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Case Report

Two Fatal Cases of Primary Coenzyme Q10 Deficiency-7: The Southern Chinese Variant c.370G>A in the *COQ4* Gene

TS **WONG**, KY **LEUNG**, EKC **YAU**, GSF **NG**

Abstract Primary coenzyme Q10 deficiency is a group of clinically heterogeneous autosomal recessive disorders caused by genes encoding proteins involved in coenzyme Q10 biosynthesis, resulting in mitochondrial dysfunction. We report two cases of primary coenzyme Q10 deficiency-7 caused by homozygous c.370 G>A pathogenic variant of the *COQ4* gene, the Chinese-specific founder mutation reported by Yu et al. Our patients presented in the neonatal or early infantile period with epilepsy, sepsis-like picture with lactic acidosis. They highlight the potential benefit of early treatment, and thus the importance of having high index of suspicion for Primary Coenzyme Q10 Defciency-7 in patients with neonatal or infantile onset epilepsy in our locality.

Key words *COQ4; Primary coenzyme Q10 deficiency-7*

Introduction

Coenzyme Q10 (CoQ10) is an electron shuttle in the electron transport chain.[1] Primary coenzyme Q10 deficiency-7 (COQ10D7) results from mutations in the *COQ4* gene, and *COQ4* is believed to stabilise the CoQ10 complex. Patients typically present with neonatal or infantile onset encephalopathy with or without cardiomyopathy.[2] Early diagnosis requires high index of suspicion due to its non-specific presentation. We reported two cases that were homozygous for the Chinese-specific founder mutation c.370G>A identified by Yu et al.[2] They illustrated the importance of early treatment and the potential role of high dose ubiquinol. Due to the founder effect, molecular testing should include the *COQ4* gene for Chinese neonates and infants presenting with a complex neurological phenotype.

Department of Paediatrics and Adolescent Medicine, Princess Margaret Hospital, 2-10 Princess Margaret Hospital Road, Lai Chi Kok, Kowloon, Hong Kong SAR, China

TS **WONG** (黃梓琛) *FHKCPaed, FHKAM(Paed)*
KY **LEUNG** (梁潔欣) *FHKCPaed, FHKAM(Paed)*
EKC **YAU** (丘建昌) *FHKCPaed, FHKAM(Paed)*
GSF **NG** (吳瑞芬) *FHKCPaed, FHKAM(Paed)*

Correspondence to: Dr TS **WONG**
Email: tszsumwong1992@gmail.com

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Methods

The clinical presentations, investigation findings, and management of the patients are described in the case reports. Consent was obtained from the parents. The molecular diagnosis for case one was established by whole exome sequencing done on a research basis using peripheral blood. The pathogenic variant was confirmed by polymerase chain reaction and Sanger sequencing. For case two, peripheral blood sample was obtained for next-generation sequencing (NGS) using TruSight One Sequencing Panel (FC-141-1006) on Illumina MiSeq Sequencing System, and the pathogenic variant was confirmed by Sanger sequencing.

Results

Case 1 (SH)

SH was a full-term boy born to non-consanguineous healthy Chinese parents in 2009, with unremarkable antenatal and perinatal history. He presented at 25-day-old with one day of repeated vomiting and generalised tonic-

clonic seizure initially responsive to phenobarbitone. Initial hyperlactataemia of 4.1 mmol/L normalised the next day. Lactate to pyruvate ratio was not checked. Cerebrospinal fluid (CSF) lactate was normal. Magnetic resonance imaging (MRI) brain at 3-month-old showed cerebral atrophy. Worsening of cerebral and cerebellar atrophy together with delayed myelination in bilateral frontal and temporal lobes were evident on follow-up MRI at 1-year-old and 4-year-old. Magnetic resonance spectrometry (MRS) was not performed.

SH developed global developmental delay (GDD), intractable epilepsy, hearing and visual impairment, apnoeic episodes, and progressive neuromuscular weakness and hypotonia. Oromotor dysfunction worsened, requiring tube feeding. An episode of aspiration pneumonia at 5-year-old rendered him ventilator dependent. However, his family preferred not to have tracheostomy performed, and he was hospitalised till his death at 7-year-old due to urosepsis.

Due to the less widespread application of NGS at that time, it was not until 6-year-old that the molecular diagnosis was made, confirming that he was homozygous for the c.370G>A variant of the *COQ4* gene. His parents were heterozygous carriers of the variant. After the molecular diagnosis was established, ubidecarenone was given at 33 milligrams per kilogram body weight per day (mg/kg/d) for one year, and was later switched to ubiquinol at 15 mg/kg/d till his death. No clinical improvement was observed. Echocardiogram done at 6-year-old was normal, and body systems other than the neurological system were spared.

Of note, his elder brother had a similar phenotype with early infantile onset GDD, hypotonia, intractable epilepsy, oromotor dysfunction, hearing and visual impairment, and respiratory failure needing tracheostomy. MRI brain showed generalised atrophy and poor frontal lobe myelination. Before reaching a diagnosis for his neurodegeneration, he succumbed at 3-year-old due to pneumonia.

Case 2 (YL)

YL was a full-term boy born to non-consanguineous healthy Chinese parents in 2019. His antenatal and perinatal course were unremarkable, but slow feeding was observed since birth.

At 2-month-old, he presented with status epilepticus, sepsis-like picture with compensated shock, and respiratory distress. Intravenous midazolam and phenobarbitone aborted the seizure. He had central hypotonia with normal deep tendon reflexes, intermittent horizontal nystagmus, and failure to thrive.

Haemodynamic instability and lactic acidosis responded to fluid and bicarbonate boluses. Blood lactate of 13.4 mmol/L on presentation normalised within 12 hours, and subsequent lactate levels ranged from 1.5 mmol/L to 5.4 mmol/L. There were increased alanine transaminase up to 944 U/L (reference: <49 U/L), creatine kinase at 2246 U/L (reference: <129 U/L), and high-sensitive troponin I level to 958 ng/L (reference: <=59 ng/L). Blood glucose and ammonia levels were normal. Sepsis workup was unrevealing.

Further workup showed blood lactate to pyruvate ratio of 22.8 (blood lactate was 5.4 mmol/L). CSF lactate was elevated at 8.0 mmol/L. MRI and MRS of the brain at 2-month-old showed delayed myelination, cerebellar atrophy, and lactate peaks in the periventricular white matter. Plasma amino acids, acylcarnitine profile, urine organic acids and amino acids, and Biotinidase activity were unremarkable. Echocardiogram showed no cardiomyopathy.

As mitochondrial disease was suspected, oral ubidecarenone at 12 mg/kg/d, along with other multivitamins, were commenced. At 4-month-old, the diagnosis was confirmed by NGS of a nuclear gene panel for mitochondrial diseases, identifying homozygous c.370 G>A variant in the *COQ4* gene. His parents were heterozygous carriers of the variant.

The generalised tonic-clonic seizures remained refractory to multiple anticonvulsants despite ubidecarenone supplement. Electroencephalogram at 2-month-old demonstrated multi-focal discharges at bilateral temporal, centro-parietal, and left posterior regions. When molecular diagnosis was established at 4-month-old, ubidecarenone was replaced by ubiquinol at 15 mg/kg/d. He was then near seizure-free for one year and the dosage of anticonvulsants was tailed down. Electroencephalogram at 4-month-old showed slight asymmetry and focal discharges from the left posterior region.

During the disease course, other organ systems were spared. Unfortunately, progressive neurological deterioration ensued. He had microcephaly and no head control at 15-month-old. There was worsening of oromotor dysfunction, prolonged visual evoked potential, sensorineural hearing loss, limb spasticity, and dystonia. Brainstem atrophy was evident on MRI brain at 12-month-old. His condition went downhill and he developed recurrent apnoea at 15-month-old. With prior advanced

care planning with the family and consensus against invasive procedures, he passed away peacefully from pneumonia at 20-month-old.

Discussion

Here we reported two patients with Primary COQ10D7 that were homozygous for the c.370G>A pathogenic variant in the *COQ4* gene. With the increasing use of NGS in the molecular diagnostics of patients suspected to have mitochondrial diseases, YL was diagnosed early using a nuclear gene panel at 4-month-old. Nonetheless, some NGS platforms cannot analyse the mitochondrial genome comprehensively; a critical limitation as mitochondrial diseases are inherited in a dual genome manner (mitochondrial and nuclear).[3,4]

YL's seizure control improved with ubiquinol supplement, while SH did not respond to CoQ10 supplement started at near 6-year-old. The benefit of early treatment echoes the findings of previous reports. In the reports by Yu et al and Lu et al, out of the six patients with the same genotype as our patients, four had CoQ10 supplement initiated before 1-year-old.[2,5] Three out of four patients improved in either seizure control or cardiac function. The patient that did not respond was in critical condition on presentation requiring invasive ventilation. CoQ10 supplements were initiated after 1-year-old for the other two patients, and only one of them responded. The irreversibility of established organ damage despite CoQ10 supplementation may explain the benefit of early treatment. Genotype may also determine treatment efficacy. All five patients carrying the splicing mutation c.402+1G>A reported by Yu et al did not benefit from CoQ10 supplement, while the patient with a genotype of compound heterozygous missense variants c.370G>A/c.371G>T responded.[2] Larger scale studies may be worthwhile to determine the disease severity and treatment response for patients with different genotypes to guide clinicians' management.

Early recognition of Primary COQ10D7 requires high index of suspicion, owing to the non-specific presentation and overlap with other disease entities. Intractable epilepsy, GDD, dystonia, and oromotor dysfunction are rather non-specific features. However, when more unique findings such as lactic acidosis and multisystem involvement are present, mitochondrial diseases should be considered. Nonetheless, hyperlactataemia lacks specificity and sensitivity despite being a classical biochemical finding of mitochondrial diseases.[6,7] As illustrated in our cases, hyperlactataemia may resolve after acute illnesses, thus mitochondrial diseases should be considered in typical clinical presentations even without persistent hyperlactataemia. Due to the founder effect of the c.370G>A variant in southern Chinese, molecular study should include the *COQ4* gene for Chinese neonates and infants suspected to have mitochondrial diseases, particularly those with epilepsy and cardiomyopathy.

Both patients were given ubiquinol at 15 mg/kg/d when they did not respond to ubiquinone. They were changed to ubiquinol (reduced form of CoQ10) as its bioavailability is believed to be greater than that of ubiquinone (oxidized form).[8] Tragni et al suggested 8 mg/kg/d for ubiquinol's dosage, but the use of higher doses was described in Primary Coenzyme Q10 deficiency patients without major problems.[8-10] Similarly, adverse effects such as gastrointestinal upset and rash were not observed in our patients at 15 mg/kg/d. To date, the literature lacks large-scale studies to assess the efficacy and safety of high dose ubiquinol, but its use was not problematic for our patients. Therefore, if response is suboptimal to lower doses, clinicians may consider stepping up ubiquinol to 15 mg/kg/d with close monitoring of adverse effects.

Conclusion

Our patients and those reported in the literature highlight the potential benefit of early treatment in Primary COQ10D7. The diagnosis should be considered in Chinese neonates or infants with a complex neurological presentation featuring epilepsy, developmental delay, and dystonia or hypotonia, even without persistent hyperlactataemia. Multisystem involvement should further raise the suspicion. In our locality, diagnostic workup should include molecular study of the *COQ4* gene for the Chinese-specific founder mutation.

Declaration of interest

None

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