

PEO Associated with a Novel POLG Mutation in a Pediatric Patient in the United Arab Emirates

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ABSTRACT

Progressive External Ophthalmoplegia (PEO) is a rare mitochondrial disorder primarily caused by mutations in the POLG gene, responsible for mitochondrial DNA replication and repair. The condition is characterized by muscle weakness, particularly in the extraocular muscles, leading to ptosis, ophthalmoparesis and other visual impairments. This case report presents an 11-year-old Pakistani patient with a novel POLG mutation. The patient exhibited generalized fatigue, muscle weakness, squint and weight loss, raising suspicion for mitochondrial dysfunction. Diagnostic tests, including nerve conduction studies and biochemical panels, pointed toward a potential neuropathic condition. Genetic testing confirmed a homozygous pathogenic variant in the POLG gene, diagnosing autosomal recessive POLG-related disease. This case highlights the importance of early genetic testing and intervention in diagnosing mitochondrial disorders in pediatric patients.

Keywords: POLG; PEO; Muscle weakness; Diagnosis

INTRODUCTION

Progressive External Ophthalmoplegia (PEO) is an uncommon mitochondrial disorder characterized by the gradual weakening of the muscles controlling eye movements (extraocular muscles), resulting in the loss of control over these movements. It typically manifests with symptoms like ptosis (eyelid drooping), ophthalmoparesis (muscle weakness around the eyes) and impaired eye movements, ultimately causing significant visual impairment. PEO can occur either as an isolated condition or as part of a more complex syndrome [1].

One of the primary underlying factors for PEO is the presence of mutations in the Polymerase Gamma (POLG) gene. This gene is vital for the replication and maintenance of mitochondrial DNA (mtDNA). The POLG gene encodes the catalytic subunit of the DNA polymerase gamma enzyme, which is responsible for the replication and repair of mtDNA. Mutations in this gene have been identified as disruptive to these critical processes, leading to mitochondrial dysfunction and the potential impact on various organs and tissues, with the ocular muscles being especially susceptible to these effects. Research has revealed a

robust connection between POLG mutations and PEO. In fact, POLG mutations have been identified as one of the most prevalent genetic triggers of this disorder. The inheritance patterns of these mutations can vary and may exhibit autosomal recessive traits as well as missense mutations [2].

The clinical presentations of PEO associated with POLG mutations can be remarkably diverse. They span from isolated cases of PEO to more complex forms, like Alpers-Huttenlocher Syndrome (AHS) and autosomal dominant progressive external ophthalmoplegia. Neurological symptoms such as epilepsy, cognitive decline and muscle weakness are frequently observed in these complex forms, illustrating the extensive impact of mitochondrial dysfunction [3].

To diagnose PEO linked with POLG mutations, a combination of clinical assessment, comprehensive family history review and molecular genetic testing is necessary. Modern sequencing techniques, such as next-generation sequencing, have significantly improved the ability to detect POLG mutations, thus facilitating accurate diagnosis and the subsequent management of patients [4].

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In this case report, we present a clinical case of PEO associated with a novel POLG mutation in a pediatric patient. We describe the clinical presentation, diagnostic approach and treatment interventions for managing this rare mitochondrial disorder. The aim of this case report is to expand the existing knowledge on the spectrum of POLG mutations and their clinical implications, ultimately contributing to improved diagnostic accuracy and treatment strategies for patients with PEO [5].

CASE PRESENTATION

Our patient is an 11-year-old Pakistani adolescent, who initially presented with vomiting for a period of 3 days, which was characterized by non-projectile, non-bilious and non-bloody episodes. The patient also complained of an on-and-off headache over the last 8 months, with moderate intensity, primarily localized to the back of the head (occipital region). In addition to these issues, there has been a significant weight loss of 7 kilograms over the past 2 months, accompanied by a loss of appetite. There were no reported night sweats or fever [6].

According to the patient's father, since 1 year back, the child has been complaining of generalized fatigue mainly towards the end of the day and has experienced difficulty in activities like holding water bottles, writing with a pen, combing their hair and using a spoon to feed themselves. They have also faced challenges when trying to rise from a sitting position in a chair. Additionally, the father noticed that the child sometimes walks on their tiptoes [7].

RESULTS AND DISCUSSION

Approximately 1 year ago, the patient began to develop a squint (crossed eyes) and experienced general weakness in their muscles, particularly in the more distant parts of their limbs. Notably, there have been no reported behavioral changes, dysphagia (difficulty swallowing), shortness of breath, dysarthria (speech difficulties), loss of consciousness, seizures, photophobia (sensitivity to light) or vision loss.

Regarding his previous medical history, he has experienced night-time urine incontinence since birth with no other urinary symptoms. In Pakistan, he underwent investigations for generalized muscle weakness, which included the following results: Serum CPK at 431, serum acetylcholine receptor antibody less than 0.25 and serum anti-MuSK antibodies less than 0.18. Electromyography was also performed and revealed normal muscle activity with no signs of denervation potential, as well as normal muscle duration and amplitude. Nerve conduction studies for the motor nerves in both the upper and lower limbs indicated normal appearance, amplitude and conduction velocity [8].

He has not been prescribed any medications and has not undergone any surgical procedures in the past. His birth history was uneventful and his immunizations are up to date. In terms of developmental milestones, he is currently in grade 6 and is thriving without the need for special care or a shadow teacher. There have been no developmental delays or regressions. Notably, his family history is marked by consanguineous parents who are second-degree cousins and he has two other healthy

siblings. There is no family history of immunodeficiency, malignancy or neurological or musculoskeletal disorders.

His vital signs were within normal limits. His growth parameters showed a weight of 23.10 kg at 0.08 centile with a z-score of -3.14, height at 136 cm at 9.93 centile with a z-score of -1.29 and a BMI of 12.25 with a z-score of -4.18.

As for the examination, he was alert and oriented and had no signs of acute distress. Well looking and well-hydrated. No signs of distinctive features.

Neurological examinations showed normal tone in both upper and lower limbs. Good passive movement and range of motion except for the right upper arm he had use of accessory muscles with abduction. Power: 4/5 in the proximal upper and lower limbs and 5/5 in the distal upper and lower limbs. Unable to dorsiflex fully. Reflexes: 1+ in the lower limbs. His gait was high step pace and was unable to walk on his heel. Negative Romberg's test with normal coordination. No signs of cerebellar deterioration. No fasciculation's, clonus and negative Babinski sign. Sensory examination was unremarkable. No neuro cutaneous lesion, however, he had one hyper pigmented patch in the abdomen, for his cranial nerve, he was having limited adduction of the right eye with exotropia and no proptosis. No neck stiffness musculoskeletal he had a normal range of motion, no tenderness, no swelling, no calf hypertrophy or scoliosis other systems were unremarkable [9].

We considered several possible differentials for the patient's condition, including axonal polyneuropathy, mitochondrial disease, leukodystrophy and nutritional deficiencies, specifically involving vitamins B₁, B₆ and B₁₂. The renal function test and electrolyte levels were within normal ranges. However, there were certain abnormalities in the patient's lab results: An elevated CK at 1,667 IU/L, a slightly elevated T4 of 21.5 pmol/L in the Thyroid Function Test (TFT), an elevated LDH at 733 IU/L and an elevated alpha-globulin at 11.1 g/L in the protein electrophoresis. CRP levels were negligible. Various specific tests, including Ach receptors, anti-musk antibodies and an immunological workup, were all negative. Additionally, the myositis panel returned negative results.

Brain Magnetic Resonance Spectroscopy (MRS) was performed but did not reveal significant findings. Nerve conduction studies and electrophysiology studies suggested axonal neuropathy, with a predominant sensory component, even though clinical symptoms indicated more motor involvement. The upper limbs were more affected than the lower limbs, further suggesting neuropathy over myopathy.

Overall, the findings pointed more toward a deficiency in micronutrients as a potential cause for the neuropathic state. The patient was initiated on vitamin B₁ and B₁₂ supplementation while awaiting the results of serum vitamin level tests. These tests showed that vitamin B₁, B₁₂, E and D were within normal ranges. However, vitamin B₆ (pyridox acid) was below the normal range at <2 mcg/L (normal range: 3-30), while Pyridoxal 5-Phosphate (PLP) was in the normal range at 29 mcg/L (normal range: 5-50) (Tables 1-5) [10].

Table 1: Laboratory test results for the patient with Progressive External Ophthalmoplegia (PEO).

Lab	Results	Normal range
Sodium	138 mmol/L	136-145
Potassium	4.1 mmol/L	3.2-5.5
Chloride	98 mmol/L	98-107
Bicarbonate	21 mmol/L	22-29
Creatinine	19 micromol/L	2.8-8.10
Urea	5.20 mmol/L	3.9-7.9
Random glucose	5.2 mmol/L	3.9-7.9
Magnesium level	0.82 mmol/L	0.70-0.90
Phosphate level	1.62 mmol/L	1.05-1.89
LDH	733 IU/L	135-225
CK level	1,667 IU/L	39-308
Ferritin	83 mcg/L	7-84
Calcium level	1.35 mmol/L	1.10-1.30
Total protein	84 g/L	66-87
Albumin	41 g/L	35-52
Total bilirubin	4.6 micromol/L	≤ 17
Direct bilirubin	2.4 micromol/L	≤ 5
Alkaline phosphate	121 IU/L	40-129
AST	117 IU/L	≤ 41
ALT	59 IU/L	≤ 41
TSH	2.280 milli IU/L	0.5-5.3
Free T4	21.5 pmol/L	12-20.6
ESR	36 mm/hr	0-20
ANA	Negative	
P ANCA	<2 RU/mL	≤ 20
C ANCA	<2 RU/mL	≤ 20
CRP	<0.3 mg/L	≤ 5
Anti-MuSK antibodies	<0, 18 U/mL	<0.4 U/mL

Table 2: Complete Blood Count (CBC) results for the patient.

CBC	Results	Normal range
WBC	$11.6 \times 10^9/L$	4.5-13
RBC	$4.62 \times 10^{12}/L$	4.10-5.20
Hgb	127 g/L	120-150
Hct	0.37 L/L	0.35-0.45
MCV	80.1 fL	77-94
MCH	27.5 pg	26-32
MCHC	343 g/L	320-370
Platelet	$430 \times 10^9/L$	140-400
RDW	0.136	11.6-14.8

Table 3: Laboratory test results for the patient at admission day 3.

Lab	Results	Normal range
Total protein	84 g/L	66-87
Albumin	41 g/L	35-52
Total bilirubin	4.6 micromol/L	≤ 17
Direct bilirubin	2.4 micromol/L	≤ 5
Alkaline phosphate	121 IU/L	40-129
AST	117 IU/L	≤ 41
ALT	59 IU/L	≤ 41
TSH	2.280 milli IU/L	0.5-5.3
Free T4	21.5 pmol/L	12-20.6
ESR	36 mm/hr	0-20
ANA	Negative	
P ANCA	<2 RU/mL	≤ 20
C ANCA	<2 RU/mL	≤ 20
CRP	<0.3 mg/L	≤ 5
Anti-MuSK antibodies	<0, 18 U/mL	<0.4 U/mL

Table 4: Vitamin and pyridoxal phosphate levels in the patient.

Lab	Results	Normal range
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Pyridoxic Acid (PA), P	<2 mcg/L	11018
Pyridoxal 5-Phosphate (PLP), P	29 mcg/L	18384
Vitamin E	7.3 mg/L	3.8-18.4
Vitamin D	74.8 nmol/L	50-150
Vitamin B ₁₂	285.0 pmol/L	128-648
Thiamin (vitamin B ₁)	82 nmol/L	70-180

Table 5: Myositis panel results.

Myositis panel	
Anti-TIF1 gamma	Negative
Anti-MDA5	Negative
Anti-NXP2	Negative
Anti-SAE	Negative
Anti-Ku	Negative
Anti-PM 100	Negative
Anti-PM 75	Negative
Anti-Jo1	Negative
Anti-SRP	Negative
Anti-PL7	Negative
Anti-PL12	Negative
Anti-EJ	Negative
Anti-OJ	Negative
ACh receptor (Muscle) binding Ab	Negative

CONCLUSION

A genetic assessment was carried out in collaboration with the genetics team, using the cento neuro panel, which can diagnose a wide range of inherited genetic diseases through massive parallel sequencing. The results from this test confirmed a homozygous pathogenic variant in the POLG gene, thus establishing the genetic diagnosis of autosomal recessive POLG-related disease.

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