Complete Hypokalemic Quadriparesis as a First Presentation of Sjögren Syndrome

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Abstract

Rationale: We hope to increase awareness that hypokalemic paralysis may be the first presentation of Sjögren syndrome, for which potassium-sparing diuretics can be an effective adjunct to potassium replenishment.

Presenting concerns: A 73-year-old female presented to a peripheral hospital with quadriparesis and a critically low serum potassium of 1.6 mmol/L with U waves on the electrocardiogram (ECG). The initial arterial blood gas showed a pH of 7.19, bicarbonate of 13 mEq/L, and a CO₂ of 33 mm Hg. Over the next 6 days, she was administered a total of 450 mEq of potassium supplements. Despite this, her potassium never increased above 2.9 mmol/L and was thus transferred to the University Hospital for further management. On arrival, her vital signs were within normal limits. Her only other symptoms were fatigue and ocular dryness. Physical exam showed slightly weakened quadriceps muscles bilaterally, graded 4/5. Examination was otherwise unremarkable. Admission investigations included a potassium of 2.8 mmol/L, chloride 118 mmol/L, sodium 136 mmol/L, and eGFR 48 mL/min/1.73 m². Renin aldosterone ratio was normal.

Diagnoses: Distal renal tubular acidosis (RTA) was diagnosed based on a normal anion gap metabolic acidosis, positive urine anion gap, and elevated urine potassium to creatinine ratio. Investigation of underlying causes revealed a positive Antinuclear antibody (ANA), elevated rheumatoid factor, and high anti-Ro/SSA titre which directed us toward a unifying diagnosis of Sjögren syndrome. A renal biopsy was undertaken as an outpatient and demonstrated severe interstitial nephritis with acute and chronic components, parenchymal scarring, atrophy, and small vessel arteriosclerosis.

Interventions: In the acute setting, the patient was treated with bicarbonate and amiloride in addition to potassium supplementation.

Outcomes: The patient’s hypokalemic paralysis and metabolic acidosis were corrected.

Lessons Learned: Severe hypokalemic paralysis in distal RTA associated with Sjögren syndrome can be successfully treated with amiloride in addition to potassium supplementation. We also review the literature on the aberrancies seen in H⁺ATPase, Band 3, Pendrin, and carbonic anhydrase that may underlie the pathogenesis of distal RTA in Sjögren syndrome.

Abridged

Justification: La paralysie hypokaliémique pourrait être une des premières manifestations du syndrome de Sjögren; syndrome pour lequel les diurétiques épargneurs de potassium pourraient s’avérer un traitement d’appoint pour la régénération du potassium.

Présentation du cas: Nous présentons le cas d’une femme âgée de 73 ans qui s’est présentée dans un hôpital périphérique avec une quadriparesie et un taux de potassium aléatoire de 1,6 mmol/L, en plus d’un tracé à l’ECG comportant des ondes U. Les analyses de gazométrie artérielle initiales montraient un pH sanguin à 7,19, un taux de bicarbonate à 13 mEq/L et un taux de CO₂ à 33 mm Hg. Malgré l’administration d’un total de 450 mEq de potassium sous forme de suppléments au cours des six jours suivants, le taux de potassium sérique de la patiente n’a jamais dépassé 2,9 mmol/L; on a donc transféré la patiente à l’hôpital universitaire pour un suivi plus poussé. À son arrivée, les signes vitaux se situaient dans les limites normales et les seuls symptômes notables étaient de la fatigue et de la sècheresse oculaire. Mis à part une légère faiblesse bilatérale des quadriceps (score de 4/5), l’examen physique n’avait rien d’anormal. Les analyses faites à cette seconde admission ont révélé des taux de 2,8 mmol/L pour le potassium, de 118 mmol/L pour le chlore et de 136 mmol/L pour le sodium. Le DFGe de la patiente se situait à 48 mL/min/1,73 m² et le rapport rénine/aldostérone était normal.

Diagnostic: Une acidosé rénale tubulaire distale (ARTD) a été diagnostiquée par le constat d’une acidose métabolique à trou anionique normale, d’un trou anionique urinaire positif et d’un rapport potassium/créatinine urinaire élevé. La recherche des causes sous-jacentes a révélé une détection d’anticorps antinucléaires ainsi que des valeurs élevées pour le facteur rhumatoïde et le tiritage des anti-SSA/Ro, ce qui nous a directement aiguillés vers un diagnostic unificateur du syndrome de
Sjögren. Une biopsie rénale pratiquée en consultation externe a révélé la présence d’une néphrite interstitielle grave avec composantes aigües et chroniques, des lésions au parenchyme, une atrophie et une artériosclérose des artérioles.

**Traitement:** Aux soins intensifs, la patiente a été traitée avec du bicarbonate et de l’amiloride en plus d’un apport supplémentaire en potassium.

**Résultats:** La paralysie hypokaliémique et l’acidose métabolique ont été corrigées.

**Conclusion:** La paralysie périodique hypokaliémique survenant en contexte d’une ARTd associée au syndrome de Sjögren peut être traitée par l’administration d’amiloride et d’un apport supplémentaire en potassium. Nous dressons également certains constats à la suite d’une revue de la littérature concernant des valeurs aberrantes (notamment dans l’activité de la H⁺ATPase et de l’anhydrase carbonique, de même que dans les taux de la protéine Band 3 et de la pendrine) qui expliqueraient la pathogénèse d’une ARTd dans les cas de syndrome de Sjögren.

**Keywords**
Sjögren syndrome, hypokalemia, distal renal tubular acidosis, quadriparesis, interstitial nephritis

Received December 9, 2017. Accepted for publication March 18, 2018.

**What was known before**
An increasing number of case reports have described paralysis as the presenting feature of Sjögren syndrome, with some illustrating abnormal distal tubular histology as a clue to its pathogenesis.

**What this adds**
We hope to increase awareness that Sjögren syndrome may present in a multitude of ways, for which hypokalemic paralysis may be one of them. Our report describes a patient with hypokalemic paralysis and distal renal tubular acidosis and highlights the utility of amiloride in severe symptomatic hypokalemia due to Sjögren syndrome. Our literature review also discusses evidence that suggests aberrancies in H⁺ATPase, Band 3, Pendrin, and Carbonic Anhydrase that may underlie the pathogenesis of distal renal tubular acidosis in Sjögren syndrome.

**Introduction**
Sjögren syndrome is an autoimmune condition characterized by lymphocytic infiltration into moisture secreting glands, manifesting in dry eyes and dry mouth (sicca syndrome). Estimated prevalence of Sjögren syndrome in the general population ranges from 0.03% to 0.08%. Sjögren syndrome is diagnosed based on a combination of clinical and laboratory findings, such as the classification criteria by the 2012 American College of Rheumatology criteria and the American-European Consensus Group revised criteria (Table 1). Although classification criteria can help guide diagnosis, the gold standard for diagnosing Sjögren syndrome remains clinical judgment.

Renal involvement occurs in 16% to 67% of Sjögren patients; the reported large range reported being due to different definitions of the disease, and the inclusion of secondary Sjögren in some studies. The most common renal presentations are tubulointerstitial nephritis and distal renal tubular acidosis (RTA). Prevalence of tubulointerstitial nephritis in Sjögren syndrome with renal involvement can be as high as 65% to 71%. This may present with hypokalemia, elevated creatinine, a relatively bland urine sediment with leukocyturia, features of proximal tubule dysfunction (Fanconi syndrome), or nephrogenic diabetes insipidus. Distal acidification defects can occur in up to 40% of all Sjögren patients, and usually exists in the setting of tubulointerstitial nephritis, but can also present in isolation.

Distal RTA can result in severe hypokalemia and development of paralysis, cardiac arrhythmias, bulbar weakness, and respiratory arrest, all of which have been reported in Sjögren patients.

**Presenting Concerns**
A 73-year-old female presented at a rural hospital in Alberta with complete quadriparesis upon wakening. Her past medical history was significant only for chronic obstructive pulmonary
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Initial laboratory investigations revealed a critically low serum potassium of 1.6 mmol/L, sodium 141 mmol/L, magnesium 0.96 mmol/L (normal 0.7-1 mmol/L), and estimated glomerular filtration rate (eGFR) of 40 mL/min/1.73 m² chronic kidney disease epidemiology collaboration equation (CKD-Epi). Hemoglobin was 114 g/L and a morning plasma cortisol was normal. U waves were present on the electrocardiogram (ECG). An arterial blood gas showed a pH of 7.19, bicarbonate of 13 mmol/L, and a CO₂ of 35 mm Hg. Over the next 6 days, she was administered a total of 450 mEq of oral and intravenous potassium supplements. Despite this, her potassium remained below 2.9 mmol/L. She was transferred to the University of Alberta Hospital for further assessment and management.

Clinical Findings

On arrival to the rural hospital, the patient was given a bolus of 30 mmol KCl in response to her initial serum potassium of 1.6 mmol/L, followed by a daily total of 60 mmol of oral potassium supplement for the next 5 days (Figure 1). As her serum potassium failed to rise above 2.9 mmol/L, daily oral potassium supplementation was increased to 120 mmol from day 6 to 7. Bicarbonate was given due to severe metabolic acidosis with the goal of stabilizing cardiac membranes, despite a theoretical risk of further decreasing plasma K⁺ and increasing tissue CO₂. Amiloride 5 mg twice daily (PO BID) was employed on day 7 till 10 and then stopped. It was restarted again on day 14 with dose of 5 mg once daily (PO OD). As serum K⁺ normalized on day 8 with bicarbonate and amiloride treatment, supplementation was stopped (on day 8).

Distal RTA was diagnosed based on a normal anion gap metabolic acidosis, inappropriately elevated urine pH of 7, positive urine anion gap of 21, low 24-hour urine citrate of 0.1 mmol (normal 1-5 mmol/24 h), and elevated urine potassium to creatinine ratio of 9.6 where a value exceeding 1.5 in the context of metabolic acidosis is consistent with RTA.

### Table 1. Classification Criteria for Sjögren Syndrome.

| I. Ocular symptoms: a positive response to at least 1 of the following questions: |
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| 1. Have you had daily persistent, troublesome dry eyes for more than 3 months? |
| 2. Do you have a recurrent sensation of sand or gravel in the eyes? |
| 3. Do you use tear substitutes more than 3 times a day? |

| II. Oral symptoms: a positive response to at least 1 of the following questions: |
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| 1. Have you had a daily feeling of dry mouth for more than 3 months? |
| 2. Have you had recurrently or persistently swollen salivary glands as an adult? |
| 3. Do you frequently drink liquids to aid in swallowing dry food? |

| III. Ocular signs, that is, objective evidence of ocular involvement defined as a positive result for at least 1 of the following 2 tests: |
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| 1. Schirmer I test, performed without anesthesia (<5 mm in 5 minutes) |
| 2. Rose Bengal score or other ocular dye score (>4 according to van Bijsterveld scoring system) |

| IV. Histopathology: in minor salivary glands (obtained through normal-appearing mucosa), focal lymphocytic sialoadenitis evaluated by an expert histopathologist, with an Focus score (FS) greater than 1, defined as several lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain >50 lymphocytes) per 4 mm² of glandular tissue |

| V. Salivary gland involvement objective evidence of salivary gland involvement defined by a positive result for at least 1 of the following diagnostic tests: |
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| 1. Unstimulated whole salivary flow (<1.5 mL in 15 minutes) |
| 2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary, or destructive pattern), without evidence of obstruction in the major ducts according to the scoring system of Rubin and Holt |
| 3. Salivary scintigraphy showing reduced concentration or delayed excretion of tracer according to the method proposed by Schall and colleagues |

| VI. Autoantibodies: presence in the serum of the following autoantibodies: |
|---|
| 1. Antibodies to Ro(SSA) or La(SSB) antigens, or both |

Note. According to the American-European Consensus Group revised criteria, Sjögren syndrome is present when 4 out of the 6 items are positive, with at least 1 of them being positive antibodies, or labial biopsy with lymphocytic infiltration.
The urine potassium to creatinine ratio is thought to be more accurate than the transtubular potassium gradient (TTKG) in quantifying hypokalemia as the TTKG does not account for intrarenal urea recycling which leads to osmole reabsorption downstream of the cortical collecting duct.10 The diagnosis of distal as opposed to proximal RTA was also supported by hypocitraturia, which likely reflects enhanced citrate metabolism in renal tubular cells due to systemic acidosis.11 The reduced intracellular citrate thus predisposes to increased passive citrate absorption from the lumen, reflected by a reduced urinary citrate excretion. As citrate binds calcium in the filtrate, low urinary citrate levels allow for reduced solubility of calcium salts in alkali urine and predisposes to nephrolithiasis,12 which our patient had evidence of on renal ultrasound.

Further investigations for underlying causes of distal RTA in our patient revealed a positive ANA, elevated rheumatoid factor, and high anti-Ro/SSA titre which in the context of progressive sicca symptoms directed us toward a unifying diagnosis of Sjögren syndrome.

Pathogenesis of Distal RTA and Subsequent Hypokalemia in Sjögren Syndrome

Primary distal RTA is due to genetic defects in critical anion exchangers within the intercalated cells. Mutations in the SLC4A1 gene encoding the Band 3 protein lead to dRTA inherited in a dominant fashion. Mutations in the ATP6V1B1 or ATP6V0A4 genes encoding subunits of the H⁺ATPase result in recessively transmitted dRTA. Recessive dRTA is clinically accompanied by sensorineural hearing loss, in contrast to its dominant counterpart which does not.13 The causes of secondary dRTA are numerous, including hypercalcemia, lithium, autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, or Sjögren syndrome.

On a molecular level, distal RTA in Sjögren syndrome is marked by the disturbance of any combination of 3 ion channels and 1 intracellular enzyme that underlie metabolic acidosis and hypokalemia.

First, various articles have shown the apical H⁺ATPase (Figure 2) on membranes of αICCs to be absent via immunostaining,14-16 although the αICCs are otherwise present and morphologically normal. This has been speculated to be due to immune cell infiltration (as seen on histological examination), with general injury to α-intercalated cells (αICCs).
However, distal RTA in some Sjögren patients do not have evidence of interstitial infiltration, suggesting a more targeted destruction of the H+ATPase pumps. Kim et al explored whether autoantibodies in the serum may be responsible for this process, but incubation of the patient’s serum with control human and rat kidney failed to show any cross reactivity. Other unproven theories of the (presumed acquired) loss include defects in expression, assembly, or insertion of the pump into the apical membrane. As the H+ATPase actively secretes protons, loss of this pump leads to metabolic acidosis and inappropriately alkaline urine.

Second, distal RTA in Sjögren patients is also marked by the absence of Pendrin (Figure 2), a Cl−/HCO3− antiporter on the apical membrane of Type B intercalated cells (βICC) which functions to secrete bicarbonate. A possible explanation for this is that the process underlying the destruction of H+ATPase on αICCs also affects Pendrin. An alternative possibility, however, may be that loss of H+ATPase on αICCs which lead to metabolic acidosis may cause βICCs to compensate by downregulating Pendrin to reduce secretion of bicarbonate. If the loss of Pendrin is due to compensation, it is likely incomplete if the state of metabolic acidosis persists. It is thus interesting to speculate that perhaps more patients with Sjögren than we observe have diminished H+ATPase, as those who completely compensate do not come to clinical attention with significant metabolic acidosis.

Third, Band 3 protein (Figure 2) has also been reported to be diminished in Sjögren patients with distal RTA. Band 3 protein is otherwise known as anion exchanger type 1, and is also a Cl−/HCO3− antiporter localized on the basolateral membrane of αICCs and functions to return bicarbonate to the systemic circulation. It is possible that the aberrant immune system in Sjögren disease also suppresses the expression or destroys the Band 3 antiporters on the basolateral membranes, resulting in systemic acidosis.

Antibody-mediated cellular destruction was explored by Konishi et al, whose case study in 1994 described autoantibodies detected by indirect immunofluorescence against both types of renal intercalated cells (Figure 2). They did not stain specifically, however, for any of the 3 deranged ion transporters discussed above. Similarly, the other 3 studies discussed above did not find any antibodies with specificity toward the H+ATPase in stained sections of the kidney, nor in the serum. It therefore remains speculative how the deranged immunologic milieu of Sjögren syndrome leads to loss of these critical ion exchangers that regulate urine and systemic pH.

Finally, some intriguing reports have identified the presence of circulating antibodies to intracellular enzymes in Sjögren syndrome. In a study of 46 patients with Sjögren (13 having either proximal or distal RTA and 19 controls), arterial bicarbonate levels were correlated with duration of disease, urine β2-microglobulin (reflecting proximal tubule dysfunction), and serum levels of autoantibodies against carbonic anhydrase II (CAII) which were measured with ELISA. It is not known whether these autoantibodies impair CAII leading to RTA, or alternatively reflect tubular damage whereby cell injury exposes intracellular antigens and stimulates autoantibody generation. In a following experiment, the same authors created a mouse model of Sjögren by injecting mice with human CAII. Anti-CAII antibodies were generated in these mice, which resulted in not only new urinary acidification defects but also histology similar to human Sjögren patients showing lymphoplasmacytic infiltration into the kidneys, liver, and salivary gland. A drawback of this study is that salivary and hepatic function was not assessed, and the population was not divided into distal versus proximal RTA. Despite these limitations, it is nonetheless plausible to speculate that autoantibodies targeting CAII may underlie the pathogenesis of distal RTA in Sjögren syndrome.

One of the many complications of distal RTA includes severe hypokalemia. In general, hypokalemia is usually due to gastrointestinal or renal losses (Figure 3). In the overall diagnostic approach to hypokalemia, the presence of hypertension could point at mineralocorticoid or cortisol excess. If blood pressure is normal or low, plasma pH can assist in determining underlying etiologies such as distal RTA.

In this case, severe hypokalemia was likely secondary to renal losses, specifically distal RTA for which there exist numerous mechanisms. First, metabolic acidosis inhibits proximal tubule sodium resorption, which would increase distal Na+ delivery with subsequent augmented ENaC activity and increased luminal electronegativity. Second, metabolic acidosis also reduces HCO3− reabsorption at the proximal tubule, which increases delivery of a non-reabsorbable anion and contributes to luminal electronegativity and thus enhanced distal K+ secretion. Third, increased sodium loss causes volume depletion and activates aldosterone which increases K+ secretion.

**Therapeutic Focus and Assessment**

In the acute setting, the priority was to reverse the severe hypokalemia with intravenous potassium supplementation, followed by correction of the underlying acidosis. Initial management of the severe hypokalemia other than potassium supplementation included sodium bicarbonate which raised serum potassium from 2.8 to 3.4 mmol/L (Figure 1) by opposing the mechanisms of acidosis-induced hypokalemia described above.

Addition of amiloride 5 mg PO twice a day the following day further raised serum potassium above 4 mmol/L. Specifically, amiloride blocks the epithelial sodium channel (ENaC) in the distal convoluted tubule as well as collecting ducts (Figure 4). ENaC normally allows entry of sodium down its electrical gradient from the filtrate into the cell, resulting in accumulation of intracellular positive charge. This leads to potassium extrusion into the filtrate via the
K-channel (renal outer medullary K⁺ [ROMK]) on the apical membrane. Concurrently, the Na⁺/K⁺-ATPase on the basolateral border pumps intracellular sodium into the interstitium in exchange for potassium. Administration of amiloride thus inhibits reabsorption of sodium into the cell from the tubular lumen which leads to K⁺ retention and correction of hypokalemia. Here, the fluctuations in serum K⁺ can be attributed to amiloride as the urine potassium was 30 to 35 mmol/L prior to administration but fell to 17.8 mmol/L after amiloride was started on day 7. When the serum K⁺ rose to 4.5 mmol/L on day 10, amiloride was stopped. The subsequent urine potassium then rose to 38 mmol/L paralleled by falling serum K⁺.

Interestingly, amiloride may also help localize the site of cellular pathology. If the underlying pathogenesis of hypokalemia was the principal cell due to reduced aldosterone release or response, or malfunctioning or absent ENaC, administration of amiloride should not raise serum potassium as its target of action is either absent or non-responsive.

Our observation that serum potassium rises on amiloride suggests that the principal cell is normal, and that the hypokalemia is more likely a secondary phenomenon due to the αICC’s failure to acidify the urine. This is in keeping with the pathological findings of Cohen et al as discussed above, where staining of the patient’s renal sections for H⁺ATPase was absent in the αICC.

Distal RTA associated with Sjögren syndrome is managed by correcting the acidosis with alkali preparations such as sodium bicarbonate and potassium citrate. As citrate is metabolized to bicarbonate, administration of potassium...
citrate can correct intracellular acidosis in addition to hypokalemia, and ameliorates development of nephrolithiasis via chelation of calcium with citrate. Treatment of Sjögren syndrome usually consists of symptom management with lubricating ocular drops and oral care including regular dental assessments, artificial saliva, and salivary stimulants such as pilocarpine. In the setting of extensive extraglandular involvement, however, corticosteroids or immunomodulators such as hydroxychloroquine, methotrexate, or rituximab may be used. Biologics such as infliximab and etanercept have also been studied, but no conclusive evidence for benefit has been found.23,24

**Follow-up and Outcomes**

The patient was discharged with a normal neurological exam and stable electrolyte levels on a daily dose of amiloride and bicarbonate (without any potassium supplementation). Follow-up 3 weeks later showed a stable potassium level at 4.3 mmol/L. A renal biopsy was undertaken as an outpatient and demonstrated a severe interstitial nephritis with acute components of plasma cell infiltration on a background of chronic parenchymal scarring. Electron microscopy showed an expanded interstitium with plasmacytic, monocytic, and lymphocytic infiltration.

**Discussion**

Sjögren syndrome is one of many fascinating, pluriform autoimmune entities whose underlying pathophysiology remains incompletely understood. This case illustrates a presentation of severe symptomatic hypokalemia in the context of distal RTA associated with underlying Sjögren syndrome. Our report emphasizes that although Sjögren syndrome is most often associated with chronic sicca symptoms, it may present for the first time with extraglandular manifestations which may be life threatening. We also review 3 ion channels within the intercalated cells that have been shown to be absent in previous studies,4-16 and discuss how their (presumably acquired) disappearance leads to non-anion gap metabolic acidosis seen in distal RTA.

Our report has a few limitations. First, we were unable to acquire the materials to stain the renal sections from our patient for the H\(^+\)/K\(^+\)-ATPase, Band 3, and Pendrin transporters to corroborate the findings of the other studies. As the patient did not respond optimally to potassium supplements, it may be argued that perhaps there was simply insufficient potassium supplement given in the context of profoundly low total body stores with ongoing renal losses. The case here highlights, however, that when the potassium deficit is significant and accompanied by muscle weakness and signs of cardiac membrane destabilization such as U waves on the ECG, amiloride may be helpful in selectively limiting renal losses while concurrently supplementing serum levels to raise potassium levels more rapidly in a monitored setting.

**Future Directions**

Although the acid base disturbances of Sjögren have been reported over the past 30 years, studies on the pathogenesis behind absent or defective ion channels have been lacking. Further understanding of such abnormalities may be facilitated by evaluating the H\(^+\)/K\(^+\)-ATPase, as well looking for the presence of circulating antibodies against the absent ion channels.

The apical H\(^+\)/K\(^+\)-ATPase of αICCs is usually upregulated in states of acidosis and hypokalemia in efforts to secrete protons and retain K\(^+\).22 The behavior of H\(^+\)/K\(^+\)-ATPase in Sjögren patients has not been explored. It is unclear whether the H\(^+\)/K\(^+\)-ATPase is also diminished (perhaps by similar immune mechanisms that affect the H\(^+\)-ATPase), or whether it might be physiologically upregulated to compensate for reduced H\(^+\)-ATPase on the apical membranes. It may be possible that the severity of metabolic acidosis and hypokalemia may depend on whether the H\(^+\)/K\(^+\)-ATPase is concomitantly affected. It would be valuable in future studies to stain sections for this pump to observe its behavior in the context of diminished H\(^+\)-ATPase, and correlate its abundance with the severity of metabolic acidosis and hypokalemia.

Given the results of the study by Takemoto et al,20 it would also be interesting to test for the presence of serum autoantibodies against H\(^+\)-ATPase, Band 3, and Pendrin, and correlate titres with arterial bicarbonate and urinary pH. Renal and exocrine organ function studies in animal models with these autoantibodies may also reveal further insights into the pathogenesis of this fascinating disease.

**Acknowledgments**

Drs Kevin Wen, Mohammed Alarifi, and Priyanka Mysore for their contribution to diagnosis and work up of this case. Dr Branko Braam holds a Research Chair in Translational Kidney Health Research in the Faculty of Medicine and Dentistry, Department of Medicine, Division of Nephrology and Immunology.

**Ethics Approval and Consent to Participate**

Ethics board approval and patient consent to participate has been attained.

**Consent for Publication**

Written consent has been provided for the case to be published.

**Availability of Data and Materials**

Data and materials can be made available by contacting the corresponding author.

**Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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