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Calcineurin inhibitor-related hyperkalemia is caused by hyporeninemic hypoaldosteronism and fludrocortisone is an effective treatment: Report of a case series and review of the literature

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Abstract

Introduction: Calcineurin inhibitors (CNIs) are widely used in transplantation. Although CNI-related hyperkalemia is common (10%–60.6%), the underlying pathogenetic mechanism is not well-elucidated and may lead to dose adjustment or treatment withdrawal.

Objective: The aim of this study is to describe CNI-related hyperkalemia due to hyporeninemic hypoaldosteronism in pediatric transplant recipients who were successfully treated with fludrocortisone.

Method: In a total of 55 hematopoietic stem cell (HSCT) and 35 kidney transplant recipients followed according to institutional immunosuppression protocols, recipients diagnosed with CNI-related hyperkalemia were reviewed. Recipients who were receiving intravenous fluid, potassium, or were diagnosed with hemolysis, acute graft rejection, or had an eGFR < 30 mL/min/1.73m^2, were excluded. A detailed analysis of clinical history as well as biochemical studies was carried out to reveal possible pathophysiology.

Results: Three pediatric transplant recipients (one HSCT, two kidney transplantation) with findings of hyperkalemia, hyponatremia, and a mild elevation in blood urea nitrogen while on CNIs were recruited. Urinary potassium excretion was diminished while sodium excretion was increased. Plasma aldosterone levels were low, and renin was not increased in response. Primary adrenal insufficiency was ruled out, and hyporeninemic hypoaldosteronism was diagnosed. CNI-related hyperkalemia was detected earlier in case 1, who had HSCT (22 days), than in the second and third cases, who had kidney transplantation (24 and 30 months post-transplantation, respectively). The discrepancy was hypothesized to be explained by higher overall CNI dose due to higher serum target CNI used in HSCT than kidney transplantation.

Electrolyte imbalance was reversed upon administration of physiologic dose fludrocortisone (0.05 mg, daily), while fludrocortisone was ceased after CNI withdrawal in case 1,

Abbreviations: BUN, blood urea nitrogen; CNI, Calcineurin inhibitor; CsA, cyclosporine; HSCT, hematopoetic stem cell transplantation; MR, Minerallocorticoid receptor; SDS, standard deviation score; MMF, mycofenolat mofetil.

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which is additional evidence for the etiological association of CNIs and hyporeninemic hypoaldosteronism.

Conclusion: Our three cases strengthen the premise that CNI-related hyperkalemia may be due to hyporeninemic hypoaldosteronism, and the timing and severity may be related to CNI dose. Fludrocortisone is a safe and effective treatment in CNI-related hyperkalemia, providing maintenance of CNIs, which are one of the essential therapeutic agents for pediatric transplantation.

KEYWORDS
aldosterone, calcineurin inhibitor, cyclosporine, hyperkalemia, hyporeninemic hypoaldosteronism, pediatric, renin, tacrolimus, transplantation

1 | INTRODUCTION

Calcineurin is essential for calcium-dependent signal transduction in a wide range of cellular processes, including T cell activation, proliferation, and differentiation.[1–8] Therefore, calcineurin is one of the main targets for post-transplantation immunosuppression. Calcineurin inhibitors (CNIs) (e.g., cyclosporine [CsA] and tacrolimus) are the mainstay of immunosuppression in hematopoietic stem cell (HSCT) and solid organ transplantation.[2,9] CsA and tacrolimus exert their calcineurin-inhibiting effect by binding their respective intracellular receptors called immunophilins, including cyclophilin and FK-binding protein 12 with high affinity.[10] The CNI-receptor complex then inhibits calcineurin activity, preventing nuclear translocation of the nuclear factor of activated T cells and transcription of interleukin-2 and other cytokines.[2]

Hypertension, hyperkalemia, hypomagnesemia, hypercalciuria, and metabolic acidosis are frequent side effects of CNIs that restrict their utilization. CNI-related hyperkalemia is a common and critical side effect (10%–60.6%) that may occasionally lead to dose adjustment or treatment withdrawal.[2] The exact pathogenic mechanism of CNI-related hyperkalemia is not well-elucidated.[3] In patients with acute kidney injury, vasoconstriction of afferent glomerular arterioles is suggested to explain CNI-related hyperkalemia. However, there must be other pathogenic mechanisms in patients with stable kidney function.[3] Mechanisms proposed are distal renal tubular acidosis, inhibition of renin-angiotensin-aldosterone system,[11] mineralocorticoid receptor (MR) downregulation in peripheral leucocytes,[12] aldosterone resistance in MR on distal tubules or with the direct effect of CNIs on Na/K ATPase on cortical collecting tubule cells, and indirect opening of ATP-sensitive K channels.[4–7] One mechanism demonstrated in mouse models is that calcineurin directly dephosphorylates Kelch-like 3, and its inhibition by tacrolimus leads to an increase in WNK4 levels. This increase resulted in increased Na-Cl cotransporter in vivo, resulting in hyperkalemia and hypertension.[13]

Herein, we present three cases of hyperkalemia while on maintenance-dose CNIs following transplantation. Hyporeninemic hypoaldosteronism was detected, and electrolyte imbalance was corrected with physiologic dose fludrocortisone. As CNIs are central to immunosuppression in post-transplant patients, clarifying the etiology of hyperkalemia and specifying the treatment will provide long-term use of CNIs with composure.

2 | MATERIALS AND METHODS

This is the report of case series from a tertiary center of pediatric transplant recipients. A total of 55 HSCT recipients and 35 kidney transplant recipients followed between June 2020 and August 2023 were retrospectively evaluated using institutional electronic patient records. Of those, pediatric transplant recipients receiving maintenance-dose CNI with a serum potassium higher than 5.5 mmol/L were evaluated. Recipients who received intravenous fluid or potassium, additional nephrotoxic drugs, were diagnosed with hemolysis, acute graft rejection, or an eGFR<30 mL/min/1.73m^2 were excluded. In pediatric transplant recipients with hyperkalemia, a repeated blood sample was collected from arterial site to minimize hemolysis. A complete blood count and peripheral blood smears drawn at the same incident were also evaluated. Recipients without signs of hemolysis were enrolled. Three transplant recipients (one HSCT, two kidney transplantations), who were diagnosed with CNI-related hyperkalemia due to hyporeninemic hypoaldosteronism and were started fludrocortisone, were enrolled.

In our institution, the preparative regimen for HSCT following acute myeloid leukemia consists of busulfan, melphalan, fludarabine, and anti-thymocyte globulin. As prophylaxis for graft versus host disease, CsA and low-dose methotrexate were administered with a target serum CsA of 150–200 μg/L during the peri-transplant period, then 100–150 μg/L until the tapering protocol. After discharge, follow-up was individualized according to the requirements of HSCT recipients.

Immunosuppressive regimen for kidney transplantation consists of mycophenolate mofetil (MMF), prednisolone, and either CsA or tacrolimus in our institution. Basiliximab is also given as an induction agent on the day of transplantation and the post-transplant 4th day. If CsA is selected, it is initiated 2–3 mg/kg/day, twice a day, with a long-term serum target CsA of 75–100 ng/mL. If tacrolimus is chosen, it is initiated with 0.1–0.2 mg/kg/day. Early after transplantation, serum target tacrolimus was 8–12, 4–6 ng/mL for recipients

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with high immunological risk, and 3–5 ng/mL for those with low immunological risk thereafter. During the first month of transplantation, kidney transplantation recipients received 1–2 mg/kg/day prednisolone. Reduction to maintenance steroid regimen (0.25 mg/kg/day prednisolone, every other day) was reached in the following 3 months. After discharge, follow-up was individualized according to requirements of kidney transplant recipients.

Data pertaining medical history, anthropometric measures, and laboratory results, including biochemical studies of blood gases, serum electrolytes, creatinine, blood urine nitrogen, uric acid levels, urine sodium, potassium as well as serum renin and aldosterone were extracted from institutional electronic patient records. Weight and height standard deviation scores (SDS) were determined according to the LMS (power transformation for normality, median, generalized coefficient of variation) method using gender- and age-specific 2000 CDC Growth Chart curves.[14] All of the recipients' diet consisted of average sodium content. eGFR was calculated using modified Schwartz formula.[15] Collection and processing of renin and aldosterone were performed on-site. Samples were collected in the morning while the patients were lying in a supine position and had a nonrestricted normal sodium intake. To optimize stability, renin samples were transported as whole blood to the on-site laboratory. To omit cryoactivation, pre-analytic handling was performed in room temperature if renin was to be analyzed right away. If not, centrifugation was performed, and plasma was frozen right away and was preserved frozen until testing. Both renin and aldosterone were measured via Multi Crystal LB 2111 Gamma Counter (Berthold Technologies, Germany). Renin was measured by immunoradiometric assay (DIASOURCE Renin IRMA kit, Belgium) with a lower limit of quantitation of 0.78 pg/mL while aldosterone was measured by radioimmune assay (DIASOURCE Aldosterone RIA kit, Belgium) with a lower limit of quantitation of 1.4 pg/mL. CsA and tacrolimus levels were measured by liquid chromatography–mass spectrometry in our institutional laboratory.

3 | CASE 1

A 15-month-old boy was diagnosed with acute myeloid leukemia while being investigated for anemia and leukopenia. BFM-2013 protocol was started. Following remission, allogeneic HSCT was performed from 9/10 HLA-matched grandfather at 24 months of age. Predefined institutional protocol consisting of CsA (3 mg/kg/day twice a day) was implemented.

Twenty-two days after HSCT (weight: 14 kg [1.2 SDS], height: 83 cm [−1.6 SDS]), hyponatremia (133 mmol/L), and hyperkalemia (5.9 mmol/L) were detected. He was normotensive (90/50 mmHg [0.3/0.8 SDS]), not receiving antihypertensives or diuretics, urine output was normal. Blood urea nitrogen (BUN) was slightly elevated (23.2 mg/dL). Bicarbonate was 19.5 mmol/L, serum electrolytes and creatinine were within normal limits, and eGFR was 84 mL/min/1.73m^2. The urine potassium level was low (6.3 mmol/L), while the urine sodium level was high (50.6 mmol/L), and potassium creatin ratio was 0.3. Renin (1.3 pg/mL, normal range: 1.3–13.8) and aldosterone (71 pg/mL, normal range: 35–300) were inappropriately low (Table 1). Mean CsA concentration in serum was 112 ± 33 ng/mL with single peak value of 234 ng/mL. Hyperkalemia was attributed to CsA-related hyporeninemic hypoaldosteronism. Fludrocortisone (0.05 mg/day, po) was initiated on the 26th day after HSCT and the potassium level decreased to the normal range (4.3 mmol/L) in 2 days. The patient remained normotensive. Fludrocortisone was continued along with CsA. Following cessation of CsA, fludrocortisone was tapered and ceased without electrolyte imbalance.

4 | CASE 2

A 3-year-old girl has been receiving peritoneal dialysis since the neonatal period for chronic kidney disease due to agenesis of the left kidney and cystic right kidney. A heterozygous *HNF1β* mutation was identified, and she underwent cadaveric donor kidney transplantation (2/3 mismatch). Predefined institutional immunosuppressive protocol for kidney transplantation recipients, which consisted of steroid, MMF (715 mg/m^2/day, twice a day), and CsA (3 mg/kg/day, twice a day), was followed.

Three months post-transplantation, CsA was switched to tacrolimus (0.1 mg/kg/day) because of hypertrichosis. Two years post-transplantation, during routine follow-up (weight: 17 kg (−1.3 SDS), height: 107 cm (−1.6 SDS)) while on tacrolimus (0.12 mg/kg/day), severe hyponatremia (128 mmol/L) and hyperkalemia (7.37 mmol/L) were detected. She was normotensive (95/55 mmHg, [0.1/0.1 SDS]) while using 0.3 mg/kg/day enalapril and urine output was normal. She was not receiving diuretics. Bicarbonate was 18.6 mmol/L, serum electrolytes and creatinine were within normal limits, and eGFR was 63.13 mL/min/1.73m^2. However, BUN was mildly elevated (30 mg/dL). Urine sodium was 52.8 mmol/L while potassium was 13.9 mmol/L. Serum renin (1.2 pg/mL, normal range: 1.3–13.8) and aldosterone (47 pg/mL, normal range: 35–300) were inappropriately low (Table 1). Mean tacrolimus concentration in serum was 4.4 ± 1.4 ng/mL (3–5). CNI-related hyporeninemic hypoaldosteronism was diagnosed; fludrocortisone (0.05 mg/day po) was initiated; and serum potassium, sodium, and creatinine were normalized within 3 days (Table 1). Tacrolimus has been administered along with fludrocortisone for 3 years without electrolyte imbalance, effect on blood pressure, or any need for dose adjustment.

5 | CASE 3

A 4-year-old boy was diagnosed with autosomal recessive polycystic kidney disease prenatally. Peritoneal dialysis, which was started at 6 months of age, was complicated by volvulus. Emergency bowel resection starting from Treitz ligament to hepatic flexura encompassing 60 cm of necrotic bowel tissue was performed at 6 months. This wide resection led short bowel syndrome and chronic diarrhea. Then, he was switched to hemodialysis, and at 19 months of age, he

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TABLE 1 Laboratory examination on admission and following fludrocortisone.

	Case 1		Case 2		Case 3		
	On admission	2 days[a]	On admission	3 days[a]	On admission	3 days[a]	Range
Serum							
Na (mmol/L)	133	137	128	139	139	134	136–146
K (mmol/L)	5.9	4.3	7.4	4.4	6.1	5.1	3.5–5.5
Ca (mg/dL)	10.2	10.5	9.6	10.4	9.1	9.9	8.8–10.8
P (mg/dL)	4.4	4.3	3.8	4.0	4.6	4.1	3.2–5.7
BUN (mg/dL)	23.2	9.9	30	17.8	4.8	13.0	5–18
Creatinine (mg/dL)	0.5	0.4	0.7	0.5	0.5	0.4	0.26–0.77
e-GFR	84	105	63.1	88.3	85.9	107.3	
pH	7.4	7.4	7.4	7.3	7.4	7.3	7.35–7.45
$cHCO_3$ (mmol/L)	19.5	20.6	18.6	22.2	22.3	20.0	22.5–26.9
Renin (pg/mL)	1.3	NA	1.2	NA	8.5	NA	1.3–13.8
Aldosterone (pg/mL)	71	NA	47	NA	9	NA	35–300
ACTH	28.7	NA	<1	12	14	NA	0–46
Cortisol (μg/dL)	28	NA	1.39	6.41	8.8	NA	6.7–22.6
Urine							
ph	6.5	5	7.5	7	NA	7	4.5–8.0
Density	1006	1025	1007	1005	NA	1007	1003–1030
Na (mmol/L)	50.6	NA	52.8	NA	148.4	NA	25–301
K (mmol/L)	6.3	NA	13.9	NA	5.6	NA	11–80
Creatinine (mg/dL)	20.2	NA	NA	NA	33.1	NA	

Abbreviation: NA, not available.

[a]Days after initiation of fludrocortisone.

underwent kidney transplantation from his HLA mismatched (3/6) mother. The recipient's panel reactive antibody and crossmatch were negative before transplantation. Predefined institutional immunosuppressive protocol for kidney transplantation recipients, which consisted of steroid, MMF (790 mg/m^2/day, twice a day), and tacrolimus (0.23 mg/kg/day), was followed.

After transplantation, parenteral nutrition was required for intractable diarrhea due to short bowel syndrome. Persistent metabolic acidosis necessitated high-dose intravenous sodium bicarbonate (6 mEq/kg/day). Thirty months after transplantation (weight: 15 kg [−2.8 SDS], height: 104 cm [−2.3 SDS]), while he was normotensive (98/60 mmHg, 0.6/1.1 SDS) with a normal urine output, hyperkalemia was detected. He was not receiving antihypertensives or diuretics. Sodium polystyrene sulfonate was started; a substantial dose (1 g/kg/dose) was required to control hyperkalemia (Table 1). Bicarbonate was 22.3 mmol/L while using sodium bicarbonate, and serum electrolytes and creatinine were otherwise normal, eGFR was 85.9 mL/min/1.73m^2. Urine sodium level was 148.4 mmol/L, while potassium was 5.6 mmol/L, potassium creatine ratio was 0.17. Renin (8.5 pg/mL, normal range: 1.3–13.8) and aldosterone (9 pg/mL, normal range: 35–300) were inappropriately low (Table 1). Mean tacrolimus concentration in serum was 5.7 ± 2.9 ng/mL (4–6) with single peak value of 29.7 ng/mL. CNI-related hyporeninemic hypoaldosteronism was diagnosed, and fludrocortisone (0.05 mg/twice a day, po) was initiated. Following fludrocortisone, the patient remained normotensive, no longer needed polystyrene sulfonate, and sodium bicarbonate was reduced to 1 mEq/kg/day.

6 | DISCUSSION

Hyperkalemia and hyponatremia while on CNIs were the predominant findings of our cases. Urinary potassium excretion was diminished in all patients. Blood levels of low sodium and high potassium, and urinary excretion of high sodium and low potassium suggested aldosterone insufficiency. Despite seemingly being within the reference values, renin and aldosterone were low relative to the hyperkalemic, hyponatremic state. As the serum values of hormones should be interpreted according to the serum electrolyte state rather than laboratory reference values, it was concluded that the response of renin and aldosterone is inappropriately low for the homeostatic state of the patients. Primary adrenal insufficiency was ruled out with low/normal ACTH levels. Absence of transcellular potassium shift, increased potassium supply, or hemolysis are common causes of hyperkalemia in hospitalized patients.[16] With the exclusion of other causes of hyporeninemic hypoaldosteronism (diabetes, ACE inhibitor use, potassium sparing diuretic use, nonsteroid anti-inflammatory use), it was concluded that hyperkalemia was a

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result of hyporeninemic hypoaldosteronism caused by tacrolimus or CsA. It was also confirmed when electrolyte imbalance was reversed upon administration of physiologic dose fludrocortisone. Fludrocortisone was ceased after CNI withdrawal, which is additional evidence for the etiological association of CNIs and hyporeninemic hypoaldosteronism.

Drug-related hyperkalemia is one of the most important causes of increased serum potassium in everyday clinical practice, being the primary cause or contributing factor in 35%–75% of hospitalized patients.[16] In pediatric studies, hyperkalemia and hyponatremia in renal transplant recipients using CNI were reported to be as high as 10%–60.6%.[2,17] In this study, CNI-related hyperkalemia was detected relatively early in case 1, who had HSCT (22 days), than in the second and third cases, who had kidney transplantation (24 and 30 months post-transplantation, respectively). Alabdulqader et al. reported 39 pediatric renal transplant recipients with CNI-related hyperkalemia where median time from renal transplantation to detection of hyperkalemia was 8 weeks.[17] A trend of earlier CNI-related hyperkalemia in patients with HSCT was previously presented. In Çalışkan et al.'s study, which presented four adults with CNI-related hyperkalemia following allogeneic peripheral blood stem-cell transplantation, the time spent from peripheral blood cell transplantation to hyperkalemia was 10–29 days. In that study, the initial CsA dose was high (12.5 mg/kg/day). According to protocols of our institution, despite initial CNI dose being the same in HSCT and kidney transplantation, target serum CNI levels are much lower in kidney transplantation than in HSCT. Earlier CNI-related hyperkalemia in case 1 may be explained by higher overall CNI dose due to higher serum target CNI used in HSCT than renal transplantation. The mineralocorticoid effect of high-dose prednisolone (120–240 mg/m^2/day HC equivalent) used in the first months of renal transplantation may be another contributing factor to delay CNI-related hyperkalemia in renal transplant recipients. Previously, it was suggested that the severity of hyperkalemia is not associated with CNI dose. However, more recent papers, like ours, denote a higher likelihood of hyperkalemia with higher doses of CNI.[17] As observed in our cases, multiple studies reported a similar trend toward more severe hyponatremia and hyperkalemia in tacrolimus-treated patients than in CsA.[3,6,18]

CNI is fundamental for graft survival and graft versus host disease management in pediatric transplantation. Despite being frequent and life-threatening, the underlying mechanism of CNI-related hyperkalemia is yet to be delineated.[17,18] Therefore, enlightening the pathogenesis of CNI-related hyperkalemia and treating it accordingly is crucial. A recent study investigated the potential nephrotoxic effects of CNI in mice, focusing on its in-vivo and real-time effect on the renin system. The study revealed that after receiving CNI (2 mg/kg/day) for 3 weeks, serum creatinine was elevated, local renin activity was enhanced, and local vasoconstriction was activated in mice.[19] MR was shown to form cytosolic heterocomplexes with heat shock protein (Hsp) 90, Hsp70, and immunophilins (e.g., cyclophilin and FK-binding protein 12), which are also binding proteins for CsA and tacrolimus. MR interaction with Hsp90 is thought to maintain MR in a ligand-binding conformation. CsA and tacrolimus were also shown to bind Hsp90.[20] Despite being logical, there is no current evidence that this mechanism of CNI binding Hsp90 and altering MR and Hsp90 interaction explain CNI-related hyperkalemia.[21] Nevertheless, these suggested mechanisms of impaired renal function, aldosterone resistance, and MR downregulation do not fit in our cases of hyporeninemic hypoaldosteronism with favorable response to the physiologic dose fludrocortisone. Thus, CNI dose may be an essential factor determining the outcome: aldosterone resistance or responsiveness.

The studies linking CNI-related hyperkalemia and aldosterone action in transplant recipients are reviewed in Table 2. Çalışkan et al.[22] showed that hyperkalemia was associated with low trans-tubular potassium concentration gradient (TTKG) and plasma aldosterone levels (23.5 pg/mL [normal range: 35–410]) in posttransplant patients receiving CNI. Nevertheless, renin was not measured in their study. Kamel et al. reported 12 adult renal transplant recipients with CNI-related hyperkalemia whose renin (0.5 ng/L/s [0.69–0.83]) and aldosterone (295 pmol/L [111–860]) levels were low. However, potassium excretion was unexpectedly unresponsive to exogenous mineralocorticoids and low urinary potassium levels persisted. So, they concluded that the underlying pathogenesis was tubular insensitivity to aldosterone,[5] which may not be the anticipated deduction since aldosterone levels should be high in case of aldosterone insensitivity. Dick et al. studied the impact of fludrocortisone on tacrolimus-related hyperkalemia in nine adult liver transplant recipients. While mean potassium decreased from 5.7 mmol/L to 4.5 nmol/L, renal function tests and blood pressure remained unchanged.[23] In Alabdulqader et al.'s study, pediatric renal recipients portrayed a significant decrease in serum potassium following fludrocortisone with a dose of 0.1–0.15 mg/day. The authors interpreted CNI-related hyperkalemia to be related to MR resistance.[17] Another study on pediatric renal transplant recipients suggested that CNI-related hyperkalemia may be due to tubulopathy, and alleviation of hyperkalemia was achieved by an initial dose of 0.025–0.050 up to 0.075–0.150 mg/day fludrocortisone.[24] Unfortunately, renin and aldosterone were not measured in the latter three studies.[17,23,24] Despite these limitations of current literature regarding laboratory findings, it was deduced in some of these studies that the underlying pathophysiologic mechanism of CNI-related hyperkalemia is aldosterone resistance.

The pathogenesis of hyporeninemic hypoaldosteronism in CNI users may be related to calcium-dependent renin secretion. Calcium is an essential secondary messenger controlling virtually all modes of biological secretion, including renin secretion from renal juxtaglomerular cells. Decreased extracellular and intracellular (in juxtaglomerular cells) calcium was shown to stimulate renin secretion.[25] Calcineurin is a complex of phosphatases, which links calcium signaling to protein dephosphorylation.[1] Calcineurin and calmodulin (calcium-sensing protein) bind calcium. This complex then forms active phosphatase. One might hypothesize that using CNIs would uncouple this reaction and increase intracellular calcium, decreasing renin secretion and explaining hyperkalemia in CNIs using transplant recipients. However, further in vitro and in vivo studies are warranted.

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TABLE 2 An overview of studies reporting isolated CNI-related hyperkalemia following transplantation.

Study (Author (year))	Design	Population	CNI		Results		*p*	Treatment	Deductions of the study	Adverse effect linked to fludrocortisone
					Admission (mmol/L)	Last control (mmol/L)				
Alabdulqader et al. (2021)	Retrospective cohort	Renal transplant (aged ≤ 16 years), (*n* = 39)	Tacrolimus (*n* = 38), CsA (*n* = 1)	**K** **HCO_3** **Renin** **A**	5.17 22.31 NA NA	4.60 24.5 NA NA	<.001 <.01	Fludrocortisone (2–6 μg/kg/day) (6 months)	The diagnosis of hyperkalemic RTA was based entirely on serum HCO3 and serum potassium without measurements of aldosterone or renin. Fludrocortisone had no effect upon blood pressure	Transient hypokalemia (*n* = 4)
Ali et al. (2017)	Retrospective cohort	Renal transplant (aged ≤ 16 years), (*n* = 47)	Tacrolimus (*n* = 4), mycophenolate mofetil and tacrolimus (*n* = 5)	**K** **Renin** **A**	5.2 NA NA	4.5 NA NA	.04	Fludrocortisone (*n* = 9) (0.8–4 μg/day) (9 months) Oral sodium (*n* = 23) and bicarbonate supplementation	Fludrocortisone effectively reduces electrolyte supplementation and serum potassium without a change in renal function or blood pressure.	Side effect was not observed.
Calıskan et al. (2002)	Brief communication	Peripheral blood stem cell transplantation (mean age: 36 years) (*n* = 4)	CsA	**K** **Renin** **A** (pg/mL)	5.9 NA 23.5 (35–410)	4 NA NA	NA	CsA was withdrawn	Mean potassium decreased with CsA withdrawal, one patient received hemodialysis. Concluded that CsA-related hyperkalemia to be the cause of hyperkalemia	NA
Sivakumar et al. (2013)	Letter to the editor	Renal transplant (*n* = 1, age: 31 years)	Mycophenolate mofetil (2 g/day) and tacrolimus (5 mg/day)	**K** **Renin** **A**	5.8 NA NA	4.2 NA NA		Fludrocortisone (0.05–0.01 mg/day)		
Kamel et al. (1992)	Clinical research	Renal transplant (*n* = 12), control group (*n* = 10)	CsA (4 mg/kg), low dose steroid and azathioprine (*n* = 12)	**Renin** (ng/L/s) **A** (pmol/L)	0.5 (0.69–0.83) 295 (111–860)	NA NA			Renal response to hyperkalemia and exogenous mineralocorticoid response in patients using CsA were studied. Patients on CsA had a relatively low excretion rate of potassium during hyperkalemia. Tubular insensitivity to exogeneous fludrocortisone (200 μg) was observed.	NA
Heering et al (2004)	Retrospective cohort	Renal transplant (*n* = 21, age: 47), control group (*n* = 12, age: 37)	CsA (10 mg/kg), low dose steroid and mycophenolate mofetil	**K** **HCO3** **Renin** **A** (pg/mL)	4.8 18.5 NA 172	3.8 23.2 NA NA		Fludrocortisone 0.05 mg	Following fludrocortisone, aldosterone significantly decreased.	Side effect was not observed.

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TABLE 2 (Continued)

Study (Author (year))	Design	Population	CNI		Results		*p*	Treatment	Deductions of the study	Adverse effect linked to fludrocortisone
					Admission (mmol/L)	Last control (mmol/L)				
Dick et al. (2011)	Retrospective cohort	Liver transplant (mean age:53 years), ($n=9$)	Tacrolimus ($n=9$)	**K**	5.7	4.5	<.001	Fludrocortisone ($n=9$) (140 μg/day) (9 months) Oral sodium supplementation ($n=23$) Oral bicarbonate supplementation	No significant change in renal function or blood pressure were observed. Concluded that tacrolimus induced hyperkalemia in those with stable serum bicarbonate concentrations can be managed with fludrocortisone while maintaining stable tacrolimus concentration.	Side effect was not observed.
				Na	135	139	.02			
				Renin	NA	NA				
				A	NA	NA				

Note: Renin (ng/L/s), (pg/mL).

Abbreviations: A, Aldosterone; CNI, calcineurin inhibitor; TTKG, transtubular potassium gradient.

Previous studies have not pinpointed the number of patients who have withdrawn CNIs because of hyperkalemia. Nevertheless, in clinical practice, decreasing CNI dose, treatment withdrawal, or adding different medications to lower serum potassium levels are not uncommon and agents used for CNI-related hyperkalemia are not optimal. Intravenous sodium bicarbonate, dextrose, and insulin do not provide long-term solutions. Loop diuretics contribute to intravascular depletion, exacerbating renal dysfunction. Resin-binding agents were linked to colonic necrosis.[23] Based on our case series, we propose a stepwise approach to hyperkalemia while on CNIs; first, urinary potassium, an indicator of aldosterone activity, should be measured. If it is low, the second step is to measure renin and aldosterone. Once hyporeninemic hypoaldosteronism is established, fludrocortisone is a very effective treatment in CNI-related hyperkalemia in pediatric transplant patients with stable renal functions. This approach will not only impede withdrawal of CNIs but also maintain CNI dose for immunosuppression. Although the optimum dosing regimen for fludrocortisone in CNI-related hyperkalemia has not been determined, a starting dose of 0.05 mg is being suggested. Despite not being observed in our study, previous studies have warned against side effects like hypertension, edema, and gastric irritation following fludrocortisone use, which are mainly dose-related.[17]

There are limitations to this study. It is being acknowledged that the number of cases are limited and similar observations in patients with kidney transplantation would strengthen our premise. However, as this case series is from a single tertiary hospital, it is expected to be more than adequate to raise awareness on this topic and hamper the utility of fludrocortisone, underlining the scarcity and ambiguity of the current literature. Another limitation was that due to retrospective nature of this case series, some of the relevant and important laboratory data such as TTKG could not be collected. However, following our observation presented in this paper, TTKG was decided to be included in diagnostic work-up of patients suspected of CNI-related hyperkalemia.

This case series underlines that hyperkalemia and hyponatremia in CNI receiving HSCT and solid organ transplant recipients should alert the clinician for treatment-related side effects. Renin and aldosterone should be measured in patients with hyperkalemia while on CNI. Hyporeninemic hypoaldosteronism is suggested to be the underlying mechanism in CNI-related hyperkalemia. The timing and severity of CNI-related hyperkalemia may be related to CNI dose. Fludrocortisone, with a starting dose of 0.05 mg, is a safe and effective treatment in pediatric transplant recipients.

AUTHOR CONTRIBUTIONS

YU collected data, drafted the initial manuscript, reviewed, and revised the manuscript; DB collected data and drafted the initial manuscript; FO, AD, and RT reviewed and revised the manuscript; BG, ZAO, and ENG conceptualized the work, analyzed the data, revised, and critically reviewed the manuscript for important intellectual and medical content; and all authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

The study was conducted in accordance with the Declaration of Helsinki. Institutional Review Board of Hacettepe University was consulted. After a detailed evaluation, due to the retrospective nature of the study and procedures being performed, and data obtained are part of the routine care, a waiver of ethical approval was granted. Written informed consent was obtained from the parents of each patient.

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