CASE SERIES

ACUTE HYPOKALEMIC PARALYSIS AND HASHIMOTO'S THYROIDITIS

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Acute hypokalemic paralysis (AHP) is a life-threatening emergency. It is exceptionally unusual for hypothyroidism to present with AHP. This association can be either primary or secondary through distal renal tubular acidosis. We report two cases who presented with acute quadriplegia. The succeeding investigations revealed severe hypokalemia and autoimmune hypothyroidism. The second case was found to have Sjogren's syndrome additionally. The underlying aetiology of hypokalemia in both cases was found to be dRTA. The combination of such conditions is reported sporadically. Here we also discuss the potential association of AHP with autoimmune conditions by proxy through dRTA.

Keywords: Acute hypokalemic paralysis; Distal renal tubular acidosis; Paralysis; dRTA, Hypothyroidism

Citation: Ullah R, Naeem A, Naim F, Zia Q, Hamayun O. Acute hypokalemic paralysis and Hashimoto's thyroiditis. J Ayub Med Coll Abbottabad 2022;34(4):864–8.

DOI: 10.55519/JAMC-04-10918

INTRODUCTION

Acute hypokalemic paralysis (AHP) is one of the fatal but curable condition[1] that needs a principal cause assessment after emergency management. Hypokalemia can be explained mainly by two mechanisms, either its loss through kidneys and gut or its displacement into the cells under various circumstances.[2] Hypokalemic periodic paralysis (HPP) is one of the recognized features of thyrotoxicosis[2] and it is considered due to intracellular potassium transit.[3] However, the association of acute hypokalemic paralysis with hypothyroidism either directly or indirectly is barely reported.[2,4,5] We present two cases of AHP who were subsequently found to have hypothyroidism (Hashimoto's), The bizarre association with distal renal tubular acidosis and severe hypokalemia with autoimmune conditions like Hashimoto's thyroiditis and Sjogren's is explained. This helps the doctors to recognize the underlying pathology of AHP and ensures its effective management. It also provides a prompt to the researchers to find out evidence on this bizarre association.

CASE-1

A 25-year-old university student from the northern region of Khyber Pakhtunkhwa (KPK) with no previous medical conditions was presented to the emergency department complaining of weakness in both the lower and upper limbs. It began with progressive weakness in the lower limbs suddenly in the morning when he woke up from sleep one week ago. After two days, it ascended to the upper limbs and left him unable to walk. He complained of sore aches in the muscles of his thighs and back. The bowel and bladder functions were normal. Any other symptoms including diarrhoea, vomiting, cough, breathlessness, chest pain, palpitations, burning or excessive urination, joint pains, or any rash were denied. Previously he was fine except for occasional constipation that was not treated. He claimed weight-gain that was unintentional and undocumented. The medications history was unremarkable except he was managing myalgia with paracetamol. There was no history of similar problems in his family. He had a good appetite and a good diet including meat, vegetables, and fruits. Smoking, alcohol consumption, and any recreational drugs were denied. He had not travelled outside the province in the previous six months. His mood was low, that was probably because of his present illness.

On examination, the young gentleman had almost a normal observation profile: blood pressure (110/77 mmHg), pulse (78/min), respiratory rate (21/min), pulse oximetry (98% on room air), and random blood sugar (107 mg/dl). He was having good breathing efforts and the systemic examination was unremarkable except the neurological examination revealed the power of 1/5 in lower limbs and 3/5 in upper limbs. The sensations were all intact. The reflexes in the lower limbs were absent and diminished in the upper limbs. The cranial nerves were found normal.

A baseline blood investigations profile including full blood profile, renal function tests, liver function tests, serum electrolytes, calcium, phosphorous, Magnesium level, serum albumin, CK, and Thyroid function tests were requested (Table-1). The severe hypokalemia prompted us for an ECG that revealed a regular rhythm with loss of "T wave" and a false prolongation of QT interval due to U waves.

He was started on low-dose intravenous (IV) potassium chloride (KCl) through a normal saline infusion in a peripheral vein until the ICU staff secured the central venous access (CVP) and 10 ml of 10%

calcium gluconate was given for hypocalcemia. He was commenced on oral levothyroxine 50 µg/day, and IV KCL of 20 mEq/hour with an overall 240 mEq/day (Strength: KCl 80 mEq in 1000 ml Ringer lactate solution) in the CVP with continuous vital signs monitoring. The serum potassium level fluctuated vigorously and was found hard to maintain within the reference range. On second day, some further investigations were carried out to find the underlying cause of the illness including anti-thyroid peroxidase (anti-TPO) antibodies, early morning cortisol, arterial blood gases, and urine ph and 24 hours urinary electrolytes (Na^+, K^+, Cl^-). The alkaline urine in the face of a normal anion gap (NAG) metabolic acidosis helped us to reach the renal acidification defect –type I renal tubular acidosis (dRTA) as the cause of hypokalemia. The levothyroxine dose was increased to 100 µg/day on the doubt of benefit in correcting hypokalemia and venous sodium bicarbonate and dexamethasone 4mg BD was added. The anti-nuclear antibodies (ANA) and extractable nuclear antigen (ENA) antibodies panel came within the reference range. Subsequently, the nephrology team was consulted for expert analysis. As the renal structural and functional status was unremarkable, they advised oral sodium bicarbonate only and switching intravenous KCl to oral potassium supplements.

The hypokalemia, muscular weakness, and metabolic acidosis had resolved after five days of therapy with a daily potassium supplement (30 mEq) and levothyroxine (100 µg) and sodium bicarbonate and dexamethasone 16mg/day. The patient was discharged on the 8th day of admission. The levothyroxine 100µg/day (oral tablets) and potassium supplements (oral tablets –for 15 days (about 2 weeks only) and tapering dose of prednisolone were continued and he was advised to come for a follow-up after one month.

On follow-up, the patient was in good health moving on his own with a 5/5 power in all four limbs. The electrolyte imbalance had resolved, arterial blood PH and bicarbonate level, and urinary PH was within the reference range. The thyroxine replacement was continued. He was referred to an endocrinologist for optimization of hypothyroidism therapy and further follow-up. He was educated regarding compliance with medication and advised to come again if the weakness returns. In the following six months, the patient continued to be healthy on levothyroxine 50µg/day.

Table-1: Laboratory investigations reports of case 1

Labs (Normal Value –NV)	Day 1–7	Day 8–42	Day 43 (follow –up)
Serum Sodium (NV: 135–150 mmol/l)	151	144	142
Serum Potassium (NV: 3.5–5.1 mmol/l)	2	4.1	4.4
Serum Chloride (NV: 96– 12 mmol/l)	117	104	108
Serum Creatinine (NV: 0.6–1.2 mg/dl)	1.17	1.1	-
Blood Urea (NV: 10–50 mg/dl)	38.5	35.5	-
eGFR (NV: 90–120 ml/min/1.73m^2)	120	-	-
Early Morning Cortisol (NV: 5–23 µg/dl)	20.3	-	-
Arterial Bicarbonate (NV: 22–28 mmol/L)	17	25.1	26.6
Blood Ph (NV: 7.35–7.45)	7.26	7.41	7.4
TSH (NV: 0.35–5.5 µIU/ml)	27.6	13.76	0.89
$T4_{(f)}$ (NV: 10–28 pmol/l)	5.62	19.62	33
$T3_{(f)}$ (NV: 0.6–2.0 nmol/l)	0.346	0.303	0.209
Anti TPO antibodies (NV: <15 IU/L)	58	-	-
Urine Ph –before sodamint replacement (NV<5.5)	6.7	<5.5	-
Urinary Potassium (mEq/L/24 hours)	56	-	-
Urine Anion Gap	+65		
Anti-nuclear antibodies (ANA)	Negative		
Extractable nuclear antigen (ENA) profile	Negative		

CASE-2

A 26-year-old homemaker presented to the ER complaining of sudden onset of weakness and pain in all four limbs since she woke up in the morning. She was also complaining of dry mouth and fatigue for the last 3 days. She denied any other symptoms including diarrhoea, constipation, vomiting, weight gain, menstrual irregularity, urinary symptoms, dryness, or redness in the eyes. She had no underlying medical illness except she had experienced deep vein thrombosis (DVT) in the right leg 4 years ago after giving birth to her last child. She was not taking any medication including OTC or herbal medications. This was the first time she had experienced such symptoms.

At the time of presentation, she had BP of 90/60 mmHg, pulse rate of 96 bpm (regular), R/R 23 per min, SpO_2 96% on room air, and temperature of 98 F with GCS 15/15. A diffusely enlarged thyroid gland was appreciated on neck examination. The systemic examination was unremarkable except for the

neurological assessment. The power in both upper and lower limbs was 3/5 with depressed deep tendon reflexes. The sensations, cranial nerves, and bowel-bladder functions were intact. The blood investigations revealed hypokalaemia, hyperchloremia, and hypothyroidism. Twelve hours after the presentation, she became tachypneic with dropping oxygen saturation and irregular heart rhythm. The R/R was 33/min, with arterial ph 7.1, PO_2 58 mmHg, PCO_2 57 mmHg, HCO_3 13.6 mEq/L, and Oxygen saturation 88%. The patient was taken to the medical ICU. In the first 24 hours of admission, the patient was started on mechanical invasive ventilation for type II respiratory failure and exhaustion. In the face of normal anion gap metabolic acidemia, the urinary ph came alkaline (before sodium bicarbonate administration). Potassium replacement was commenced through the central line and sodium bicarbonate (200 mEq) was given besides 150 mg of hydrocortisone, 10 ml of Calcium gluconate 10% and 2 gm of Magnesium sulphate. The next day, the patient was commenced on thyroxine 100 µg/day and venous potassium replacement was continued. Per nasogastric tube sodium bicarbonate and potassium supplements were also started. In the first 48 hours, the potassium level hardly rose to 2.5 mEq/L despite continuous intravenous and enteral replacement. The urinary electrolytes revealed potassium wasting in the face of hypokalaemia (Table-2). On the 3rd day of admission, the potassium level began to rise. However, she developed hypernatremia (as high as 164 mEq/L) that was attributed to the excessive use of normal saline infusions and enteral soda-mint tablets, so hypotonic infusions (5% Dextrose water and half-strength saline) and enteral plain water were used to bring sodium to the reference range. Only on the 4th day, the potassium level just touched the reference range. An autoimmune workup revealed positive ANA with high titers of Sjogren's related antibodies (Table-2) and the renal assessment revealed proteinuria with reduced creatinine clearance (Table-2).

On the 7th day, the patient was successfully weaned off from the mechanical ventilator and shifted to HDU for further care. During her stay in the hospital, a close liaison was maintained with the nephrology team and followed their advice on electrolytes correction, sodium bicarbonate replacement. The potassium and bicarbonate levels fluctuated widely despite their continuous replacement. Until she was discharged, she had received sodium bicarbonate, potassium supplements, steroids and levothyroxine 100 mg/day. The patient was referred to rheumatology for further management including biopsy confirmation of Sjogren's syndrome.

The patient was discharged on the 14th day, with normal serum electrolytes (Table-2) and a 5/5 power in all four limbs. She was continued on levothyroxine 100 mg/day with enteral sodium bicarbonate, potassium supplements and prednisolone for the next 14 days. After one month of discharge, she was reviewed in the general medicine OPD and found to have no symptoms of weakness. She was asymptomatic in terms of Sjogren's syndrome, so an observe and follow-up strategy was adopted by the rheumatologist. Unfortunately, after two follow-up sessions with us, we lost her tracing.

Table-2: Laboratory investigations reports of case 2

Labs (Normal Value –NV)	**Day 1–3**	**Day 4–13**	**Day 14 (Discharged)**
Serum Sodium (NV: 135 – 150 mmol/l)	147	160	144
Serum Potassium (NV: 3.5 – 5.1 mmol/l)	1.6	3.4	4.1
Serum Cholride (NV: 96 – 112 mmol/l)	130	118	109
Serum Creatinine (NV: 0.6 – 1.2 mg/dl)	1.6		
Blood Urea (NV: 10 – 50 mg/dl)	47		
24 hours Urinary protein (less than 150 mg/24 hours)			486
Creatinine clearance (75 – 115 ml/min)			41
Blood Ph (NV: 7.35 – 7.45)	6.97	7.3	7.37
PCO_2 (NV: 35 – 45 mmHg)	67	21.8	38
Arterial Bicarbonate (NV: 22 – 28 mmol/L)	8.8	13.0	18.5
TSH (NV: 0.35 – 4.2 µIU/ml)	87.49	_	24
$T4_{(f)}$ (NV: 66 – 181 nmol/l)	38.9	_	110
$T3_{(T)}$ (NV: 1.23 – 3.07 nmol/l)	0.66	_	_
Anti TPO antibodies (NV: < 35 IU/L)	353	_	_
Urine Ph –before sodamint replacement (NV< 5.5)	7	6	4.5
Urinary Potassium (mEq/L/24 hours)	42	_	_
Urine Anion Gap	+44	_	_
Anti-nuclear antibodies (ANA)	Positive (Speckled pattern)		
Extractable nuclear antigen (ENA) profile	High titer of antibodies related to Sjogren's syndrome Anti Rho: 159 U/mL Anti La: 51U/mL		
Neck sonography	Mild – diffusely enlarged thyroid gland		

DISCUSSION

Acute hypokalemic paralysis is one of the fatal but reversible conditions that present to the emergency doctors.[1] Therefore, early recognition and timely treatment are paramount. To address the problem completely, a meticulous chase of aetiology is indispensable. The association of this condition with thyrotoxicosis is well established[2,3], however, in the literature, hypothyroidism is rarely reported in association with AHP[2,4,5].

Although the second patient experienced a more dramatic and severe deterioration of muscular strength, both were presented with progressive quadriplegia and diminished reflexes in all four limbs without any sensory or autonomic dysfunction and were newly found to be hypothyroid with the laboratory reading of severe hypokalaemia. The peculiar presentation prompted us to think of hypokalaemia more than the neurological cause behind quadriplegia, so we did not venture into the neurological investigations. The clinical improvement with potassium supplements proved us right.

Acute hypokalemic paralysis (aka Hypokalemic periodic paralysis -HPP) can be primary or secondary.[1,6] The primary AHP is considered with a family history (Autosomal dominant variant) and after discarding the secondary causes. The history (no diarrhoea, no vomiting, no medications, no past medical conditions or a family history) and urinary K^+ wasting in the face of hypokalaemia helped us focus on the renal causes rather than the causes related to intracellular potassium shift and gastrointestinal loss.[7] The age of presentation, normal sodium level, normal or low blood pressure and NAG metabolic acidosis excluded the possibility of primary hyperaldosteronism, hyperreninism, Gitelman, Bartter's, and Liddle's syndromes.[1] The NAG metabolic acidosis, hypokalemia, alkaline urine with a positive urinary anion gap brought us to the diagnosis of dRTA.[7]

Acquired distal renal tubular acidosis is most often associated with autoimmune diseases particularly Sjogren's syndrome, systemic sclerosis, rheumatoid arthritis and SLE.[1,5,8] Most of the other possible associations of dRTA e.g., nephrocalcinosis, tubulointerstitial diseases, multiple myeloma, medications, and toxicity can be easily ruled out by history, renal function tests and normal abdominal sonography. From the history and laboratory findings in case one, we could only associate Hashimoto's thyroiditis (HT) with dRTA and in the second case, Sjogren's syndrome in addition to Hashimoto's thyroiditis were found in association with dRTA leading to AHP. The association of dRTA with Sjogren's syndrome is well known, however, the consistent response of AHP to levothyroxine and potassium replacement without specific treatment for Sjogren's syndrome drew our interest to searching the literature for a possible association of Hashimoto thyroiditis with AHP and it is rarely reported in the literature.[1,9]

Kadeeja *et al*[10] and Meregildo *et al*[5] reported cases of autoimmune hypothyroidism with dRTA leading to AHP, similar to our case one. However, Kadeeja *et al* reported a patient who had a long history of recurrent AHP, but both our cases visited the hospital for the first time with acute paralysis. The correction of dRTA with levothyroxine in both our cases is consistent with the case reported by Meregildo *et al.*[5] Similarly, Yilmaz *et al*[11] reported a case of Sjogren's syndrome who presented with AHP secondary to dRTA and responded to potassium and bicarbonate replacement and prednisolone, which is similar to our second case except that ours had Hashimoto's thyroiditis as well. After thorough literature search, we could not find a particular case of Hashimoto's thyroiditis together with Sjogren's syndrome in association with AHP. Although our patient had Sjogren's syndrome, a renowned cause of hypokalemic paralysis but we could not discard the role of Hashimoto thyroiditis because, her electrolytes returned and maintained in the normal range with potassium and levothyroxine replacement. Therefore, we propose a relationship of dRTA and AHP with Hashimoto thyroiditis.

Regarding the etiopathogenesis, thyroxin is considered to modulate the function of trans-membrane transporters.[1] The lack of effect of thyroxin on the acid-base transporters particularly the H^+ ATPases on the brush border of distal nephron may explain the acid retention and K^+ loss seen in dRTA.[1,5] Usually, it is extremely rare for an isolated dRTA to present with AHP[1,5] and the AHP has also been reported with hypothyroidism without dRTA.[2,4,10] From the facts mentioned earlier, we can assume that hypothyroidism can also cause hypokalaemia directly in addition to causing dRTA. This assumption is based on the recurrence of AHP with thyroxin withdrawal.[5] Besides the role of thyroxin, the presence of autoimmune antibodies against the distal nephron has been suggested as another possible etiopathogenesis of dRTA in association with autoimmune conditions.[1,6] Both our cases support the above two assumptions regarding the pathogenesis of AHP in hypothyroidism (Hashimoto's thyroidits). On the other hand, Inagaki *et al*[12] reported a case of hypothyroidism associated with AHP suggesting apparent mineralocorticoid access (AMA) as the underlying mechanism. In patients with Sjogren's syndrome, Tala *et al*[11,13]

found renal lymphocytic infiltrations in a case of dRTA associated with Sjogren's syndrome. The uncertainty regarding the pathogenesis AHP in autoimmune conditions needs to be further elucidated on molecular basis to tell us about the exact mechanism.

CONCLUSION

Considering the literature and the above cases, in the clinical setup, hypothyroidism should be considered as one of the potential causes of acute hypokalemic paralysis (AHP). In the face of Sjogren's syndrome, patients need to be investigated for hypothyroidism. Moreover, the replacement of levothyroxine, potassium, sodium bicarbonate parallel with a short course of steroids helps to ameliorate the condition easily. Further research is needed to find out evidence on the proposed relation of dRTA and AHP with Hashimoto thyroiditis.

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Submitted: April 23, 2022	*Revised: June 11, 2022*	*Accepted: June 12, 2022*

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