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Chronic Progressive External Ophthalmoplegia (CPEO) Associated with "Twilight Lactic Acidosis": Case Report and Literature Review

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1. Abstract

Chronic Progressive External Ophthalmoplegia (CPEO) is a rare mitochondrial disorder characterized by bilateral, slowly progressive ptosis and external ophthalmoplegia. In this article, we present the case of a 33-year-old female patient who exhibited atypical symptoms of CPEO, with initial symptoms of lower limb weakness and atypical external ophthalmoplegia. The diagnosis was confirmed through mitochondrial gene sequencing, revealing a mitochondrial DNA deletion. To the best of our knowledge, this is the first case reported in China where CPEO initially presented with lower limb weakness as a neurological/muscular symptom. Given its potential for misdiagnosis in orthopedics and neurology, this case holds significant clinical reference value.

2. Introduction

Mitochondrial DNA Depletion Syndrome (MDS) is a clinical spectrum caused by mutations in the mitochondrial and nuclear genomes, which lead to impaired function of the electron transport chain and subsequent energy deficits(Jacoby et al. 2022). The most common form is Single Large-Scale Mitochondrial DNA Deletion Syndrome (SLSMDs). In probands with characteristic clinical features, the diagnosis of SLSMDs is established by identifying mitochondrial DNA (mtDNA) deletions ranging in size from 1.1 to 10 kb through molecular genetic testing(Shanske et al. 2002; Remes et al. 2005; Hanisch et al. 2015).

Different subtypes encompass overlapping clinical phenotypes, including Kearns-Sayre Syndrome (KSS)(Berenbaum et al. 1990; Tsang et al. 2018), the KSS spectrum, Pearson Syndrome (PS) (Farruggia et al. 2018; Yoshimi et al. 2022), Chronic Progressive External Ophthalmoplegia (CPEO), and CPEO-plus(Fan et al. 2021). Most cases are sporadic, but familial cases may follow an autosomal dominant, autosomal recessive, or maternal inheritance pattern. Muscle biopsy is the gold standard for diagnosis, revealing characteristic cytochrome c oxidase deficiency and ragged red fibers(Chanprasert et al. 2013; Al-Hussaini et al. 2014; da Silva Rocha et al. 2023). Orbital imaging typically shows atrophy of the extraocular muscles.

Translation:

KSS is a progressive multisystem disorder that manifests before the age of 20 years, characterized by pigmentary retinopathy, CPEO, and cardiac conduction abnormalities(Berenbaum et al. 1990; Tsang et al. 2018). Other features may include cerebellar ataxia, tremor, intellectual disability or cognitive decline, dementia, sensorineural hearing loss, oropharyngeal and esophageal dysfunction, exercise intolerance, myopathy, and endocrine disorders. Brain imaging typically reveals bilateral lesions in the globus pallidus and white matter(Nguyen et al. 2019; Arun and Kaur 2021). The symptoms of KSS include ptosis and/or ophthalmoplegia, as well as at least one of the following: retinopathy, ataxia, cardiac conduction defects, hearing loss, growth retardation, cognitive impairment, tremor, or cardiomyopathy. Compared with CPEO-plus, patients in the KSS spectrum have more severe muscle involvement (e.g., weakness, atrophy) and a poorer overall prognosis.

Pearson Syndrome (PS) is characterized by pancytopenia (typically transfusion-dependent sideroblastic anemia with variable lineages affected), exocrine pancreatic dysfunction, poor weight gain, and lactic acidosis(Nilay and Phadke 2020; Shahid et al. 2023). The manifestations of PS also include renal tubular acidosis, short stature, and elevated liver enzymes. PS can be fatal in infancy due to infections related to neutropenia or refractory metabolic acidosis.

Chronic Progressive External Ophthalmoplegia (CPEO) is a rare mitochondrial disease within the spectrum of mitochondrial DNA depletion syndromes. CPEO is characterized by ptosis, ophthalmoplegia, oropharyngeal weakness, varying degrees of proximal limb weakness, and/or exercise intolerance(Liu et al. 2023; Ali et al. 2024). CPEO-plus includes CPEO combined with involvement of other multisystems, such as neuropathy, diabetes, migraine, hypothyroidism, neuropsychiatric manifestations, and optic neuropathy.

3. Case Presentation

The patient is a 33-year-old female who was admitted to the Department of Neurology on October 18, 2023, due to bilateral lower limb weakness for over 9 months. The patient reported that the weakness in her lower limbs had developed without any obvious cause 9 months prior. She did not experience fever, headache, nausea, vomiting, chest pain, or any other discomfort.

Annals of Clinical and Medical Case Reports

At that time, she did not seek medical treatment. One month prior to admission, the patient reported a significant worsening of her lower limb weakness, to the extent that she could no longer climb stairs. She continued to have no fever, headache, nausea, vomiting, chest pain, or other discomforts. Seeking further diagnosis and treatment, she visited our hospital's outpatient clinic. The outpatient clinic conducted a series of examinations, which revealed the following findings: 1. Focal demyelinating changes in the left frontal, parietal, and temporal lobes; 2. Partial empty sella; 3. Mild degenerative changes in the cervical spine; 4. No significant abnormalities in the thoracic vertebral bone signal; 5. Linear high T2 signal within the cervical and thoracic spinal cord, with possible slight dilation of the central canal in some areas; 6. Lumbar spine degenerative changes; 7. No significant abnormalities in the sacral and coccygeal vertebrae.

Based on these findings, the outpatient clinic admitted her to the hospital with a provisional diagnosis of "demyelinating disease."

Specialist Physical Examination: The patient was conscious and oriented. Her neck was soft without resistance. Bilateral pupils were equal in size and round, approximately 2.5 mm in diameter. Cardiopulmonary auscultation was normal. The abdomen was soft, without tenderness or rebound tenderness. No obvious edema was observed in the lower limbs.

The MRI images and examinations obtained in the outpatient clinic were not specific. The MRI images are shown in Figure 1, where the red arrows indicate slight demyelinating changes in the brain and linear high T2 signals within the spinal cord.

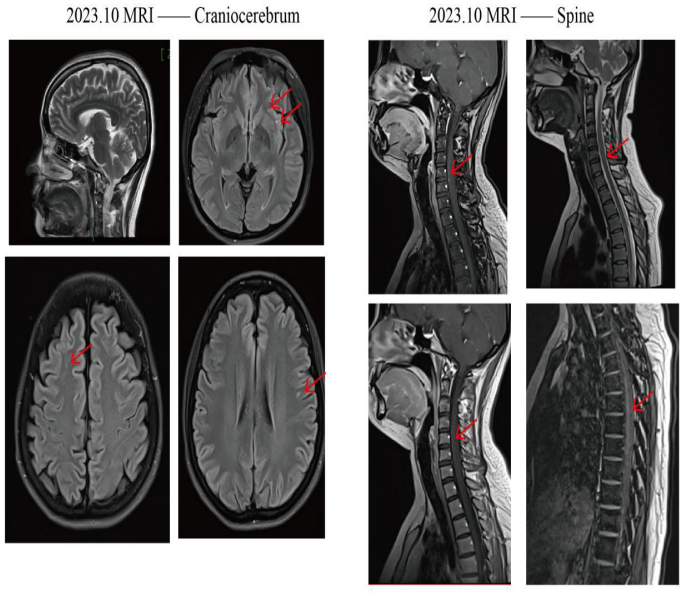

Figure 1: Axial and sagittal MRI images of the brain and whole spine obtained on October 6, 2023. Red arrows indicate areas of demyelinating signal abnormalities and high T2 signal within the spinal cord.

After admission, the patient was treated for demyelinating disease, and relevant examinations were actively completed. Corticosteroid pulse therapy was administered: Methylprednisolone, 60 mg, once daily (qd) for three days, followed by Methylprednisolone 1000 mg, qd for one week. After discharge, Prednisone 5 mg, qd was added orally. On October 23, 2023, a lumbar puncture was performed to confirm the diagnosis. Cytological examination of the lumbar puncture revealed a few lymphocytes and residual nuclei.

The patient underwent a follow-up MRI on October 23, 2023. The results indicated:

The structures of the bilateral cerebral hemispheres are symmetrical, with normal contrast between gray and white matter. Scattered punctate and small patchy high FLAIR signals are observed in the bilateral frontal lobes and the left parietal and temporal lobes, with clear margins. No ventricular enlargement, no significant widening or deepening of sulci and fissures, and the midline structures are centrally located. No significant abnormal enhancement is observed in the enhanced scan.

TOF-MRA: The lumen of the bilateral anterior, middle, and posterior cerebral arteries and the internal carotid arteries is patent, with no significant localized stenosis or abnormal dilation observed. No other significant abnormal vascular malformations are noted. Mild enhancement of the dura mater at the level of the C5-C6 vertebrae is observed, with no significant abnormal enhancement in the remaining cervical and thoracic vertebrae.

Conclusion: 1. Scattered punctate high white matter signals in the bilateral frontal lobes and the left parietal and temporal lobes, with no change compared to the previous scan, no enhancement observed, suggestive of possible demyelinating lesions. 2. Partial empty sella. 3. No significant abnormalities observed in brain TOF-MRA. 4. Mild enhancement of the dura mater at the level of the C5-C6 vertebrae, with no significant abnormal enhancement in the remaining cervical and thoracic vertebrae. The previously noted "linear high T2 signal within the cervical and thoracic spinal cord" shows no enhancement in the corresponding area.

Laboratory Test Results: Serum GFAP antibody: Positive. October 22, 2023: ENA panel - 1 [Serum]: Anti-nuclear antibody titer 1:100 ↑. Cerebrospinal fluid (CSF) biochemistry 7 items - 1 [CSF]: CSF glucose 5.49 mmol/L ↑. CSF routine, CSF immunoglobulin + albumin (CSF) were all normal. Acid-fast bacilli and Cryptococcus neoformans were not found in the CSF. CSF cytology revealed a few lymphocytes and residual nuclei. Further diagnosis should be made in combination with clinical manifestations and relevant examinations. External tests for CSF anti-GFAP antibody (2 items) and oligoclonal bands in serum and CSF were all negative. No other significant abnormalities were noted.

After corticosteroid pulse therapy, the patient experienced significant improvement in limb weakness and had a generally good condition. Following discharge, the patient adhered to the prescribed medication regimen: Prednisone: 5 mg per tablet, 12 tablets once daily. The dosage will be reduced by 2 tablets per week until reaching 4 tablets, at which point a follow-up visit is required. Mycophenolate Mofetil: 0.25 g per tablet, 1 tablet twice daily.

Four months later, on February 28, 2024, the patient experienced a relapse and was readmitted to the hospital. An MRI of the thoracic spine with and without contrast was performed on February 29, 2024. The conclusions are as follows: Scattered punctate high white matter signals in the bilateral frontal lobes and the left parietal and temporal lobes, with no change compared to the previous scan.

Annals of Clinical and Medical Case Reports

Follow-up is recommended. Partial empty sella. Mild degenerative changes in the cervical spine, similar to the previous findings. No significant abnormalities in the thoracic vertebral bone signal. Linear high T2 signal within the cervical and thoracic spinal cord, as previously observed, with possible slight dilation of the central canal in some areas.

The previously noted "mild enhancement of the dura mater at the level of the C5-C6 vertebrae" is not evident in this scan.

The high white matter signals and linear high T2 signals within the spinal cord mentioned in the examination are not significantly specific and show no significant changes compared to the previous examinations. The patient's condition still cannot be further clarified through MRI or other imaging studies. The MRI images are shown in Figure 2, with red arrows indicating the high white matter signals and the linear high T2 signals within the spinal cord.

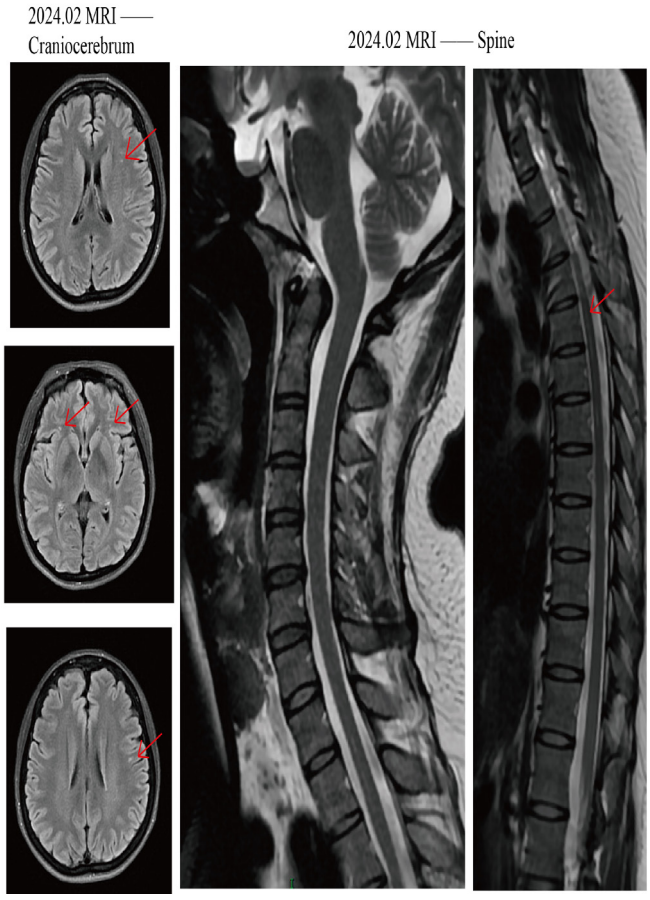

Figure 2: Axial and sagittal MR images of the brain and whole spine obtained on February 29, 2024. Red arrows indicate areas of abnormal white matter signals in the brain and high T2 signals within the spinal cord.

Laboratory Test Results on February 29, 2024:
Biochemistry 26 items + TNI [Serum]:
Creatinine: 42.3 μmol/L ↓
Triglycerides: 2.49 mmol/L ↑
Low-density lipoprotein cholesterol: 3.49 mmol/L ↑
High-density lipoprotein cholesterol: 0.97 mmol/L ↓
Glomerular filtration rate: 129.43 ml/min/(1.73m²) ↑
Urinalysis on March 1, 2024:
Urinalysis - 1 [Urine]:
Occult blood in urine: 1+ ↑
Thyroid Function Tests on March 9, 2024:
Thyroid function three items - 1 [Serum]:
Free T4 (FT4): 13.4 pmol/L
Free T3 (FT3): 3.6 pmol/L
Thyroid-stimulating hormone (TSH): 2.1963 μIU/ml

After admission, the patient underwent comprehensive examinations and was provided with symptomatic treatments aimed at nourishing the nerves, improving circulation, regulating lipid levels, lowering blood glucose, and controlling blood pressure. The patient's symptoms showed slight improvement, and she was discharged again to continue oral medication therapy: Idebenone Tablets: 1 tablet, three times daily. Prednisone: 10 tablets after meals, to be maintained for 4 weeks, followed by gradual tapering. The dosage will be reduced by 2 tablets every two weeks until reaching 2 tablets, which will then be maintained.

On November 16, 2024, after more than half a year, the patient's symptoms had significantly progressed, and she had developed dyspnea, leading to her readmission. The admission details were as follows: Chief Complaints:Bilateral lower limb weakness for over six months; Palpitations for three days; Dyspnea for 17 hours. Medical History: More than six months ago, the patient developed bilateral lower limb weakness without any obvious cause. She could not climb stairs but did not experience fever, headache, nausea, vomiting, chest pain, or other discomforts. She had been hospitalized multiple times for treatment. Tests revealed positive GFAP (glial fibrillary acidic protein) antibodies and spinal cord lesions. Three days prior to admission, the patient experienced intermittent palpitations following an episode of diarrhea. She noticed a rapid heart rate, especially when sitting up, with a rate of approximately 150 beats per minute, accompanied by dyspnea that improved when lying flat. She denied any relief of the rapid heart rate, chills, nausea, vomiting, fatigue, sore throat, or back pain. Seventeen hours prior to admission, her palpitations and dyspnea worsened, prompting her to visit the emergency department of our hospital. She was admitted to the Department of Neurology with a provisional diagnosis of "myasthenia gravis, moderate generalized type." No significant edema was observed in the lower limbs. Muscle strength in the lower limbs was graded 2-3, while muscle strength in the upper limbs was graded 4.

On the second day of admission, November 17, 2024, the patient experienced worsening palpitations and dyspnea. She was treated with neostigmine methylsulfate infusion, oral pyridostigmine bromide, eculizumab, and anti-inflammatory therapy. However, the treatment effects were poor. At 11:00 AM, her heart rate was 150 beats per minute, SpO_2 was 100%, and respiratory rate was 40 breaths per minute. She was confused, had difficulty breathing, and her speech was slurred and indistinct. Her pupils were equal in size and round, with a diameter of 3 mm, and the light reflex was present. She was then transferred to the ICU of our hospital for further treatment. After admission, she was intubated and provided with mechanical ventilation support. The patient was in a sedated and analgesic state, with the following parameters: FiO_2 30%, PEEP 5 cmH_2O, SpO_2 100%, respiratory rate 15 breaths per

Annals of Clinical and Medical Case Reports

minute, heart rate 135 beats per minute, and blood pressure 188/111 mmHg. Blood gas analysis revealed the following results: On November 17, 2024: Arterial blood gas analysis + four electrolytes: pO_2 145.0 mmHg ↑, sO_2 99.2% ↑, ctO_2 22.2 Vol% ↑, Hct 49.1% ↑, cK^+ 3.4 mmol/L ↓, cCl^- 114 mmol/L ↑. At 15:00 PM on the same day, repeat blood gas analysis: Arterial blood gas analysis: pH 7.37, pCO_2 40 mmHg, pO_2 93 mmHg, HCO_3^- 23.1 mmol/L, ctHb 15.4 g/dL, cK^+ 2.6 mmol/L, cNa^+ 135 mmol/L, cCa^{2+} 0.9 mmol/L, cGlu 13.3 mmol/L, Lac 5 mmol/L, FiO_2 30%, oxygenation index 310 mmHg.

The patient remained in the ICU with continuous endotracheal intubation and ventilator support, under sedation and analgesia. A consultation with the Department of Neurology was arranged, and the possibility of Guillain-Barré syndrome was considered. During the treatment, it was observed that the patient's lactate levels increased every afternoon, fluctuating between 4.0 and 5.0 mmol/L, while decreasing from evening to the next morning, ranging from 1.3 to 3.0 mmol/L, presenting a phenomenon known as "twilight lactic acidosis." The specific details are shown in Figure 3.

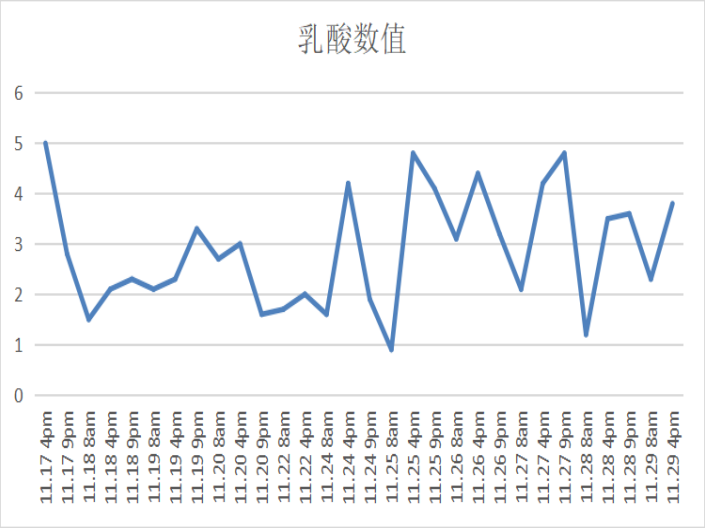

Figure 3: Blood lactate levels of the patient from November 17 to November 29. The x-axis represents the time of measurement, and the y-axis represents the lactate levels.

After admission to the intensive care unit, the patient continued with the treatment plan from the Department of Neurology, which included pyridostigmine bromide, prednisone, and eculizumab. She was intubated and provided with mechanical ventilation, and sputum cultures were obtained. In addition, she received anti-infective treatment, nutritional support, and thromboprophylaxis. However, her symptoms did not significantly improve. On November 26, she underwent a tracheostomy. Subsequently, a muscle biopsy was performed, and the results are as follows: Gross Examination: A heap of grayish-white fragmented tissue with a diameter of 0.5 cm. Microscopic Examination: The submitted tissue was entirely sampled and repeatedly sectioned. Under the microscope, muscle fibers were of varying thickness but were arranged in a relatively regular pattern. No distinct ragged red fibers were observed, and no significant inflammatory cell infiltration was seen in the interstitium. No other significant findings were noted. Please correlate with clinical findings.

As shown in Figure 4A and the biopsy results, muscle HE staining still lacks specific signs, making it impossible to diagnose a muscle system disease. However, we further stained the sections with immunofluorescence using anti-human Tom20 antibody (CST company 42406). Since Tom20 is a marker protein of the mitochondrial outer membrane, Tom20 antibody is commonly used to label mitochondria and can be used to observe changes in mitochondrial morphology, distribution, and quantity in cell biology experiments.

Positive Tom20 antibody staining (indicated by red markers in Figure 4B) suggests that the structure and localization of mitochondria are essentially normal. As an important component of the mitochondrial outer membrane translocase complex, Tom20 is responsible for recognizing and transporting precursor proteins into the mitochondria. A high number of positively stained cells and strong staining intensity may indicate vigorous cellular metabolic activity, requiring a large number of mitochondria to provide energy (ATP). Conversely, weak positive staining may suggest relatively lower cellular metabolic activity.

As shown in Figure 4B, the number of mitochondria is significantly reduced, and the staining intensity varies, indicating inconsistent mitochondrial function. The weak positive staining suggests poor cellular metabolism and weak mitochondrial function.

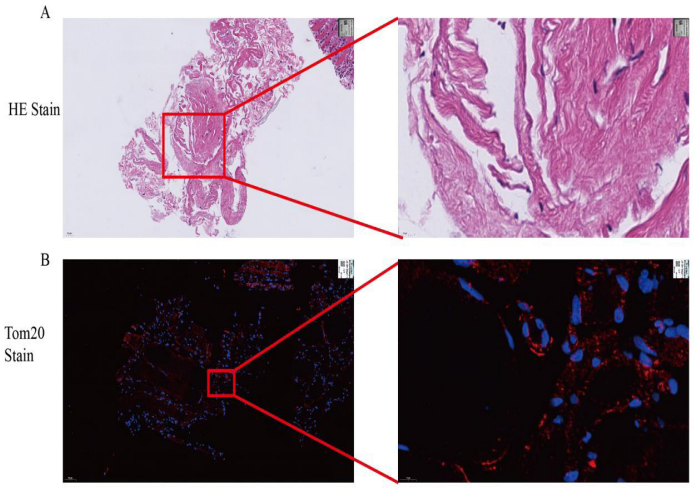

Figure 4: Histological sections of the patient's muscle biopsy. (A) Schematic diagram of hematoxylin and eosin (HE) staining. (B) Schematic diagram of Tom20 mitochondrial immunofluorescence staining.

Based on the patient's electromyogram characteristics (neurogenic damage + myogenic damage), poor response to neostigmine test, absence of thymoma, fluctuating lactate levels, HE staining, and Tom20 antibody staining, the patient's medical records were reviewed again. It was considered that mitochondrial myopathy and metabolic diseases could not be ruled out. Therefore, mitochondrial DNA testing and blood/urine organic acid tandem mass spectrometry analysis were ordered.

While awaiting the results of mitochondrial sequencing, on December 10, 2024, the patient was empirically started on a

Annals of Clinical and Medical Case Reports

cocktail therapy for mitochondrial diseases: Coenzyme Q10 tablets (Nengqilang), idebenone tablets (Jinborui), and (Miya) treatment. After treatment, the patient's mental state significantly improved, and she became responsive to calls. On December 15, an attempt was made to wean her off the ventilator, but she experienced rapid breathing, and the weaning attempt failed. Sedation and analgesia were continued. On December 17, the patient had difficulty weaning off the ventilator. After multiple attempts, the patient became agitated and indicated respiratory distress through gestures and mouth movements. Mechanical ventilation support was continued. Then, the patient's pulmonary infection improved, and her mental state also improved. She reported that her memory of the time before intubation was gradually becoming blurred and fading away. On December 19, the patient's infection symptoms further improved. She continued with the cocktail therapy of coenzyme Q + idebenone + escitalopram and gradually tapered off the corticosteroids and reduced the dose of pyridostigmine bromide. On the same day, the results of mitochondrial sequencing were obtained, as shown in Figure 5. Figure 5A shows the blood test results, Figure 5B shows the urine test results, and Figure 5C shows the Sanger sequencing peak for breakpoint validation. It can be seen that the exact breakpoint of the mitochondrial DNA segment in the sequencing is chrMT:610-15912.

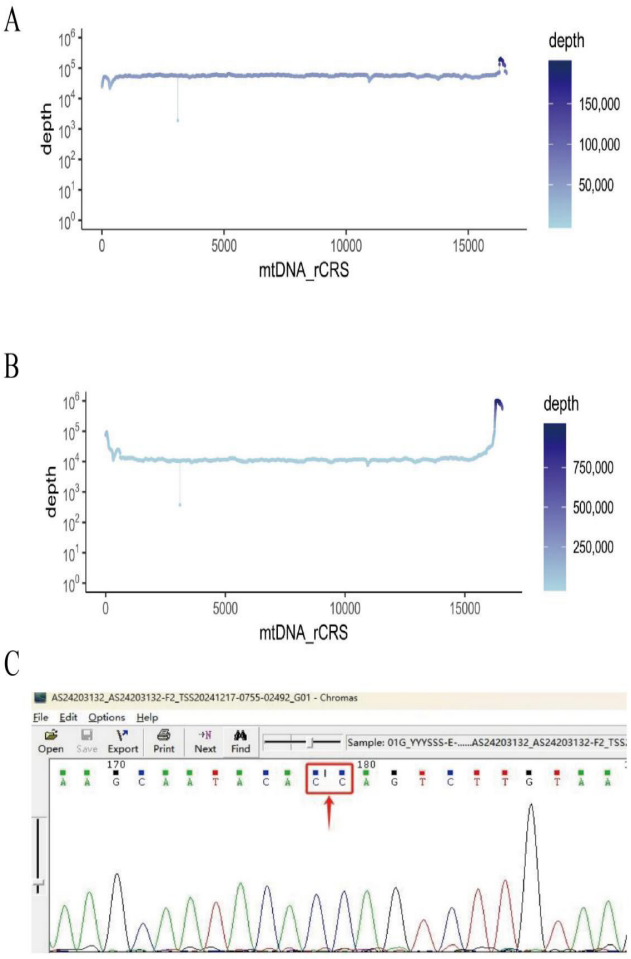

Figure 5: Mitochondrial gene sequencing results of the patient. A. Blood test results; B. Urine test results; C. Sanger sequencing peak for breakpoint validation.

The sequencing results indicate that a pathogenic large-scale deletion was identified in the mitochondrial genome of the proband's urine sample, spanning the MT: 610-15912 region. This deletion encompasses the genes MT-ND2, MT-CO1, MT-CO2, MT-ATP8, MT-ATP6, MT-CO3, MT-ND3, MT-ND4L, MT-ND4, MT-ND5, MT-ND6, and MT-CYB. Additionally, no pathogenic gene mutation sites highly correlated with the patient's phenotype were detected in the mitochondrial genome of the tested sample.

On December 20, a consultation with Tongji Hospital regarding the mitochondrial sequencing results led to a diagnosis of Single Large-Scale Mitochondrial DNA Deletion Syndrome (SLSMDs), CPEO subtype. The consultation recommended the addition of methylcobalamin and vitamin C to the treatment regimen. The patient was discharged on December 22 to continue rehabilitation therapy at a local hospital. Follow-up results indicate that the patient has been successfully weaned off the ventilator.

4. Discussion

Reviewing the patient's entire medical journey, it is evident that her symptoms manifested as ascending weakness starting from the lower limbs. Initial MRI scans of the brain and spinal cord suggested demyelinating disease with abnormal signals in the spinal cord, leading to a diagnosis of myelitis. However, corticosteroid pulse therapy and other interventions yielded poor results. Subsequently, the differential diagnosis included neuromyelitis optica spectrum disorder and encephalomyelitis, but these diagnoses were also not supported by the clinical response. Myasthenia gravis was then considered, but the relevant antibody tests and electromyography findings were atypical. The neostigmine test showed some improvement, leading to a presumptive diagnosis of myasthenia gravis and treatment with pyridostigmine and corticosteroids, which resulted in some symptom improvement.

Later, a common cold exacerbated the patient's symptoms. Despite treatment with pyridostigmine, corticosteroids, and monoclonal antibodies, the patient's condition deteriorated, with significant respiratory weakness and severe lower limb weakness. In the ICU, metabolic diseases were ruled out through extensive workup, including exome sequencing, autoimmune encephalitis testing, and rheumatological evaluations. A muscle biopsy was also performed, but histopathological examination did not reveal any mitochondrial abnormalities.

4.1. Translation:

Blood gas analysis revealed that the patient's lactate levels were normal in the morning but significantly increased in the afternoon, with heart rate acceleration and lactate levels reaching up to 4 mmol/L. This increase was not related to fluid management, and lactate levels would normalize by the next morning, occurring almost daily. Considering mitochondrial issues, combined with the Tom20 mitochondrial staining results from the muscle biopsy, we strongly suspected a mitochondrial disease. Subsequently, we empirically initiated cocktail therapy for mitochondrial diseases, which resulted in significant improvement in the patient's mental state after treatment. Therefore, summarizing

the above points (twilight lactic acidosis, low Tom20 staining, and effective treatment with coenzyme Q), all mutually corroborate the diagnosis of mitochondrial disease. However, the lower limb muscles had already atrophied and could not be restored, but the mental improvement was significant, with even the memory before medication being lost, further supporting the diagnosis of mitochondrial disease. The medical and examination process was relatively tortuous, with pathology still unable to confirm the diagnosis. Ultimately, mitochondrial sequencing confirmed the diagnosis, providing valuable experience for the diagnosis and treatment of mitochondrial genetic diseases. The entire process reflects the gradual exploration and correction of the diagnosis for this case, as well as the indicative role of treatment responses at different stages in disease diagnosis.

As previously introduced, CPEO is a rare mitochondrial myopathy characterized by bilateral, slowly progressive ptosis and external ophthalmoplegia, leading to drooping eyelids and eye muscle paralysis, and is often accompanied by oropharyngeal weakness, varying degrees of proximal limb weakness, and/or exercise intolerance. Most cases are sporadic, and the clinical phenotypes are highly variable. In this case, the patient did not present with typical ptosis or external ophthalmoplegia. Her vision was normal and instead, the initial symptom was bilateral lower limb weakness, which later progressed to respiratory muscle weakness, described as a "bottom-up" pattern of muscle weakness. This presentation is highly susceptible to misdiagnosis as myasthenia gravis or other neuromuscular diseases.

Most cases of CPEO (up to 60%) are caused by large-scale deletions in mitochondrial DNA (mtDNA), ranging from 1.3 to 9.1 kb. A smaller proportion (approximately 15%) carry point mutations, such as the m.3243A>G mutation in the MT-TL1 gene, which encodes mitochondrial tRNALeu (UUR). This mutation is associated with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). In the genetic testing of this case, a pathogenic large-scale deletion was identified in the mitochondrial genome of the patient's urine sample, spanning the MT: 610-15912 region. This deletion encompasses the genes MT-ND2, MT-CO1, MT-CO2, MT-ATP8, MT-ATP6, MT-CO3, MT-ND3, MT-ND4L, MT-ND4, MT-ND5, MT-ND6, and MT-CYB. Additionally, no pathogenic gene mutation sites highly correlated with the patient's phenotype were detected in the mitochondrial genome of the tested sample. Therefore, this is an atypical case of CPEO. The patient has mitochondrial myopathy and lactic acidosis but lacks pathogenic gene mutation sites. Her clinical manifestations are not primarily characterized by ptosis and external ophthalmoplegia, which poses diagnostic challenges. The most significant feature in the laboratory tests of this case is "twilight lactic acidosis," characterized by significantly higher blood lactate levels in the afternoon and evening compared to the morning. This is a key clue in searching for diagnostic evidence.

In terms of the diagnostic basis for the patient, the large-scale deletion in the mitochondrial genome confirmed the diagnosis of SLSMDs. Among the subtypes of SLSMDs, Kearns-Sayre Syndrome (KSS) was excluded because there was no retinitis pigmentosa, no night blindness, and the onset of symptoms was relatively late (after the age of 20). Pearson Syndrome (PS) was also excluded because the patient did not have pancytopenia, exocrine pancreatic dysfunction, or poor weight gain. Since the patient had relatively isolated symptoms and did not have neuropathy, diabetes, migraine, hypothyroidism, neuropsychiatric manifestations, or optic neuropathy, CPEO-plus was also ruled out. Regarding the confirmation of the CPEO subtype, the typical features were still not present because the patient did not have a history of typical bilateral progressive ptosis and external ophthalmoplegia, no diplopia, and no abnormality in the pupils. However, the patient did have varying degrees of limb weakness/intolerance to exercise and objective "twilight lactic acidosis," which is consistent with CPEO. Therefore, the patient had atypical manifestations of this disease. Given this clinical presentation, as well as the results of muscle biopsy and mitochondrial deletion sequencing, various differential diagnoses were considered and excluded, leading to this diagnosis.

In summary, to the best of our knowledge, this is the first reported case in China of CPEO presenting with lower limb weakness as the initial neurological/muscular symptom. Given its propensity for misdiagnosis in orthopedics and neurology, this case holds significant clinical reference value.

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Clinical trial number - not applicable

Ethics approval and consent to participate - not applicable

Consent for publication: All authors unanimously agree to the publication in the thesis.

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