
After consultation with experts from the neurology, neuroelectrophysiology, pediatrics, imaging and oncology departments, genetic examination was arranged with the patient and her family to determine the genetic basis for the symptoms.

The patient's younger sister also had similar symptoms of unsteady walking and seizures that were induced by light stimuli. A genetic family map was constructed (Figure 4) on the basis of clinical symptoms, laboratory examinations and imaging examinations of patients to exclude other related diseases.



DOI: 10.12998/wjcc.v11.i15.3533

Figure 1 History of present illness.



DOI: 10.12998/wjcc.v11.i15.3533

Figure 2 Brain magnetic resonance imaging showed that the patient had obvious brain atrophy. A: T1 fluid-attenuated inversion recovery (FLAIR); B: T2 FLAIR; C: T3FLAIR.

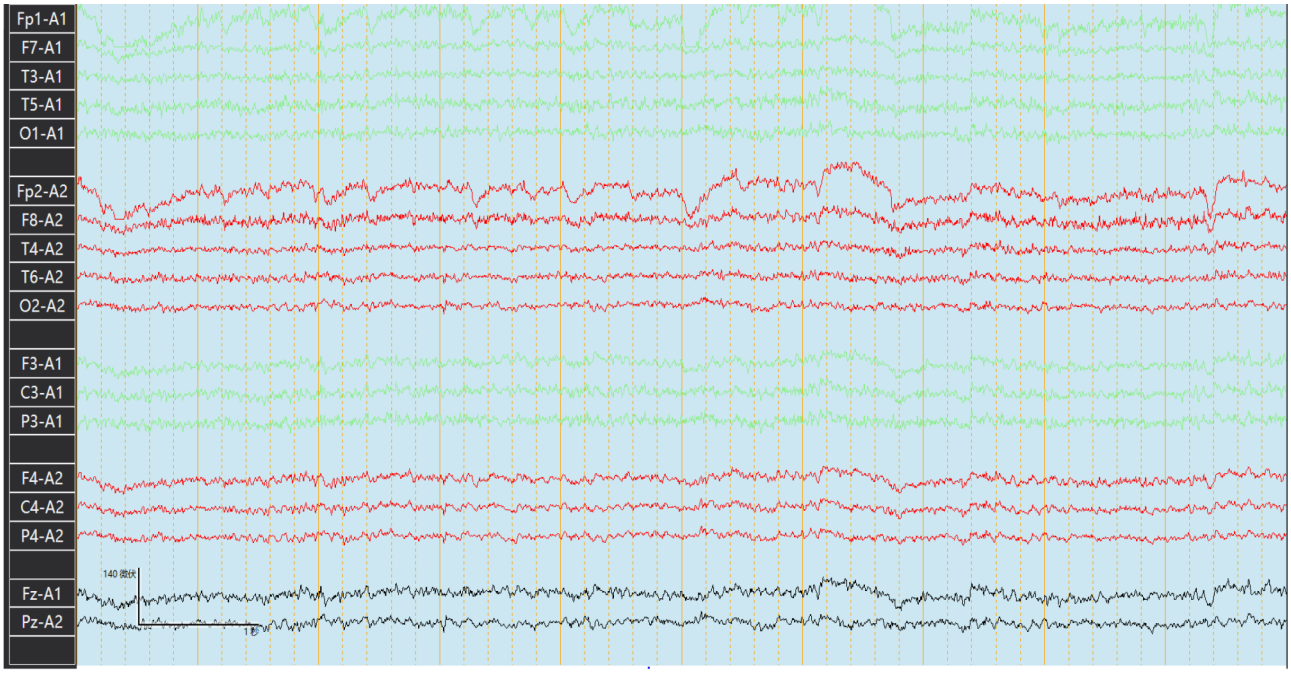
The patient and her immediate family members consented to peripheral blood collection for gene detection and analysis. Whole exome sequencing revealed the following *CLN6* gene mutation in the patient and the patient's father and sister: Exon 7 c.872C>T (p.Pro291Leu). This mutation causes amino acid 291 of the encoded protein to change from a proline to a leucine, which is a missense mutation (Figure 5), and results in impaired protein function. Another mutation in the *CLN6* gene was identified in the patient and the patient's mother and sister: Intron 5 c.542+5G>A(p.?) (Figure 6). The recessive compound heterozygous mutations in the proband were considered to be pathogenic based on the clinical and laboratory findings. Consistent with autosomal recessive inheritance, it is a recessive compound heterozygous mutation.

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.

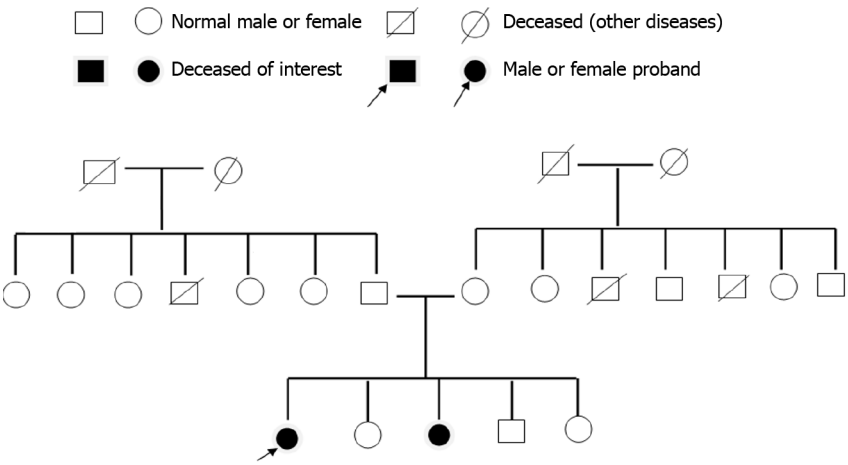
TREATMENT

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



DOI: 10.12998/wjcc.v11.i15.3533

Figure 3 Electroencephalogram findings. 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.



DOI: 10.12998/wjcc.v11.i15.3533

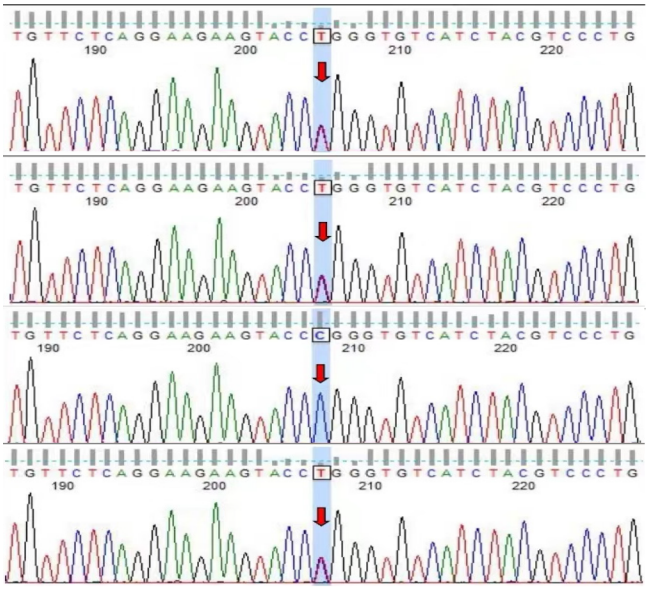
Figure 4 Pedigree of the patient.

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.

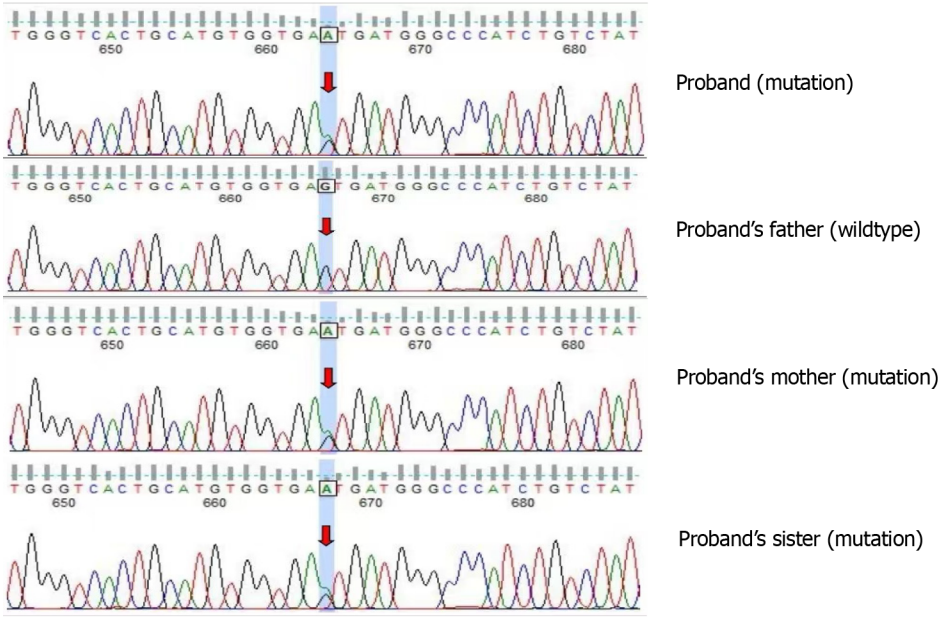
DISCUSSION

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



DOI: 10.12998/wjcc.v11.i15.3533

Figure 5 Whole exome sequencing revealed a mutation in the proband and the proband's father and sister. The mutation was *CLN6* chr15:68500542 exon 7 NM_017882.3:c.872C>T(p.Pro291Leu).



DOI: 10.12998/wjcc.v11.i15.3533

Figure 6 Whole exome sequencing revealed a mutation in the proband and the proband's mother and sister. The mutation was *CLN6* chr15:68503596 intron 5 NM_017882.3:c.542+5G>A(p.?).

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 1987, by Martin *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: Kufs type A and Kufs type B. Kufs type A presents with intractable epilepsy, dementia and myoclonus with no visual impairment. Kufs type 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 (Kufs type 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 ceroidlipochromes 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 leukoaraiosis. 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 had progressed; she was bedridden, unable to walk, and experiencing 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 Xue-Qiang Wang sincerely thanks Prof. Yu Zhai, Director Chuanbi Chen and Wen-Jie Zhao for their insightful comments on the report.

FOOTNOTES

Author contributions: Wang XQ, Chen CB and Zhai Y contributed to manuscript writing and editing; Wang XQ, Zhai Y and Fu GB contributed to manuscript data collection; Wang XQ and Zhai Y examined the patient and carried out the treatment strategy; Wang XQ, Chen CB, Zhai Y and Zhao WJ acquired and analyzed all the clinical data; Fu GB analyzed and interpreted the neuroelectrophysiological examination findings; All authors read and approved the final version of the manuscript.

Informed consent statement: Informed written consent was obtained from the patient for the publication of this report and any accompanying images.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: China

ORCID number: Yu Zhai 0000-0003-0323-9722.

S-Editor: Fan JR
L-Editor: A
P-Editor: Yuan YY

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