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Autosomal Recessive Spinocerebellar Ataxia Type 9 With a Response to Phosphate Repletion

A Case Report

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Abstract

Objective

Autosomal recessive spinocerebellar ataxia type 9 (SCAR9) has received attention due to its potential response to coenzyme Q10 (CoQ10) supplementation; however, the response has so far been limited and variable.

Methods

We report a SCAR9 patient with severe hypophosphatemia who responded well to CoQ10 and phosphate repletion.

Results

A 70-year-old man (the offspring of a consanguineous marriage) presented with cerebellar ataxia and intense fatigue after exercise. Whole-exome sequencing identified a novel homozygous deletion mutation (NM_020247.5:c.1218_1219del) in *COQ8A*. We thus diagnosed him with SCAR9. Supplementation of CoQ10 alleviated his symptoms, with the Scale for the Assessment and Rating of Ataxia (SARA) dropping from 16 to 14. During the course of the disease, he demonstrated continuous hypophosphatemia caused by renal phosphate wasting. Gait dysfunction due to weakness and eye movement was partially alleviated, and SARA dropped from 17 to 13 after phosphate repletion.

Discussion

Phosphate repletion should be considered for patients with severe hypophosphatemia without any apparent subjective symptoms. In this case, phosphate repletion could have improved myopathy leading to partial improvement in the patient's symptoms. Further analyses regarding the association between COQ8A mutation and phosphate wasting are required to elucidate the detailed pathogenesis.

Classification of Evidence

This provides Class IV evidence. This is a single observational study without controls.

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Class of Evidence
Criteria for rating therapeutic and diagnostic studies
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Video

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Autosomal recessive spinocerebellar ataxia type 9 (SCAR9) is a rare form of inherited cerebellar ataxias with a heterogenous condition including a slowly progressive gait abnormality, mild cognitive dysfunction, exercise intolerance, epilepsy, ptosis, strabismus, and dystonia.[1,2]

SCAR9 is caused by a *COQ8A* gene mutation, also called aarF-domain–containing kinase 3 (*ADCK3*), and the gene product synthesizes and regulates coenzyme Q10 (CoQ10).[1,3] Given the genetic background, SCAR9 may constitute a group of partially treatable forms among inherited cerebellar ataxias, many of which are currently untreatable. However, the clinical response of CoQ10 for SCAR9 has been limited and highly variable.

We report a case of SCAR9 with hypophosphatemia who responded well to CoQ10 and phosphate repletion.

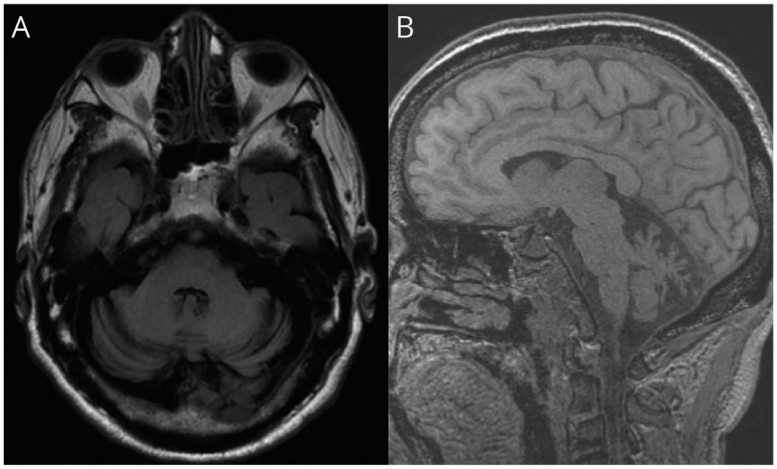
Case Report

A 70-year-old man presented with a medical history of mild glucose intolerance. He was born to consanguineous parents and had a healthy sister. His developmental milestones were not significant; however, he showed poor physical and academic performance in school. He had frequently moved his head to visually grasp objectives since childhood, although he did not find this troublesome or abnormal. His sister had noticed his eye expression to be "queer," and his eye movements were restricted. He frequently felt intense fatigue after exercise and needed 20–30-minute rest to regain his muscle strength. Walking difficulties gradually progressed from age 40 years, although he experienced multiple episodes of acute deterioration triggered by a low temperature.

He first visited our hospital at age 60 years. He exhibited a moderate ataxic gait, and MRI of the brain revealed atrophy in the cerebellum (Figure 1, A and B). At age 70 years, he demonstrated a myopathic face, bilateral ptosis, baldness, left exotropia, and mild hearing loss (Figure 2). His full-scale IQ was 74, with a performance IQ well below the verbal IQ on the Wechsler Adult Intelligence Scale–Third edition. Electrophysiology and a muscle biopsy detected mild myogenic changes in the right biceps brachii. Whole-exome sequencing identified a novel homozygous deletion mutation (NM_020247.5:c.1218_1219del, NP_064632.2:p.Cys406Ter) in *COQ8A*. We thus diagnosed him with SCAR9. The mutation was evaluated as pathogenic (PVS1 + PM2) in the ACMG Classification. Supplementation of CoQ10 (30 mg/d) partially alleviated the eye movement and cerebellar ataxia, with the Scale for the Assessment and Rating of Ataxia (SARA) dropping from 16 to 14. Supplementation of CoQ10 was continued, but thereafter, his symptoms gradually worsened.

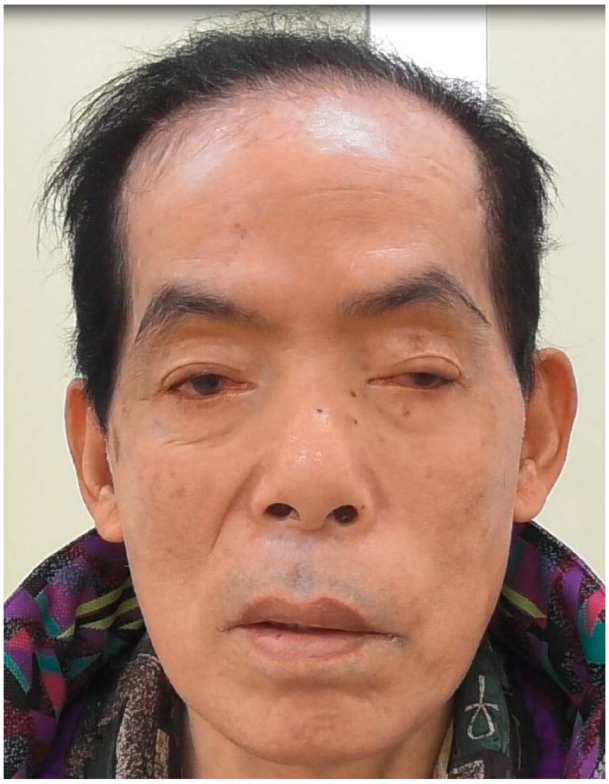
During the disease course, the patient had continuous hypophosphatemia (1.3–2.4 mg/dL) and a low value of 25-hydroxy vitamin D. The blood test showed normal HbA1c, creatinine clearance, and mildly reduced estimated glomerular filtration rate. The laboratory test results are summarized in Table. We evaluated the fractional excretion of filtered phosphate as 20.2%, and the ratio of tubular maximum reabsorption of phosphate to glomerular filtration rate was 1.6 mg/dL (0.52 mmol/L), indicating renal phosphate wasting. His bone density was 101% of the young adult mean. Renal echography showed normal size, no renal artery acceleration, and a normal resistive index as 0.66/0.60 indicating no evidence for arterial nephrosclerosis. The left biceps brachii muscle biopsy specimen was examined in paraffinized, and cryostat sections stained with hematoxylin and eosin (H&E) and in cryosections evaluated by stains including the modified Gomori trichrome, adenosine triphosphatase (ATPase), cytochrome c oxidase (COX), and succinate dehydrogenase (SDH). These preparations showed moderate variations in fiber size including some type 2C fibers. Several ragged red fibers (RRFs) were seen, and the COX activity was positive in most RRFs. Strongly SDH-reactive

Figure 1 Brain MRI Findings



Fluid-attenuated inversion recovery (FLAIR) axial (A) and spoiled gradient recalled echo (SPGR) sagittal images (B) showed atrophy of cerebellum.

Figure 2 Facial Appearance of the Patient



The patient had a myopathic face, bilateral ptosis, baldness, and left exotropia.

blood vessels were not highlighted. No additional abnormalities were found in other stains. With phosphate repletion, the serum phosphate level increased from 1.3 mg/dL to 2.5 mg/dL. In addition, 25-hydroxy vitamin D repletion had no effect, but phosphate repletion partially alleviated the eye movement (Video 1) and gait dysfunction due to weakness, resulting in the SARA dropping from 17 to 13 after phosphate repletion.

Discussion

Our patient with a *COQ8A* mutation showed severe hypophosphatemia with a response to CoQ10 and phosphate repletion. In patients with hypophosphatemia, decreased muscle adenosine-5′-triphosphate (ATP) synthesis may be associated with muscle weakness.[4] Muscle function and muscle ATP synthesis in patients with hypophosphatemia returns to normal when the plasma inorganic phosphate levels are restored.[4]

However, the mechanism underlying how *COQ8A* mutations induce hypophosphatemia remains unclear, although the following mechanisms were speculated. *COQ8A* may synthesize and regulate CoQ10, which is an essential electron carrier in the mitochondrial respiratory chain contributing to ATP biosynthesis.[5] Considering the constant and high dependence of the renal reabsorption process to ATP, mitochondrial dysfunction may be a pivotal mechanism in the pathogenesis of renal reabsorption process, including phosphate wasting.[6] Further analyses regarding the association between *COQ8A* mutations and phosphate wasting will be required to elucidate the detailed pathogenesis and mechanism underlying the effects.

Phosphate repletion should be considered if patients with CoQ8A mutations had hypophosphatemia without any apparent subjective symptoms which may help to partially improve some of the symptoms, including muscle wasting. In this case, SCAR9 patients with severe hypophosphatemia may have latent myopathy and weakness which respond to phosphate repletion.

Table Laboratory Test Results

Blood								**Urine**			
LDH	170	(124–222)	U/L	**25-(OH) D**	11.3	(≥30.0)	ng/mL	**pH**	5.5	(5.0–7.5)	
CK	162	(59–248)	U/L	**FGF23**	31.9	(<30.0)	pg/mL	**Phosphate**	23.6		mg/dL
Potassium	4.0	(3.6–4.8)	mmol/L	**eGFR**	61	(≥90)	mL/min/1.73m^2	**Creatinine**	54.2		mg/dL
Calcium	8.1	(8.8–10.1)	mg/dL	**CCr**	68.16	(67–214)	mL/min	**Glucose**	24	(<20)	mg/dL
Magnesium	2.2	(1.6–2.3)	mg/dL	**TSH**	4.46	(0.61–4.23)	μU/mL	**Protein**	4		mg/dL
Albumin	3.9	(4.1–5.1)	g/dL	**FT4**	0.74	(0.70–1.25)	ng/dL	**Beta 2-MG**	2,355	(<360)	μg/L
Glucose	125	(73–109)	mg/dL	**PTH intact**	39	(10–65)	pg/mL				
HbA1c	5.5	(4.9–6.0)	%	**Arterial pH**	7.449	(7.35–7.45)					
Creatinine	0.93	(0.65–1.07)	mg/dL								

Abbreviation: 25-(OH) D = 25-hydroxy vitamin D; CCr = creatinine clearance; CK = creatine kinase; eGFR = estimated glomerular filtration rate; FGF23 = fibroblast growth factor 23; FT4 = free T4; HbA1c = hemoglobin A1c; LDH = lactate dehydrogenase; MG = microglobulin; PTH = parathyroid hormone; TSH = thyroid stimulating hormone.

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Disclosure

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