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Sialidosis type 1 without cherry-red spots: a case report and literature review

Congcong Zhang,[1] Zhongkai Liao ,[2] Yanhui Zhou ,[1] Xiaohui Su[1]

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CZ and ZL contributed equally.

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[1]Haikou Municipal People's Hospital and Central South University Xiangya Medical College Affiliated Hospital, Haikou, Hainan, China
[2]The Second Affiliated Hospital of Hainan Medical University, Haikou, Hainan, China

Correspondence to
Dr Yanhui Zhou;
zyhxysm@126.com

ABSTRACT

Background Sialidosis is a rare disorder caused by mutations in the NEU1 gene located on chromosome 6p21.3, constituting a group of autosomal recessive diseases. Enzyme activity analysis, electron microscopy examination and genetic testing are reliable methods for diagnosis. Despite previous reports on the disease, its rarity means that its clinical manifestations and prognosis still warrant attention due to the limited amount of information available.

Methods We report a case of a 40-year-old woman who was admitted to our hospital for worsening dysarthria of 16 years duration and facial and limb twitching that had been present for 2 years. Genetic testing was undertaken.

Results Genetic testing confirmed type I sialidosis, the first reported instance of this disease in the Hainan Free Trade Port in China. The patient did not have the typical cherry-red spot in the fundus. Despite aggressive treatment, she died of status epilepticus 2 months later. This result indicates that the disease has a poor prognosis.

Discussion Cherry-red spots in the fundus are characteristic features of type I sialidosis and it has been referred to as the cherry-red spot myoclonus syndrome. We hypothesise that environmental factors may also play a significant role. Overemphasis on the presence of cherry-red spots may mislead clinicians and delay diagnosis. Furthermore, patients presenting with isolated myoclonus should undergo visual evoked potential and somatosensory evoked potential tests, as well as genetic testing to confirm or rule out sialidosis.

INTRODUCTION

Sialidosis is a group of rare autosomal recessive genetic disorders caused by mutations in the NEU1 gene located on chromosome 6p21.31.[1] This disease is categorised into types I and II, with type I characterised mainly by late-onset (10–20 years) progressive visual impairment, cherry-red spot in the retina, myoclonic epilepsy and cerebellar ataxia.[2] However, the rarity and diversity of this disease pose challenges in understanding and identifying it.

Diagnosing sialidosis typically requires enzyme activity analysis, electron microscopy examination and genetic testing, which may not be readily accessible, especially in resource-limited settings. Additionally, the symptoms of this disease can resemble those of more common conditions, potentially leading to misdiagnosis as other diseases, such as psychiatric disorders, and consequently delayed diagnosis. The cherry-red spot in the retina is a hallmark of sialidosis type I and was once referred to as the cherry-red spot myoclonus syndrome.[3] However, previous case reports suggest that not all patients with sialidosis type I present with a cherry-red spot.[4] This observation may carry significant clinical implications for the diagnosis and understanding of the disease, as overemphasis on the cherry-red spot could mislead clinicians and delay diagnosis.

CASE DESCRIPTION

A 40-year-old female patient was admitted to our hospital on 16 October 2020, due to dysarthria that had persisted for 16 years, and facial and limb twitching that had been ongoing for 2 years, with a significant increase in symptoms over the last 2 months. The patient had gradually developed unclear speech 16 years ago without any obvious cause, her expression was not fluent, but it did not affect normal communication. The condition was not taken seriously and was not formally diagnosed or treated, with the dysarthria slowly worsening over time. Two years ago, without any obvious cause, she suddenly began to have involuntary twitching of her face and limbs. The symptoms were easily triggered and aggravated during menstruation and periods of tension but would gradually alleviate after rest and relaxation. The patient could independently dress, unbutton clothes, eat, walk and ride a bicycle, occasionally choking on water. After the onset of the disease, she had been treated at a local hospital and reported some improvement in symptoms, but the specific medication was not known. The involuntary twitching of her face and limbs worsened 2 months ago, persisted without any alleviation, and she could no longer walk independently. She had

difficulty dressing, unbuttoning clothes and eating independently, and drooling was observed. She had visited a psychiatric hospital for further diagnosis and treatment and was given antianxiety and antidepression treatments, but the specifics were not known and the symptoms did not alleviate. There were no similar medical histories in her family, no history of consanguineous marriage, no history of prematurity or birth trauma, her menstruation was regular and she had one son and one daughter. On hospital admission, her articulation was not clear, and visual acuity was diminished on coarse testing, coarse visual acuity can see finger shaking within 1 m. Visibly uncontrollable muscle twitching was observed in her face and limbs. Her limb strength was slightly poor, sensation was normal and coordination was poor, including poor completion of the finger-nose test, heel-knee-shin test and alternating movement test. The tendon reflex was normal, and pathological reflex was not elicited. On further examination, mild anaemia was observed. The results of tests for coagulation function, infectious diseases, liver and kidney function, electrolytes, blood lipids, fasting blood sugar, myocardial enzymes, homocysteine, routine urine and faeces tests, tumour markers, hepatitis B antibodies, and blood autoimmune encephalitis-related antibody detection showed no obvious abnormalities. After admission, a lumbar puncture was performed. The cerebrospinal fluid pressure was 165 mm H2O. Cerebrospinal fluid examination: glucose: 3.68 mmol/L (2.5–4.5), microalbumin: 236 mg/L (120–260), white cell count: 0×10^{6}cells/L. Tests for cerebrospinal fluid bacterial and fungal cultures (Ink dyeing), cerebrospinal fluid Cryptococcus detection, cerebrospinal fluid film test, cerebrospinal fluid autoimmune encephalitis-related antibody detection and cerebrospinal fluid pathogenic micro-organism metagenomic detection showed no abnormalities. MRI of the brain: Cerebellar atrophy was not observed (figure 1A, B). MR spectroscopy spectrum showed no obvious abnormalities. Electroencephalogram: Slow activity and sharp slow-wave discharge in the posterior head (figure 2). Electromyogram: Multifocal abnormalities of nerve–muscle conduction (mild, uneven distribution) in the limbs, including autonomic nerve, sensory, motor, F wave, somatosensory evoked potential, blinking reflex were abnormal. The initial diagnosis after admission was primary dystonia and epilepsy, and the patient was mainly treated with fluphenazine, sodium valproate, benzocaine and vitamin B_6, vitamin B_1, vitamin B_{12}. After the aforementioned treatment, the patient's dysarthria improved, and the involuntary twitching of the face and limbs improved. The patient was discharged and scheduled for a follow-up. However, about 10 days after discharge, the patient's facial and limb twitching worsened again, and she was readmitted. Genetic testing indicated an NEU1 mutation, c.544A > G(P.S182G). Further testing of the patient's parents revealed that this mutation came from both parents and were both heterozygous mutations. Based on the genetic testing results, the diagnosis was sialidosis type 1. Due to financial constraints, enzyme analysis was not performed. Further ophthalmic examination revealed a significant decrease in vision: visual acuity in left eye: 0.02, visual acuity in right eye: 0.02. Fundus photos: no cherry-red spots were observed (figure 3). Optical coherence tomography (OCT) of the macula: The echo of the retinal neuroepithelial layer in the macula area of both eyes was enhanced (figure 4A). OCT of the optic disc: The retinal nerve fibre layer of both eyes was thin, especially on the nasal side and temporal side (figure 4B). After treatment with diazepam, agomelatine and sodium valproate,the patient's symptoms did not improve significantly and died of status epilepticus 10 days after discharge.

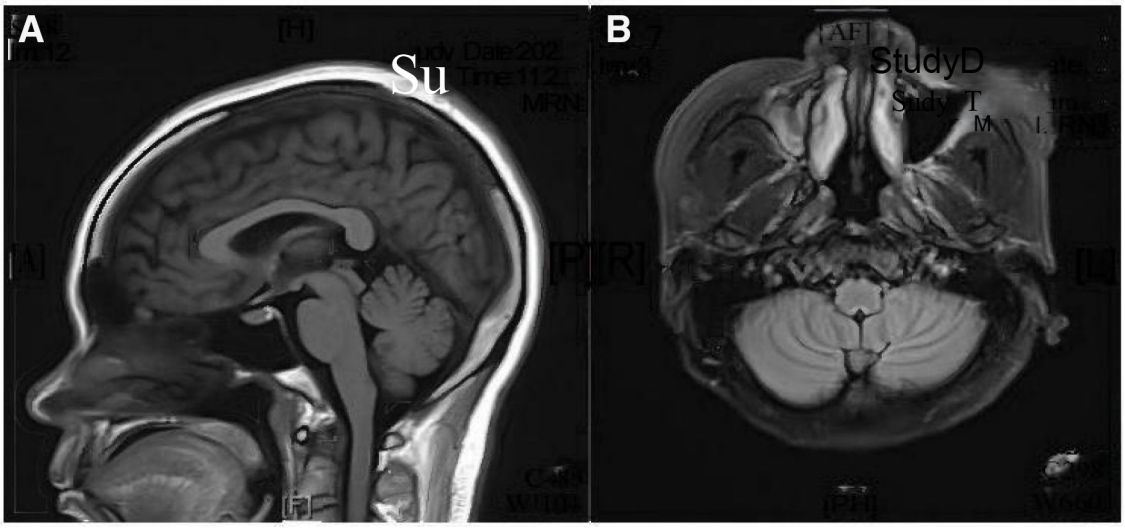

Figure 1 (A, B) (MRI T1): cerebellar atrophy was not observed.

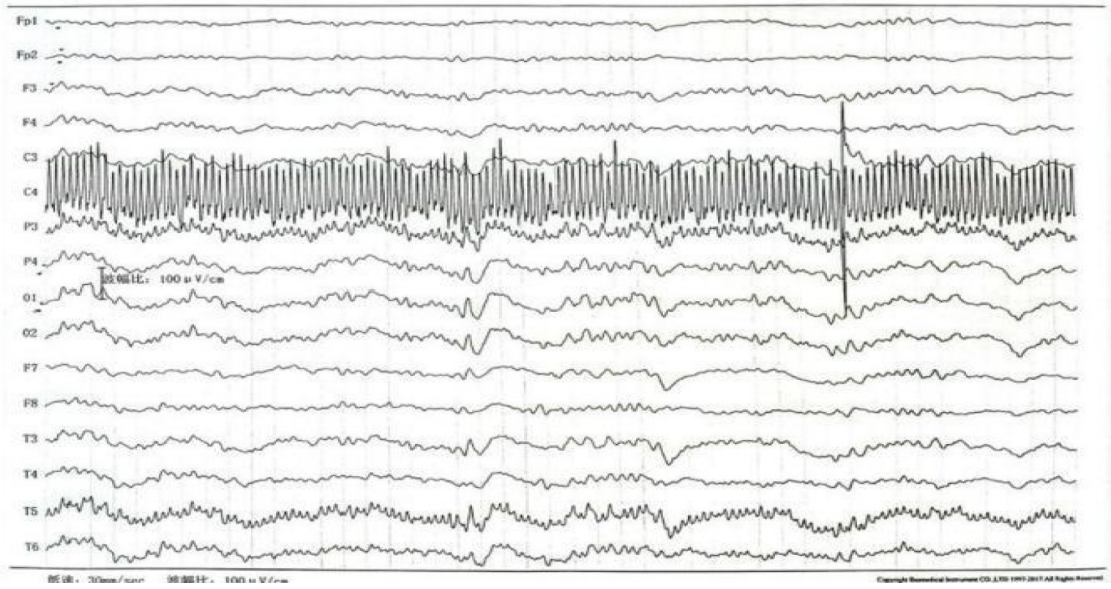

Figure 2 Dynamic electroencephalogram: slow activity and sharp-slow wave discharges in the occipital region.

DISCUSSION

Since the first report of sialidosis by Guazzi *et al*[5] in 1968, it has been identified as a specific neurological disorder.[6] It was later confirmed that this group of autosomal recessive genetic diseases is caused by mutations in the NEU1 gene.[1] This mutation leads to a deficiency in neuraminidase, an enzyme that plays a critical role in removing terminal sialic acid molecules from oligosaccharides and glycoproteins. This deficiency results in the storage of large molecules rich in sialic acid and excretion of sialic oligosaccharides in urine,[7] leading to a buildup of sialic acid and a series of clinical symptoms. According to these symptoms, sialidosis can be classified into types I and II. Type I is characterised by late-onset (10–20 years old) progressive visual impairment, cherry-red spots in the fundus, myoclonic epilepsy and cerebellar ataxia.[2] On the other hand, type II features morphological traits such as facial coarseness, short trunk, barrel-shaped chest, spinal deformities and skeletal dysplasia, and may sometimes be accompanied by corneal clouding, hepatomegaly and inner ear hearing loss. The onset of type II is earlier, with early death. This metabolic disorder exhibits characteristic manifestations in the macula, such as the appearance of 'cherry-red spots', which could potentially lead to ganglion degeneration and significant late-stage visual impairment. However, these cherry-red spots may not

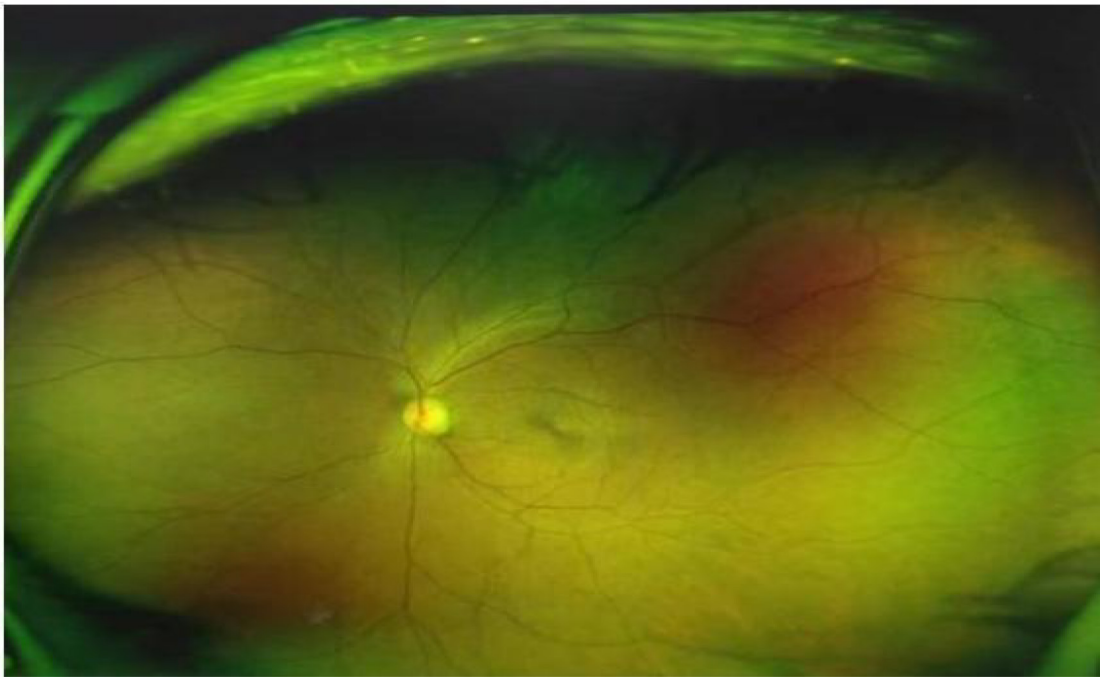

Figure 3 Fundus examination reveals no signs of cherry-red spots.

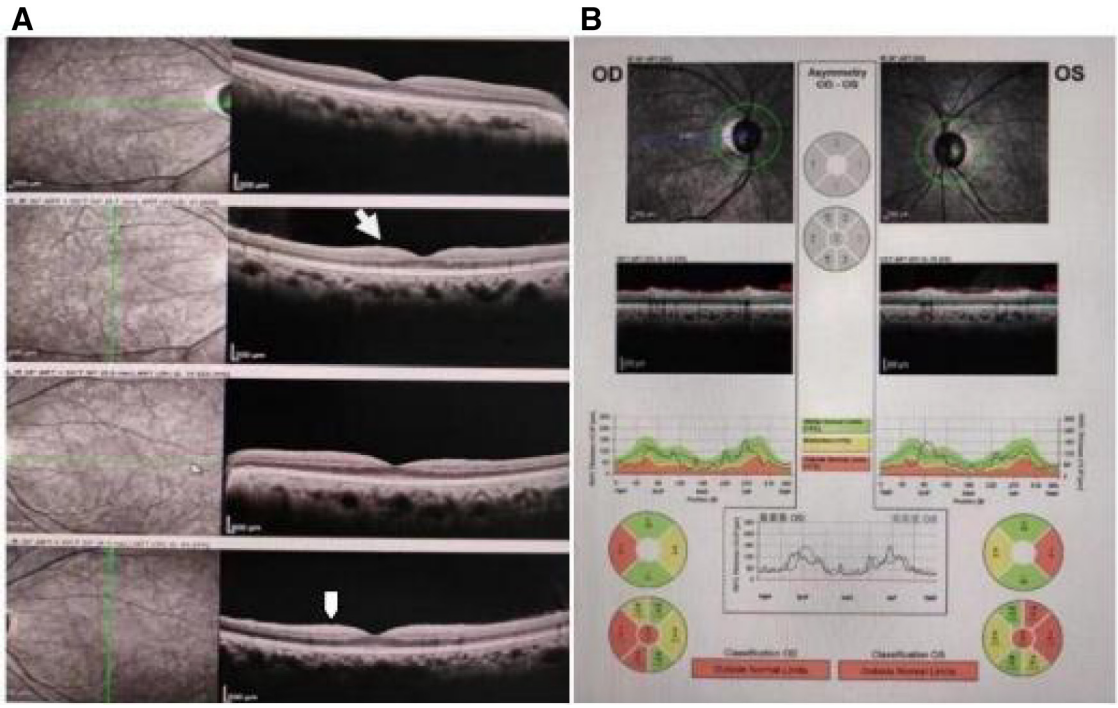

Figure 4 (A) Macular OCT: enhanced echo in the retinal neuroepithelial layer of both macular regions,we have marked the areas with significant echo enhancement using arrows; (B) Disc OCT examination: thinning of the retinal nerve fibre layer in both eyes, more evident on the nasal side and temporal side. OCT, optical coherence tomography. OD denotes the right eye, and OS denotes the left eye.

be detected in clinical examinations for many years and may disappear in the late stages of the disease. Studies by Kivlin *et al* suggest that these spots may appear early and disappear later,[8] while Qun Wang *et al* summarise that these spots could disappear as the disease progresses or appear 20 years after onset.[9] Given the presence of cherry-red spots in the fundus, type I sialidosis is also known as cherry-red spot myoclonus syndrome.[3] However, Bou Ghannam AS *et al* reported a case where no cherry-red spots were observed in the fundus.[10] Likewise, Coppola *et al* observed patients for as long as 30 years and found no cherry-red spots in the fundus.[11] Therefore, while cherry-red spots may appear in type I sialidosis, using it to name the disease is imprecise and may mislead clinicians in making early diagnoses.

In 2009, 17 confirmed cases of type I sialidosis were reported in Taiwan, with a significantly lower incidence of cherry-red spots than other regions. Only three cases were detected with cherry-red spots after over 10 years of follow-up.[12] In patients diagnosed in Taiwan and mainland China, the most common types of mutations arec.544A>G. In contrast, the chance of cherry-red spots appearing in type I sialidosis reported in mainland China is notably higher than in Taiwan.[9] In this report, our first patient from the Hainan Free Trade Port caused by a mutation in this gene c.544A>G, and the patient did not show cherry-red spots in the fundus. Given the geographical proximity to Taiwan, we hypothesise that the presence of cherry-red spots may be related to the environment. Additionally, besides macular cherry-red spots, some reports have noted that punctate cataracts and corneal clouding are characteristic ophthalmic signs of sialidosis.[13]

From the currently reported cases, the primary manifestation of type I sialidosis is myoclonus, which can be exacerbated by menstruation, stress, light stimulation, voluntary movement, passive joint motion, light touch or sound stimulation.[3 11 12] Among reported cases with complete visual and somatosensory evoked potentials, all patients presented with abnormal somatosensory evoked potentials accompanied by giant cortical waves. Prolonged latencies of P100 peaks in visual evoked potentials were observed even under normal vision.[4 12–15] Thus, we suggest routine genetic testing for sialidosis in patients with unexplained myoclonus and those with the aforementioned manifestations in visual and somatosensory evoked potentials. Type 1 sialidosis needs to be distinguished from progressive myoclonic ataxia and progressive myoclonic epilepsy. Sialidosis type I, presenting with cortical myoclonus as the main symptom, should be differentiated from other forms of progressive myoclonus epilepsy.[2]Clinical type 1 sialidosis is mostly consistent with the diagnosis of progressive myoclonic epilepsy, which is difficult to distinguish according to clinical manifestations, or active genetic testing should be conducted for patients with myoclonus. Type 1 sialidosis was initially discovered in relatively early patients to have no apparent abnormalities in cranial MRI, but as time went on, the disease manifested as cerebellar atrophy, primarily in the vermis, which is in line with the clinical symptoms of cerebellar ataxia.[11 16] The diagnosis of this disease may not

be appropriate if it solely relies on the enzymatic assessment because the enzyme activity might be affected by the sample location and experimental conditions. Detection of neuraminidase alone is not specific. Typically, researchers diagnose sialic acid disease by detecting neuraminidase activity in cultured fibroblasts or leucocytes. The enzyme activity is unstable and generally serves as a screening tool, but genetic testing is also key to a definitive diagnosis.[9] Type 1 sialidosis is a progressively worsening disease without any particularly effective cure. However, due to the rarity of this disease, there are no statistical data available about the life expectancy of the patients. As time goes on, patients gradually lose their ability to move. Our patient died of status epilepticus at the age of 40, which may greatly assist in the future statistics and prognosis judgement of this disease.

At present, the treatment for this disease is mainly symptomatic, targeting epileptic seizures and myoclonus. Patients are given levetiracetam, sodiumvalproate,phenobarbital, zonisamide, topiramate and piracetam,[11] and benzodiazepines are beneficial in improving epilepsy and myoclonus symptoms.[2 17] However, it is necessary to avoid drugs such as carbamazepine, phenytoin, gabapentin and vigabatrin, which can exacerbate myoclonus. Lamotrigine can be used cautiously because it can worsen myoclonus in some patients.[3] Some studies have shown that dietary supplementation with betaine, a natural amino acid derivative, may benefit the treatment of type I sialic acid poisoning by serving as a histone deacetylase inhibitor, inducing a sustained increase in the residual activity of mutated NEU1 in patient primary fibroblasts.[11 18]

In summary, the manifestation of cherry-red spots in the fundus in type 1 sialidosis might be environment related. Moreover, for patients with clinical myoclonus, especially those with giant cortical waves in somatosensory evoked potentials and prolonged latency of P100 peaks in visual evoked potentials, they should actively improve genetic testing to ascertain if they have sialidosis.

Contributors ZC and LZ conceived the idea and drafted the manuscript, XS collected clinical materials, ZY modified the article. All authors read and approved the final version of the manuscript.

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Data availability statement The data that support the findings of this study are available upon reasonable request from the corresponding author. The original contributions presented in this study are included in this article/online supplemental material, further inquiries can be directed to the corresponding authors.

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ORCID iDs
Zhongkai Liao http://orcid.org/0009-0009-2639-5526
Yanhui Zhou http://orcid.org/0009-0004-2581-1130

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