Pearls & Oysters: An unusual cause of hypokalemic paralysis

Ritu Shree, MD
Manoj Kumar Goyal,
MD, DM
Rajveer Singh, MD
Manish Modi, MD, DM
Vivek Lal, MD, DM
Nandita Kakkar, MD,
DM

Correspondence to
Dr. Vivek Lal:
vivekl44@yahoo.com

PEARLS

- Hypokalemic paralysis (HP) is a rare treatable cause of acute flaccid paralysis (AFP). Secondary causes (thyrotoxicosis, renal disorders, endocrinopathies, and gastrointestinal diseases) account for 43% of all paralysis cases occurring due to hypokalemia.^{1,2}
- Sjögren syndrome (SS) is a rare treatable cause of HP, with fewer than 40 cases reported in the literature so far.

OY-STERS

- The contribution of SS to causation of HP continues to be undetermined, as more often patients with HP are not evaluated for underlying SS.

CASE 1 A 47-year-old woman presented with history of recurrent episodes of transient quadriparesis associated with documented hypokalemia for the last 12 years (serum K⁺ levels documented during those episodes were 1.7–3.2). She was diagnosed with HP at another center and was on supplemental potassium for the last 6 years. She also complained of transient, postprandial, binocular blurring of vision, progressing to persistent progressive painless vision loss bilaterally for the last 2 months. There was a history of dry mouth and eyes. There were no other systemic or neurologic complaints. General examination results were normal. Visual acuity was reduced to perception of light in the left eye and 6/60 in the right eye. There was bilateral optic atrophy and left-sided relative afferent pupillary defect. The rest of the neurologic and general physical examination was normal. MRI revealed hyperintense signal changes in bilateral optic nerves, optic chiasma, and optic tracts with mild contrast enhancement. Serum anti-aquaporin 4 antibodies were negative. CSF analysis was normal (no cells, normal glucose [86 mg/dL], and normal protein [42 mg/dL]). Investigations revealed metabolic acidosis (arterial pH 7.24), persistent hypokalemia (serum potassium 2.9 mEq/L [normal range 3.5–5.5]), hyperchloremia (serum chloride

122 mEq/L vs normal upper limit of 108 mEq/L), low serum bicarbonate (9 mEq/L [normal range 23–26 mEq/L]), and high urinary pH (6) without aminoaciduria or glycosuria (table). Renal, thyroid, and liver function tests and serum calcium, magnesium, and phosphorus were normal. The overall picture was that of hyperchloremic metabolic acidosis with normal anion gap, suggestive of distal renal tubular acidosis (RTA). Antinuclear antibody (ANA) was strongly positive; anti-Ro and anti-La titers were highly raised (24,952 U/mL and 12,713 U/mL, respectively, vs normal upper limits of 10 U/mL). Schirmer test revealed markedly reduced lacrimation (0 mm bilaterally). Ninety-nine meter TcO₄ scintigraphy revealed negligible tracer uptake in both parotid and submandibular glands. Nerve conduction studies revealed autonomic neuropathy (absent sympathetic skin response) and ultrasonography of kidneys revealed simple cortical cysts. Final diagnosis of SS with distal RTA and hypokalemic paralysis, optic nerve involvement, and autonomic neuropathy was made and the patient was started on 60 mg prednisolone daily with oral potassium supplements. She improved initially in visual acuity, but developed acute right ophthalmoplegia with nasal obstruction (onset to peak 2 days) after 3 weeks of treatment. Repeat MRI of brain revealed findings suggestive of invasive rhino-orbitocerebral fungal infection. Nasal biopsy revealed invasive mucormycosis. She received IV amphotericin B but died of her illness after 2 weeks. A whole-body autopsy was done that confirmed invasive rhinocerebral mucormycosis along with pulmonary and hepatic dissemination along with evidence of SS in the form of tracheobronchial submucosal layer lymphocytic infiltration (figure, A) and medullary and papillary nephrocalcinosis (figure, B and C).

CASE 2 A 45-year-old woman presented with acute onset quadriparesis with dysphagia and respiratory weakness over a period of 4–6 hours. She had fever for 4 days before symptom onset. There was no history of neck pain, trauma, recent vaccination, dark-colored

From the Departments of Neurology (R.S., M.K.G., R.S., M.M., V.L.) and Histopathology (N.K.), Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India.

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Table List of investigations of cases 1 and 2			
Investigation	Case 1	Case 2	Normal range
Hemoglobin	12.2	12.0	12-14 g/dL
TLC	9,500	8,500	4,500-11,000/mm ³
Platelet	142,000	379,000	150,000-400,000/mm ³
ESR	42	64	0-20 mm/h
AST/ALT	39/35	55/44	2-50 U/dL
Serum creatinine/urea	1.10/31	1.0/37	0.6-1.0 mg/dL/10-50 mg/dL
Serum Na ⁺	141	140	135-145 mEq/L
Serum K ⁺	2.5	2.2	3.5-5.0 mEq/L
Serum Cl ⁻	122	125	95-105 mEq/L
Serum Ca ⁺⁺ /Mg	9.98/2.29	8.3/1.68	8.4-10/1.5-2.5 mEq/L
Serum protein/albumin	8.58/4.57	6.5/3.51	6.0-7.5/3.5-5.5g/dL
pH	7.24	7.16	7.35-7.45
pCO ₂ /pO ₂	20/113	17.5/130	35-45/75-100 mm Hg
HCO ₃ ⁻	9.0	6.0	23-26 mEq/L
Serum anion gap	15	9	8-16
Urine pH	6.0	6.5	4.5-8
HBsAg/anti-HCV/HIV	Nonreactive	Nonreactive	—
Thyroid function test	WNL	WNL	—
RA factor/anti-CCP	Negative	—	—
Serum ACE level	70	—	—
ANA	Positive (3+)	3 + speckled	—
Anti-Ro	Positive (24,952)	Positive (>240)	>10 U/mL
Anti-La	Positive (12,713)	Positive (>320)	>10 U/mL
ANCA	Negative	Negative	—
Antimitochondrial antibodies	Negative	—	—
CSF examination	86 mg/dL sugar, 52 mg/dL protein, no cells	95 mg/dL sugar, 46 mg/dL protein, no cells	

Abbreviations: ACE = angiotensin-converting enzyme; ALT = alanine transferase; ANA = antinuclear antibodies; ANCA = antineutrophil cytoplasmic antibodies; AST = aspartate transferase; CCP = cyclic citrullinated peptide; ESR = erythrocyte sedimentation rate; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; RA = rheumatoid arthritis; TLC = total leucocyte count; WNL = within normal limits.

urine, abdominal pain, numbness, paresthesias, bladder, bowel, facial, or ocular involvement. She had a history of joint pain and dry mouth and eyes. Examination revealed flaccid paralysis affecting all 4 limbs and neck muscles (power grade 0-1). There was mild facial muscle weakness, palatal movements were decreased, and gag reflex was sluggish. The rest of the neurologic examination including deep tendon reflexes and sensory system was normal. Single breath count was 5 and her voice was hypophonic. She was intubated and put on mechanical ventilation. She was evaluated as a case of AFP. The possibilities considered were of acute inflammatory demyelinating polyneuropathy (AIDP) (odd—no sensory symptoms, elicitable deep tendon reflexes), porphyric neuropathy, other toxic neuropathies (odd—no history of toxin exposure), and acute transverse myelitis (odd—no sensory symptoms,

no bladder or bowel involvement). In view of the absence of sensory symptoms as well as preserved deep tendon reflexes, possibilities such as HP, neuromuscular junction disorder, as well as some other channelopathy were also considered. She was evaluated. Serum potassium was low (2.2 mEq/L), chloride was raised (127 mEq/L), anion gap was normal, and arterial pH was low (7.16). Renal, liver, and thyroid function tests had normal (table) results. Serum calcium, magnesium, and phosphorus were normal. ANAs were positive; anti-Ro and anti-La antibodies were raised (240 U/mL and 320 U/mL, respectively, vs normal upper limits of 10 U/mL). CSF analysis revealed normal sugar (95 mg/dL), normal protein (46 mg/dL), and no cells. She was treated with parenteral potassium followed by oral potassium in a dose of 2 mEq/kg body weight. Her power improved within 2 days to near normal. However, she

(A) Lymphomatous infiltration destroying submucosa of tracheobronchial tree ($\times 100$). (B) Medullary nephrocalcinosis ($\times 40$). (C) Papillary nephrocalcinosis ($\times 20$).

required prolonged intubation, as she developed ventilator-associated pneumonia. Nerve conduction studies done on day 6 of illness revealed mild axonal sensorimotor neuropathy. Though there was evidence of axonal sensorimotor neuropathy, it was thought to be related to underlying SS rather than AIDP. The absence of sensory symptoms, preserved deep tendon reflexes, as well as recovery of motor power within 2 days of starting potassium supplementation strongly attest to the fact that cause of weakness in our index case was hypokalemia rather than AIDP. Ultrasonography of kidneys was normal. She recovered fully within 2 weeks and is currently asymptomatic. She is on prednisolone at a dosage of 1 mg/kg body weight.

DISCUSSION AFP is a clinical syndrome characterized by rapid onset of weakness of lower motor neuron type, progressing to maximum severity within 4 weeks of onset of symptoms. HP accounts for approximately 7.5% of AFP. The basic mechanism of muscle weakness in hypokalemia is hyperpolarization of resting membrane potential resulting in increased threshold for excitation. Approximately 40%–45% of all cases of HP are due to secondary causes.^{1–3}

The common secondary causes of HP include thyrotoxicosis, renal disorders (RTA, either proximal type 2 or distal type 1, Fanconi syndrome, medullary

sponge kidney, SS, and chronic toluene exposure), endocrinopathies (Conn syndrome, pseudohyperaldosteronism induced by licorice [glycyrrhizic acid] ingestion and carbenoxolone), gastrointestinal diseases (acute gastroenteritis, celiac sprue, tropical sprue, and short bowel syndrome), and barium poisoning.¹ In one study² ($n = 10$) evaluating etiology of secondary HP, thyrotoxicosis accounted for 50% of cases, followed by infective diarrhea (20%), Crohn disease (10%), Conn syndrome (10%), and distal RTA (10%). Another study ($n = 31$) found RTA and primary hyperaldosteronism to be the commonest causes (41.9% each), followed by thyrotoxicosis (6.4%).⁴ In another study,⁵ thyrotoxicosis accounted for 40% of all cases of documented HP, while distal RTA, Conn syndrome, and Bartter syndrome accounted for approximately 6% each; 50% of patients with distal RTA had SS.

Distal RTA is an important cause of secondary HP. It can be familial (autosomal dominant or recessive of X-linked) or sporadic secondary to a number of causes such as galactosemia, Ehlers-Danlos syndrome, Fabry disease, Wilson disease, hereditary elliptocytosis, SS, hypogammaglobulinemia, and chronic active hepatitis. In distal RTA, defective distal tubular function results in impaired acidification of urine. The basic abnormality is either an excessive back diffusion of H^+ from lumen of collecting duct into blood or

impaired transport of H^+ across the tubule. In addition, there is impaired handling of K^+ by the renal tubules resulting in urinary K^+ losses and hypokalemia.⁶ The diagnosis of distal RTA is suggested by hyperchloremic metabolic acidosis with high urinary pH (>5.5). Though well-recognized as a cause of HP, respiratory involvement and severe paralysis as seen in our 2nd patient is rare in RTA and to date <20 cases of severe respiratory weakness secondary to RTA have been described.⁶

SS is a systemic autoimmune disorder secondary to a cell-mediated autoimmune process directed against exocrine glands with a prevalence of 0.5%–2% in various populations.⁷ Approximately two thirds of patients with SS develop extraglandular manifestations affecting the kidneys, liver, lungs, pancreas, and nervous system. Rate of renal involvement (one of the commonest extraglandular manifestations) ranges from 2% to 67% in different series. The spectrum of renal involvement includes interstitial nephritis, RTA, tubular proteinuria, nephrogenic diabetes insipidus, glomerulonephritis, and renal failure.⁸ The most common renal manifestation related to tubular dysfunction results from underlying chronic interstitial nephritis. RTA results from either a complete absence of H^+ ATPase pumps in the intercalated cells or autoantibodies directed against carbonic anhydrase II.

Though there are case reports^{6,9,10} in the literature describing HP secondary to SS with distal RTA, our cases are unique for several reasons. Our first patient had HP as the only clinical manifestation of SS for nearly a decade before developing optic neuropathy, dry eyes, and dry mouth. The correct diagnosis in this patient was made 12 years after onset of illness. Our second patient had HP as the only manifestation of SS. HPP as a presenting manifestation of SS is exceedingly rare. All these facts stress on need to consider distal RTA in HP and evaluate accordingly. Also, all patients with distal RTA should undergo evaluation for SS. We lost our first patient due to disseminated mucormycosis. Our second patient is unique in that the severe respiratory weakness she developed is very rare in distal RTA, with <20 cases reported in the literature so far.

The mainstay of treatment in HPP secondary to SS with distal RTA is symptomatic treatment (oral potassium and bicarbonate) along with immunosuppression. Both our patients received these treatments. However, our first patient developed disseminated mucormycosis following steroid therapy and died of

her illness. Our second patient is doing well (returned to baseline status) at 6 months follow-up with reduction in joint pain and no further attacks of weakness.

It is important to consider all secondary causes of hypokalemia in HP. In patients with RTA, it is important to screen for underlying SS as treatment in these patients differs from the treatments used for other varieties of HP.

AUTHOR CONTRIBUTIONS

Ritu Shree: drafting the article, analysis and interpretation of the data, manuscript preparation. Manoj K. Goyal: drafting the article or revising its intellectual content, analysis or interpretation of the data, manuscript preparation. Rajveer Singh: drafting the article and revising its intellectual content. Manish Modi: drafting the article and revising its intellectual content. Vivek Lal: drafting the article and revising its intellectual content. Nandita Kakkar: drafting the article and revising its intellectual content.

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DISCLOSURE

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