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Refractory Epilepsy in Adult Patient With *COQ8A* Variant Improves With CoQ10 Supplementation

A Case for Exome Sequencing in the ICU

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Abstract

Objectives

Describe a case of stroke-like episodes and refractory status epilepticus diagnosed with primary CoQ10 deficiency-4 (COQ10D4) using whole-exome sequencing in the intensive care unit (ICU), with treatment implications.

Methods

A patient presented to the emergency department with 1 month of progressively worsening focal motor status epilepticus and stroke-like imaging abnormalities. Multiple seizure medications, ketogenic diet, and elective intubation for anesthetic drips failed to achieve sustained seizure freedom. Genetic testing was pursued for prognostic information and identified potential treatment.

Results

Whole-exome sequencing revealed compound heterozygous variants of *COQ8A*, including 1 allele not previously described as pathogenic. The patient's history, imaging, and genetic testing supported a diagnosis of COQ10D4. High-dose coenzyme Q10 supplementation was started with gradual clinical improvement.

Discussion

Whole-exome sequencing is a fast and cost-effective means to diagnose rare neurologic disease in critically ill patients and can uncover treatment options. While primarily used in the neonatal ICU, appropriately selected adult patients may also benefit.

Introduction

COQ8A (aka *ADCK3*, *CABC1*) is a nuclear gene encoding an atypical protein kinase crucial for coenzyme Q10 (CoQ10) biosynthesis.[1] CoQ10 has multiple functions, including its role in the mitochondrial respiratory chain and cellular energy production.[2]

Abnormal variants of *COQ8A* cause primary CoQ10 deficiency-4 (COQ10D4), a rare mitochondrial disorder with fewer than 70 cases reported in the literature. COQ10D4 is typically associated with childhood-onset progressive ataxia and cerebellar atrophy, which may be mild-moderate.[2] However, other neurologic manifestations occur, including hyperkinetic movement disorders, epilepsy, psychiatric symptoms, and cognitive disability.[3] Multisystem manifestations include ocular and auditory dysfunction, myopathy, cardiomyopathy, and renal dysfunction.[2]

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COQ10D4 may cause stroke-like episodes with refractory epilepsy, presenting similarly to the more common disorders polymerase gamma (*POLG*)-related disease and mitochondrial encephalopathy with lactic acidosis and stroke-like episodes.[4,5] These symptoms typically present early but may occur at any age, including late adulthood.[6] These patients are at risk of severe disability and early death due to refractory status epilepticus.[4]

We report a case of COQ10D4 diagnosed through exome sequencing in the ICU, with clinical improvement of refractory seizures following CoQ10 supplementation.

Clinical Report

A 28-year-old man presented with 1 month of progressive focal seizures refractory to multiple anti-seizure medications (ASMs). Seizure semiology consisted of rhythmic high-amplitude jerking movements of the entire left side of the body, with occasional right-sided movements. His seizures were refractory to levetiracetam, lacosamide, eslicarbazepine, clobazam, phenobarbital, and cenobamate. He remained conscious and verbal, although alertness and attention were impaired. He became nonambulatory and required full assistance with all daily activities, including eating and bathing.

History revealed that he had mild intellectual disability and required special education as a child. He developed epilepsy at age 11, which was well-controlled with levetiracetam. He was "clumsy" his entire life, including frequently dropping or spilling, and he was poor at sports.

Two years prior, he was seen at an outside hospital for a prolonged breakthrough seizure. Motion-degraded MRI demonstrated left occipital-temporal T2 hyperintensities with patchy diffusion restriction (Figure, A and B) and laminar necrosis. CSF analysis was normal. He was treated with IV methylprednisolone for presumed inflammatory etiology, although atypical posterior reversible encephalopathy syndrome (PRES) was considered.

He was readmitted 1 month later with ongoing occipital lobe seizures seen on EEG. MRI demonstrated improvement of left hemisphere abnormalities, but new right occipital-parietal abnormalities (Figure, C and D) were seen with associated leptomeningeal enhancement. CSF was again normal; infectious studies and autoimmune antibody panels were negative. He was discharged on 4 ASMs. He had persistent visual impairment following this and was diagnosed with rod/cone retinal dystrophy by ophthalmology.

The patient was seizure-free for 1 year before admission for epilepsia partialis continua involving the left arm. MRI demonstrated bilateral occipital-parietal abnormalities, some improved and others more extensive than prior. He was diagnosed with atypical PRES. His seizures continued to worsen over the next month, ultimately leading to presentation to our emergency department with focal status epilepticus.

Evaluation and Treatment

We strongly suspected a mitochondrial disorder. His worsening seizures despite 6 ASMs caused severe disability, inability to maintain adequate nutrition, and aspiration risk. We thus pursued aggressive measures to control the seizures.

He was admitted to the ICU for elective intubation and placed on continuous EEG. The EEG was obscured by EMG artifact but demonstrated high-amplitude 8–10 Hz activity intermixed with bilateral occipital predominant 5–6 Hz frequencies time-locked with the jerking movements.

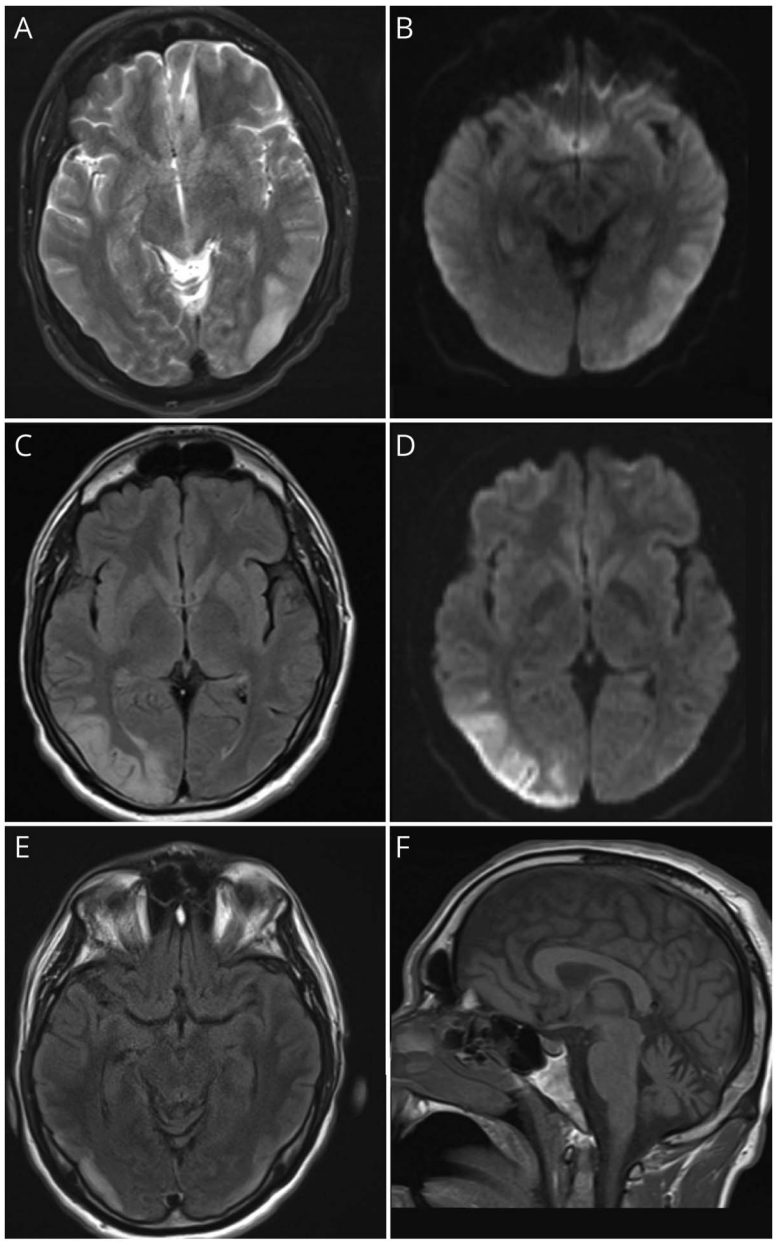
MRI demonstrated bilateral occipital-parietal abnormalities and cerebellar atrophy (Figure, E and F). In retrospect, the cerebellar atrophy was also visible on earlier imaging. No lactate peak was seen on MR spectroscopy. Serum and CSF lactate were normal. Testing for infectious and autoimmune etiologies in the serum and CSF was unremarkable. Serum and urine screening for metabolic disorders was unrevealing.

Left-sided jerking movements were visible even at high doses of anesthetics. Burst suppression was achieved with propofol and midazolam infusions, and later with pentobarbital, but seizures recurred during weaning. Combinations of infusions with midazolam, ketamine, and magnesium were tried without success. No improvement was seen with arginine infusion, high-dose thiamine and biotin, and ketogenic diet. ASMs were adjusted, including the additions of lamotrigine, perampanel, and primidone.

The jerking movements became bilateral and increased in amplitude during the admission, leading to ventilator dyssynchrony. His course was further complicated by ventilator-acquired pneumonia. Attempts to ventilator weaning were unsuccessful, and a tracheostomy was performed after 3 weeks.

Genetic testing was pursued for a definitive diagnosis that could inform prognostic discussions with family. He underwent rapid whole-exome sequencing (rWES) with "XomeDxXpress" and "XomeDx mitochondrial sequencing and deletion testing" through GeneDx. Within 1 week, testing confirmed compound heterozygous missense variants of *COQ8A*. His mother shared a known pathogenic variant in exon 7 of *COQ8A*, c.901 C>T p.(R301W). The other variant, c.1651 G>C p.(E551Q) in exon 14, was not present in his mother and was likely inherited from his father (father was unavailable for testing). The latter was reported as a variant of

Figure Evolution of Brain MRI Findings



Left occipital-temporal hyperintensities are seen on brain MRI T2-weighted imaging (A) and diffusion-weighted imaging (B) 2 years prior to admission to our hospital. One month later, near-resolution of left-sided lesions with new right occipital-temporal hyperintensities on T2/FLAIR (C) and diffusion-weighted imaging (D). During admission to our hospital, less extensive bilateral lesions are seen on T2/FLAIR (E); cerebellar atrophy is also appreciated, seen here on sagittal T1-weighted imaging (F).

uncertain significance, although in silico analysis by GeneDx supported the variant having a deleterious effect on protein structure and function.

He was diagnosed with COQ10D4. CoQ10 supplementation was started and increased up to 20 mg/kg divided twice daily. A leukocyte CoQ10 level was collected prior to supplementation and returned normal at 95 pmol/mg. The jerking movements decreased in amplitude over the following week. He began following commands and attempting to verbalize with sedation paused. Over the next 2 weeks, the movements significantly improved, and he was liberated from the ventilator. Low-amplitude myoclonus of the left arm persisted, which worsened with action. He demonstrated cognitive impairment, severe ataxia, and blindness (light perception only). His final ASMs were cenobamate, clobazam, lacosamide, lamotrigine, levetiracetam, perampanel, and primidone. He was ultimately discharged to a rehabilitation center.

Discussion

Although our patient's clinical history, imaging, and genetic testing support the diagnosis of COQ10D4, it is worth noting that his leukocyte CoQ10 level prior to supplementation was normal. Despite one author's suggestion that mononuclear cell CoQ10 concentration is useful for

assessing deficiency,[7] muscle tissue and skin fibroblast concentrations are most reliable.[2]

Our case highlights that genetic testing of adult ICU patients can influence treatment options, in agreement with a recent report.[8] A genetic diagnosis directly led to the decision to treat with high-dose CoQ10. Other authors have reported that only half of patients with COQ10D4 are responsive to CoQ10 supplementation.[3,9] Although we tried multiple aggressive interventions and ASM adjustments, our patient only demonstrated sustained improvement after CoQ10 supplementation.

Despite overall improvement, our patient remained very disabled. We question if earlier diagnosis and supplementation could have prevented some of the neurologic sequelae. However, a recent review suggested very limited response to CoQ10 supplementation even in those diagnosed with COQ10D4 in childhood.[10]

The authors from the pediatrics literature have argued that rWES in the neonatal ICU is cost-effective and invaluable for early diagnosis of rare disease.[11,12] Our case illustrates that rWES should be considered for appropriately selected adult patients in the ICU with suspected genetic disease. For our patient, rWES proved to be more cost-effective than other considered diagnostics and treatments (e.g., brain biopsy and palliative epilepsy surgery) and likely shortened overall time on the ventilator. We hope future advances allow for more widely available testing of adult critically ill patients with suspected genetic disorders so that prognostic information and possible treatment options may be offered.

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References

1. Paprocka J, Nowak M, Chuchra P, Śmigiel R. *COQ8A*-ataxia as a manifestation of primary coenzyme Q deficiency. *Metabolites*. 2022;12(10):955. doi:10.3390/metabo12100955
2. Mantle D, Millichap L, Castro-Marrero J, Hargreaves IP. Primary coenzyme Q10 deficiency: an update. *Antioxidants*. 2023;12(8):1652. doi:10.3390/antiox12081652
3. Traschütz A, Schirinzi T, Laugwitz L, et al. Clinico-genetic, imaging and molecular delineation of *COQ8A*-ataxia: a multicenter study of 59 patients. *Ann Neurol*. 2020;88(2):251-263. doi:10.1002/ana.25751
4. Hikmat O, Tzoulis C, Knappskog PM, et al. ADCK3 mutations with epilepsy, stroke-like episodes and ataxia: a POLG mimic? *Eur J Neurol*. 2016;23(7):1188-1194. doi:10.1111/ene.13003
5. Santamarina E, Alpuente A, Maisterra O, et al. Perampanel: a therapeutic alternative in refractory status epilepticus associated with MELAS syndrome. *Epilepsy Behav Case Rep*. 2019;11:92-95. doi:10.1016/j.ebcr.2019.01.008
6. Ramesh R, Hariharan S, Sundar L. Stroke-like episodes and epilepsy in a patient with *COQ8A*-related coenzyme Q10 deficiency. *Ann Indian Acad Neurol*. 2023;26(6):980-982. doi:10.4103/aian.aian_511_23
7. Duncan AJ, Heales SJ, Mills K, Eaton S, Land JM, Hargreaves IP. Determination of coenzyme Q10 status in blood mononuclear cells, skeletal muscle, and plasma by HPLC with di-propoxy-coenzyme Q10 as an internal standard. *Clin Chem*. 2005;51(12):2380-2382. doi:10.1373/clinchem.2005.054643
8. Gaillard JR, Whitt Z, Selwa LM, Harris D, Lee KN. Pearls & oy-sters: whole-genome sequencing in critically ill neurologic patient leads to diagnosis with treatment implications. *Neurology*. 2023;101(13):588-592. doi:10.1212/WNL.0000000000207552
9. Chang A, Ruiz-Lopez M, Slow E, Tarnopolsky M, Lang AE, Munhoz RP. ADCK3-related coenzyme Q10 deficiency: a potentially treatable genetic disease. *Mov Disord Clin Pract*. 2018;5(6):635-639. doi:10.1002/mdc3.12667
10. Wang Y, Hekimi S. The efficacy of coenzyme Q_{10} treatment in alleviating the symptoms of primary coenzyme Q_{10} deficiency: a systematic review. *J Cell Mol Med*. 2022;26(17):4635-4644. doi:10.1111/jcmm.17488
11. Śmigiel R, Biela M, Szmyd K, et al. Rapid whole-exome sequencing as a diagnostic tool in a neonatal/pediatric intensive care unit. *J Clin Med*. 2020;9(7):2220. doi:10.3390/jcm9072220
12. Kingsmore SF, Cole FS. The role of genome sequencing in neonatal intensive care units. *Annu Rev Genomics Hum Genet*. 2022;23:427-448. doi:10.1146/annurev-genom-120921-103442