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Idiopathic hypokalemia in lupus nephritis – A newly recognized entity

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Emmanuel Adomako, Saira Bilal, Yu-lun Liu, Ayesha Malik, Peter Van Buren, Shani Shastri, and Kamalanathan Sambandam

Key Points:
* Hypokalemia may occur in patients with lupus nephritis in the absence of RTA or other known causes.
* Patients with lupus nephritis and idiopathic hypokalemia have a distinct pattern of markers of autoimmunity.
* Clinically evident RTA in lupus nephritis exhibits a distinct pattern of markers of autoimmunity.

Abstract:
Background: Various causes of hypokalemia from renal potassium wasting, including distal renal tubular acidosis, have been described in lupus nephritis (LN). We report a phenomenon of otherwise unexplained hypokalemia among a population with LN. Methods: From our population of 403 patients with LN, we identified a cohort of 20 patients with idiopathic hypokalemia (HK), defined by serum potassium < 3.5 mmol/L without any apparent explanation. This cohort is compared to 90 LN controls (CON) and 10 LN patients with distal renal tubular acidosis (RTA) from the same population. Results: The HK cases had lower median serum potassium compared to CON and RTA subjects (3.26 vs 4.00 vs 3.75 mmol/L; p < 0.001). The median serum bicarbonate was normal in HK and CON but low in RTA (26.0 vs 25.0 vs 19.4 mmol/L; p < 0.001). The median urine pH was abnormally high only in the RTA group (6.00 vs 6.25 vs 6.67; p = 0.012). The median serum magnesium was modestly lower in HK compared to the CON and RTA groups (1.73 vs 2.00 vs 1.85 mg/dL; p = 0.002). While both HK and RTA showed a higher rate of seropositivity than CON for anti-Ro/SSA (79% vs 80% vs 37%, respectively; p < 0.001), only HK revealed a higher rate of seropositivity than CON for anti-RNP (84% vs 42%; p = 0.003) and only RTA showed a higher rate of seropositivity than CON for anti-La/SSB (40% vs 12%; p = 0.046). Conclusions: A syndrome of idiopathic hypokalemia was revealed in 20/403 (5%) of patients within our LN population and proved to be distinct from the renal tubular acidosis that occurs in LN. Furthermore, it was associated with a distinct pattern of autoantibodies. We speculate that idiopathic hypokalemia is the result of a novel target of autoimmunity in LN affecting renal tubular potassium transport.

Disclosures: The authors have nothing to disclose

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- Clinically evident RTA in lupus nephritis exhibits a distinct pattern of markers of autoimmunity.

ABSTRACT:

BACKGROUND: Various causes of hypokalemia from renal potassium wasting, including distal renal tubular acidosis, have been described in lupus nephritis (LN). We report a phenomenon of otherwise unexplained hypokalemia among a population with LN.

METHODS: From our population of 403 patients with LN, we identified a cohort of 20 patients with idiopathic hypokalemia (HK), defined by serum potassium < 3.5 mmol/L without any apparent explanation. This cohort is compared to 90 LN controls (CON) and 10 LN patients with distal renal tubular acidosis (RTA) from the same population.

RESULTS: The HK cases had lower median serum potassium compared to CON and RTA subjects (3.26 vs 4.00 vs 3.75 mmol/L, respectively; p < 0.001). The median serum bicarbonate was normal in HK and CON but low in RTA (26.0 vs 25.0 vs 19.4 mmol/L; p < 0.001). The median urine pH was abnormally high only in the RTA group (6.00 vs 6.25 vs 6.67; p = 0.012). The median serum magnesium was modestly lower in HK compared to the CON and RTA groups (1.73 vs 2.00 vs 1.85 mg/dL; p = 0.002). While both HK and RTA showed a higher rate
of seropositivity than CON for anti-Ro/SSA (79% and 80% vs 37%, respectively; p < 0.001),
only HK revealed a higher rate of seropositivity than CON for anti-RNP (84% vs 42%; p =
0.003) and only RTA showed a higher rate of seropositivity than CON for anti-La/SSB (40% vs
12%; p = 0.046).

CONCLUSION: A syndrome of idiopathic hypokalemia was revealed in 20/403 (5%) of patients
within our LN population and proved to be distinct from the renal tubular acidosis that occurs in
LN. Furthermore, it was associated with a distinct pattern of autoantibodies. We speculate that
idiopathic hypokalemia is the result of a novel target of autoimmunity in LN affecting renal
tubular potassium transport.
INTRODUCTION:

As in the general population, sustained hypokalemia in systemic lupus erythematosus (SLE) and lupus nephritis (LN) may be due to either extra-renal potassium losses, such as occurs with diarrhea, or from renal losses. Renal potassium wasting may occur in SLE and LN because of exposure to diuretics and corticosteroids, medications commonly used in the management of LN. Hypokalemia as a result of distal renal tubular acidosis is also well described in SLE, with or without LN\textsuperscript{1,2}.

During the usual care of our large population of LN patients, we identified a subset of patients with recurrent hypokalemia that was not otherwise well explained by extrarenal losses, medications, or renal tubular acidosis. The primary objective of our study was to characterize the patients who exhibit this phenomenon. We also aimed to distinguish this clinical phenotype of LN patients with idiopathic hypokalemia by comparing them with two other groups of patients: patients with LN and overt distal renal tubular acidosis as well as a control group of LN patients without renal tubular acidosis.

METHODOLOGY:

This is a retrospective, observational study conducted at Parkland Health and Hospital System in Dallas, Texas. The protocol for the study was approved by the institutional review board of the University of Texas Southwestern Medical Center.

Study Population
Electronic health records at Parkland Health and Hospital System were used to identify adult patients diagnosed with LN who were followed in the Parkland Glomerulonephritis Clinic from May 2010 to March 2020. LN was diagnosed from renal biopsy specimens and was classified according to the 2018 International Society of Nephrology/Renal Pathology Society classification criteria\(^3\). Chronic Kidney Disease and Acute Kidney Injury were defined according to the Kidney Disease Improving Global Outcomes (KDIGO) definitions\(^4,5\).

We identified idiopathic hypokalemia cases (HK) as patients with LN who had unexplained and recurrent hypokalemia, defined as a serum potassium < 3.5 mmol/L in greater than 40% of the lab analyses in the 12 months prior to the initiation of potassium supplements or potassium-sparing diuretics, but without evidence of renal tubular acidosis. Renal tubular acidosis cases (RTA) were identified as patients with LN, serum bicarbonate < 22 mmol/L, and urine pH ≥ 6.0. Controls (CON) without evidence of renal tubular acidosis as defined were randomly selected from the total population at a ratio of 3 controls for every HK or RTA case. Patients with known or suspected alternate causes of hypokalemia, including active diuretic therapy, primary hyperaldosteronism, and chronic diarrhea were excluded from all groups.

**Study Outcomes**

The primary outcomes of interest were the median serum potassium, serum bicarbonate, and urine pH across the HK, RTA, and CON study groups. Secondary outcomes included the median serum magnesium and the rate of seropositivity for anti-Ro/SSA, anti-La/SSB, and anti-RNP.

Data was extracted from the medical record capturing the last 3 months of usual ambulatory care for each subject during the period from May 2010 to March 2020. For data with
multiple values over that interval, including serum and urine chemistries, blood pressure, and daily prednisone and hydroxychloroquine doses, the 3-month average for that measure was utilized for each subject. Data was censored after reaching any of the following events that could affect potassium or bicarbonate homeostasis: estimated glomerular filtration rate < 60 mL/min/1.73 m² or exposure to potassium supplements, diuretics (including potassium sparing diuretics), alkali therapy, or calcineurin inhibitors. However, data was not censored during angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) therapy since hypokalemia was noted to occur in the HK group despite use of these medications which would be expected to bias the results to a negative outcome (i.e., no difference between HK and CON). Data during hospitalizations, pregnancy, and periods of KDIGO Stage I or greater Acute Kidney Injury were also censored. Most recent serologic test results and renal histology was utilized for each subject regardless of how far in the past these were obtained, given the infrequency of these tests.

**Statistical Analysis**

Descriptive analyses were used to summarize baseline characteristics of the subjects by study group. Continuous variables are presented as median (interquartile range) or mean with standard deviation (SD) as appropriate and categorical variables are given as proportions. Continuous variables were compared across the 3 groups using ANOVA or Kruskal-Wallis testing as appropriate, and categorical variables were compared using Pearson’s chi-squared or Fisher’s exact testing. For paired comparisons of continuous variables between groups, the student’s t-test was employed. Statistical analysis was done using R statistical software version 3.6.1 (R Project for Statistical Computing).
RESULTS

Characteristics of Study Participants

Baseline characteristics of the patients are summarized in Table 1. From the total population of 403 patients, we identified 20 HK cases and 10 RTA comparators corresponding to a prevalence of 5% and 2.5%, respectively. The distribution of race differed between the three groups with HK patients more likely to be African American compared to CON (50% vs 20%, \( p = 0.013 \)).

Overall, immunosuppression regimens were similar between the groups. There were however differences noted in the 3-month average daily corticosteroid dose. Compared to HK, the CON group had higher rates of high-dose (\( \geq 40 \) mg/d) steroid exposure (5% vs 16%, respectively; \( p = 0.02 \)). Hydroxychloroquine exposure did not differ between the groups, nor did ACEi and ARB use.

Primary Outcomes

The HK group had a lower median serum potassium compared to CON and RTA subjects (3.26 vs 4.00 vs 3.75 mmol/L, respectively; \( p < 0.001 \)) (Figure 1). The RTA group had a lower median serum bicarbonate compared to HK and CON (19.4 mmol/L vs 26.0 mmol/L vs 25.0 mmol/L, respectively; \( p < 0.001 \)) and a higher median urine pH (6.67 vs 6.25 vs 6.00 \( p = 0.012 \)) (Figure 1). There were no statistically significant between-group differences between HK and CON in serum bicarbonate or urine pH.

Secondary Outcomes

Serum Magnesium Among the Groups
The median serum magnesium level was lower in HK compared to CON and RTA (1.73 vs 2.00 vs 1.85 mg/dL, respectively; p = 0.002), however, the median values for all 3 cohorts were in the normal range (1.7-2.2 mg/dL) (Figure 2). Given the known inhibition of intestinal magnesium absorption by proton pump inhibitors (PPI), rates of active therapy were compared across the groups but did not differ (Table 1). Similarly, PPI exposure did not influence the median serum magnesium within the HK group (1.75 vs 1.75 mg/dL with and without PPI, respectively; p = 1.00).

**Association Between Autoantibodies and Idiopathic Hypokalemia**

There were remarkable differences in the presence of specific autoantibodies among the groups (Figure 3). Only the HK group had a statistically greater proportion of seropositivity for anti-RNP than CON (84% vs 42%, respectively; p = 0.003). Both HK and RTA had greater rates of seropositivity than CON for anti-Ro/SSA (79% vs 80% vs 37%, respectively; p < 0.001) but only RTA had a higher rate of seropositivity than CON for anti-La/SSB (40% vs 12%, respectively; p = 0.046).

**Studies of Renal Potassium Handling in HK**

Among the 20 cases of idiopathic HK, 9 patients had assessments of renal potassium handling during concurrent hypokalemia (Table 2). All demonstrated renal potassium wasting as revealed by urine potassium to creatinine ratio > 15 mmol/g, transtubular potassium gradient > 3, or 24-hour urine potassium > 20 mmol/d. Six patients underwent testing for primary hyperaldosteronism, all with negative studies. All 20 patients ultimately required either potassium supplementation or mineralocorticoid antagonist therapy to maintain normokalaemia (data not shown) despite an 85% rate of ACEi or ARB use.
Other Notable Between-Group Differences

The median serum phosphate was lower in HK and RTA compared to CON (3.25 vs 3.15 vs 3.40 mg/dL, respectively; p = 0.011). The median 25-hydroxyvitamin D level was lower in HK compared to RTA and control (17.4 vs 30.5 vs 23.8 ng/mL; p = 0.02). There was however no significant difference in the median serum parathyroid hormone level (Table 1). We analyzed the groups regarding the occurrence of some expected comorbidities including autoimmune overlap syndromes and kidney stones. Nephrolithiasis or nephrocalcinosis occurred in none of the HK cohort and in 1% of the controls but was documented in 40% of the RTA cohort (p < 0.001). Overlap syndromes, defined as SLE with concomitant Sjögren’s syndrome, mixed connective tissue disease, rheumatoid arthritis, interstitial lung disease, or dermatomyositis, occurred in a larger proportion of RTA subjects, but this did not reach statistical significance.

DISCUSSION

This is the largest study in the literature to identify and describe a unique subset of adults with LN with idiopathic hypokalemia. The present analysis not only introduces the novel finding of idiopathic hypokalemia in LN, but it also begins to explore its mechanisms. These patients manifested clinically relevant hypokalemia, sometimes even falling below 3 mmol/L, and universally eventually required either maintenance potassium supplementation or a potassium sparing diuretic. This was even though 85% of them were on ACEi or ARB therapy, which tends to raise the serum potassium. The fact that potassium sparing diuretics could ameliorate the hypokalemia was indicative that renal potassium loss was the cause of this phenomenon. Indeed,
inappropriate potassium wasting was revealed in all 9 HK subjects who had assessments of renal potassium handling (Table 2).

As a first step of phenotyping this phenomenon of idiopathic hypokalemia, we set out to distinguish it from the hypokalemia that can occur in association with distal renal tubular acidosis. Distal renal tubular acidosis as a cause of hypokalemia is well described in association with autoimmune conditions including SLE\textsuperscript{6}. Rigorous evaluation by provocative testing may not uncommonly reveal renal acidification defects\textsuperscript{1,7-9}. However, clinically overt renal tubular acidosis in SLE and LN is rare. For instance, in a retrospective review of a large health system in Taiwan spanning more than 2 decades, Li et al. identified only 6 cases of overt renal tubular acidosis in patients with SLE, 5 of whom had LN\textsuperscript{10}. A recent cross-sectional study involving 108 patients with SLE in 2 hospitals in Turkey reported a significantly larger prevalence of overt renal tubular acidosis (16.7%). A little over half of the patients in this study had biopsy proven LN\textsuperscript{11}. Differences in ethnicity and study methodology may explain the variation in the occurrence of overt RTA in our study and those cited. With 10 patients (representing a prevalence of 2.5%), our study is one of the largest LN cohorts with clinically overt renal tubular acidosis that has been described. We defined RTA cases as patients with low serum bicarbonate and inappropriately high urine pH. Interestingly, we found that while some RTA patients did exhibit hypokalemia, as a group their median serum potassium was not statistically different from controls. As expected, the occurrence of kidney stones or nephrocalcinosis, a key feature of distal renal tubular acidosis, was higher in the RTA group. In contrast, the HK group exhibited a lower median serum potassium and a serum bicarbonate and urine pH that was indistinguishable from controls with no nephrocalcinosis or nephrolithiasis.
We next evaluated for differences in demographics, clinical status, and drug exposures between HK, RTA, and CON as further means to infer disease mechanisms. An obvious possible explanation for hypokalemia was from the mineralocorticoid effects of prednisone\textsuperscript{12}. This was ruled out by the fact that compared to HK, controls were on a higher 3-month average daily prednisone dose. Further, there were no meaningful differences in current immunosuppressive or hydroxychloroquine therapy.

The finding of idiopathic hypokalemia more commonly in African Americans is remarkable because of the known influence of race on LN. African American race is considered a risk factor for more severe LN, poor response to therapy, and mortality\textsuperscript{13}. Additionally, some studies suggest distinctive patterns of distribution in autoantibodies by race. In a study in Oklahoma, McCarty et al. found the occurrence of anti-Ro/SSA, anti-RNP, and anti-Smith to predict severe and progressive LN in African Americans\textsuperscript{14}. A contemporaneous study based on a cohort in Louisiana however countered this finding\textsuperscript{15}. More recent studies from the United States and the United Kingdom have also found higher occurrences of anti-Ro/SSA, anti-RNP, and anti-Smith in African Americans with severe LN and Afro-Caribbean people with SLE\textsuperscript{13,16}. Whilst we do not report the racial distribution of these autoantibodies in our study, it is certainly remarkable that the higher rates of occurrence of anti-Ro/SSA and anti-RNP as well as African American race associate with HK in our population of LN.

Autoantibodies may have a pathogenic role in the renal manifestations of autoimmune disease. For instance, anti-dsDNA plays a role in the pathogenesis of LN and is associated with increased disease activity\textsuperscript{17}. Alternatively, autoantibodies may simply serve as disease markers. In Sjögren’s syndrome for example, some authors have reported an association between urine acidification defects and the presence of anti-La/SSB, even though the pathogenic mechanism
typically involves other autoantibodies directed to H-ATPase, anion-exchange protein, or carbonic anhydrase. The association of renal tubular acidosis in Sjögren’s syndrome with anti-La/SSB however is not a consistent finding. Ours is the first study to suggest an association between clinically overt renal tubular acidosis and the occurrence of anti-Ro/SSA and anti-La/SSB antibodies in LN. Furthermore, while the prevalence of anti-Ro/SSA, anti-La/SSB, and anti-RNP in our LN cohort is comparable to what is reported in the literature, the association of idiopathic hypokalemia in LN with the presence of autoantibodies to Ro/SSA and RNP is a novel finding. Though there is clearly a trend that anti-RNP positivity was able to discriminate between the hypokalemia and the renal tubular acidosis that we describe in LN, this did not reach statistical significance. No prior reports have suggested an association between anti-Ro/SSA, anti-La/SSB, and anti-RNP with tubular transport defects in LN.

Although the HK cohort did not exhibit overt hypomagnesemia, the serum magnesium was significantly lower compared to the other 2 groups. The possibility of an intestinal malabsorption related to PPI therapy as an explanation for this finding is argued against given the similar 3-month average serum magnesium with and without PPI exposure in the HK group. Chronic diarrhea as an alternate cause was excluded by history. Hypomagnesemia is a known cause of hypokalemia through magnesium’s role in modulating renal outer medullary K\(^+\) (ROMK) channel conductance. The relatively lower serum magnesium in HK was not to the extent that one would expect it to cause hypokalemia. However, we recognize that serum magnesium may not always reflect total body magnesium content.

Combining the finding of a slightly lower serum magnesium in HK patients together with the novel patterns of autoantibodies in this group perhaps provides further insight into mechanisms. We hypothesize that an acquired immune-mediated impairment in distal
convoluted tubule transport explains this phenotype, albeit the defect must be incomplete. Others have described an acquired Gitelman’s syndrome-like phenotype in the setting of autoimmunity. Most of these reports have been in patients with Sjögren’s syndrome, though associations with systemic sclerosis and SLE have also been reported. To rigorously prove the hypothesis that this is an acquired form of Gitelman’s syndrome, we would need to detect an autoantibody to sodium-chloride cotransporter (NCC) and show that there was a deficiency of this transporter in the distal convoluted tubule in the absence of SLC12A3 mutations.

Limitations of the study arise from its retrospective design. Therefore, we could not perform rigorous studies of renal potassium and magnesium handling or provocative testing to conclusively rule out the presence of renal tubular acidosis in the patients with idiopathic hypokalemia. Further studies including formal assessments of renal electrolyte handling, genotyping, and immunohistochemistry for renal tubular transport proteins are needed to definitively describe this phenomenon. Another limitation of the analysis is the stringent criteria that was used to define the HK and RTA groups. This may have led to underestimation of the occurrence of idiopathic hypokalemia and renal tubular acidosis. However, this study also has several unique strengths. The large size of our population of patients with LN has afforded us the opportunity to describe this somewhat uncommon phenomenon of idiopathic hypokalemia and find meaningful differences from the larger group. Our data is also the largest report from North America on overt renal tubular acidosis in lupus nephritis to date. Finally, we are also the first to report on the association of autoantibodies with distinct tubular transport defects in LN.

Conclusion:
From our large population of patients with LN, we have reported on a novel finding of idiopathic hypokalemia and explored its clinical features and autoantibody associations. Idiopathic hypokalemia is a clinically relevant phenomenon in LN. Though we offer a preliminary hypothesis for the pathophysiology of this entity, further research is required to define its mechanisms.

**Disclosures:** The authors have nothing to disclose.

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**Author Contributions:** Emmanuel Adomako: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft; Writing - review and editing

Saira Bilal: Conceptualization; Data curation; Investigation

Yu-lun Liu: Formal analysis; Investigation; Methodology; Software

Ayesha Malik: Data curation; Investigation

Peter Van Buren: Formal analysis; Investigation; Writing - review and editing

Shani Shastri: Formal analysis; Investigation; Writing - review and editing

Kamalanathan Sambandam: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Writing - original draft; Writing – review and editing
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# TABLES AND FIGURES

Table 1. Demographic, clinical and laboratory parameters.

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<td>124.50 [117.75–132.25]</td>
<td>121.00 [115.00–135.00]</td>
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<td>4 (40)</td>
<td>46 (51)</td>
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<td>CYC n (%)</td>
<td>MMF n (%)</td>
<td>Other immunosuppressive, n (%)</td>
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</tr>
<tr>
<td></td>
<td>3 (15)</td>
<td>2 (10)</td>
<td>8 (40)</td>
<td>1 (5)</td>
<td>6 (30)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 (20)</td>
<td>0 (0)</td>
<td>4 (40)</td>
<td>0 (0)</td>
<td>4 (40)</td>
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</tr>
<tr>
<td></td>
<td>3 (3)</td>
<td>9 (10)</td>
<td>51 (51)</td>
<td>5 (5.6)</td>
<td>22 (24.4)</td>
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</tr>
<tr>
<td>Current PPI therapy, n (%)</td>
<td>9 (45)</td>
<td>4 (40)</td>
<td>33 (37)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>0.809</td>
</tr>
<tr>
<td>Current ACEi/ARB therapy, n (%)</td>
<td>17 (85)</td>
<td>6 (60)</td>
<td>56 (90)</td>
<td>3 (30)</td>
<td>4 (40)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>History of kidney stone disease, n (%)</td>
<td>0 (0)</td>
<td>4 (40)</td>
<td>1 (1)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>0.077</td>
</tr>
<tr>
<td>History of overlap syndrome *, n (%)</td>
<td>1 (5)</td>
<td>3 (30)</td>
<td>7 (8)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (mg/dL), median (IQR)</td>
<td>0.74 [0.62 – 0.85]</td>
<td>0.91 [0.78 – 1.03]</td>
<td>0.73 [0.62 – 0.88]</td>
<td>0.74 [0.62 – 0.85]</td>
<td>0.91 [0.78 – 1.03]</td>
<td>0.73 [0.62 – 0.88]</td>
</tr>
<tr>
<td>Serum PTH (pg/mL), median (IQR)</td>
<td>41.0 [24.0 – 55.8]</td>
<td>31.0 [20.1 – 39.7]</td>
<td>38.5 [27.1 – 56.9]</td>
<td>41.0 [24.0 – 55.8]</td>
<td>31.0 [20.1 – 39.7]</td>
<td>38.5 [27.1 – 56.9]</td>
</tr>
</tbody>
</table>

The categorical outcome measures were compared between the three groups using chi-squared test or Fisher’s exact test, while the one-way ANOVA or Kruskal-Wallis test was used to compare continuous outcome measures.

*Overlap syndrome includes any of the following: rheumatoid arthritis, mixed connective tissue disease, Sjogren’s syndrome, interstitial lung disease, dermatomyositis.

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CON, control group; CYC, cyclophosphamide; DBP, diastolic blood pressure; HCQ, hydroxychloroquine; HK, group with idiopathic hypokalemia; IQR, interquartile range; LN, lupus nephritis; MMF, mycophenolate mofetil; PPI, proton pump inhibitor; PTH, parathyroid hormone; RTA, group with renal tubular acidosis; SBP, systolic blood pressure.
Table 2. Assessment of hyperaldosteronism and renal potassium wasting in cases with idiopathic hypokalemia.

<table>
<thead>
<tr>
<th>LN Case</th>
<th>Plasma Aldosterone Concentration (ng/mL)</th>
<th>Plasma Renin Activity (ng/mL/hr)</th>
<th>Urine Potassium-Creatinine ratio (mmol/g) *</th>
<th>Transtubular Potassium Gradient*</th>
<th>24 hr Urine Potassium (mmol/d) *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>&lt; 1.6</td>
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<td>Case 2</td>
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<td>27</td>
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<td>Case 4</td>
<td>7.9</td>
<td>1.1</td>
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<tr>
<td>Case 5</td>
<td>&lt; 1.6</td>
<td>16</td>
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<tr>
<td>Case 6</td>
<td>&lt; 1.6</td>
<td>22</td>
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<tr>
<td>Case 7</td>
<td>&lt; 1.6</td>
<td>&lt; 0.6</td>
<td>23</td>
<td>9</td>
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<tr>
<td>Case 9</td>
<td>3.7</td>
<td>2.3</td>
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<td>Case 11</td>
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<td>13</td>
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<td>Case 13</td>
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<tr>
<td>Case 15</td>
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<tr>
<td>Case 16</td>
<td></td>
<td>18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 17</td>
<td>&lt; 1.6</td>
<td>7.1</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Case 19</td>
<td></td>
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<td>57</td>
</tr>
</tbody>
</table>

* All urine studies were obtained simultaneously with serum potassium ≤ 3.5 mmol/L.
Figure 1. Box-plots of serum potassium, serum bicarbonate, and urine pH among the three patient groups. The boxes span the 25th and 75th percentile of data points. The thick bar within the box indicates the median. The whiskers represent 1.5 times interquartile range, and the circles describe outliers. CON, control group; HCO3, serum bicarbonate; HK, group with idiopathic hypokalemia; K, serum potassium; RTA, group with renal tubular acidosis; UpH, urine pH.

Figure 2. Box-plot of serum magnesium amongst the three patient groups. The boxes span the 25th and 75th percentile of data points. The thick bars within the box indicate the median. The whiskers represent 1.5 times interquartile range, and the circles specify outliers. CON, control group; HK, group with idiopathic hypokalemia; Mg, Magnesium; RTA, group with renal tubular acidosis.

Figure 3. Frequency of autoantibodies among the study cohort
Figure 1
Figure 3

Frequency of anti-Ro/SSA
p < 0.001

***  **

Frequency of anti-La/SSB
p = 0.046

**  ***

Frequency of anti-RNP
p < 0.003