



Contents lists available at ScienceDirect

AAACE Clinical Case Reports

journal homepage: www.aaaceclinicalcasereports.com



Case Report

Liddle Syndrome due to a Novel c.1713 Deletion in the Epithelial Sodium Channel β -Subunit in a Normotensive Adolescent

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ARTICLE INFO

Article history:

Available online 27 November 2020

Key words:

Liddle syndrome
hypokalemia
SCNN1B
hypertension

ABSTRACT

Objective: Liddle syndrome (LS) is a rare autosomal dominant condition secondary to a gain-of-function mutation affecting the epithelial sodium channels (ENaCs) in the distal nephron. It presents with early-onset hypertension, hypokalemia, and metabolic alkalosis in the face of hyporeninemia and hypoaldosteronism. We report a novel mutation affecting the ENaCs in a normotensive adolescent with LS. **Methods:** We describe a pediatric case of LS with a novel mutation and review the condition's presentation and management. To date, 31 different mutations in the β - or γ -subunit of ENaCs have been reported as associated with LS.

Results: We describe a 16-year-old girl presenting with muscle cramps with a strong family history of hypertension and hypokalemia. Initial investigations revealed hypokalemia together with hypoaldosteronism and hyporeninemia. Subsequent genetic testing revealed a novel mutation in *SCNN1B* (deletion: c.1713delC), leading to the premature termination of the sodium channel epithelial 1 subunit- β protein and the LS phenotype. Treatment with triamterene (50 mg, twice daily) and potassium chloride (20 mEq, once daily) normalized the serum potassium and led to resolution of her muscle cramps.

Conclusion: It is essential to consider investigating the presence of rare genetic syndromes, like LS, when a patient presents with hypokalemia. Further studies are needed to understand the variable presentation of this condition.

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Introduction

Liddle syndrome (LS) is a rare autosomal dominant disorder typically presenting during childhood that is characterized by aldosterone-independent hypertension, hypokalemia, and metabolic alkalosis. The underlying mechanism in LS is increased activity of the epithelial sodium channels (ENaCs) in the distal nephron.^{1,2} Resultant clinical signs and symptoms include headache, dizziness, vision changes (associated with hypertension), muscle weakness/cramping (secondary to hypokalemia), and risk

of early death due to heart failure, cerebrovascular events, and myocardial infarction, all of which are consequences of severe hypertension. Long-term complications of LS include hypertension-induced end-organ damage leading to retinopathy, nephrosclerosis, and left ventricular hypertrophy.^{3,4} Because it is inherited in an autosomal dominant manner, there is usually a strong family history of early hypertension and/or hypokalemia. Hypertension is present in 92.4% of patients with LS and hypokalemia in 71.8%.³

Diagnosing LS can be challenging because there are several conditions presenting with hypokalemia, hypertension, and low levels of renin. These include congenital adrenal hyperplasia secondary to 17α -hydroxylase or 11β -hydroxylase enzyme deficiency, syndrome of apparent mineralocorticoid excess (AME; presenting with early-onset severe hypertension and failure to thrive), primary hyperaldosteronism, deoxycorticosterone (DOC)-producing adrenal tumors, and kidney disorders, such as renal tubular acidosis type 1 or 2 and Geller syndrome (Fig. 1).^{5,6} Therefore, investigations

Abbreviations: AME, apparent mineralocorticoid excess; DOC, deoxycorticosterone; ENaC, epithelial sodium channel; LS, Liddle syndrome; PY, proline-tyrosine.

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<https://doi.org/10.1016/j.aaace.2020.11.017>

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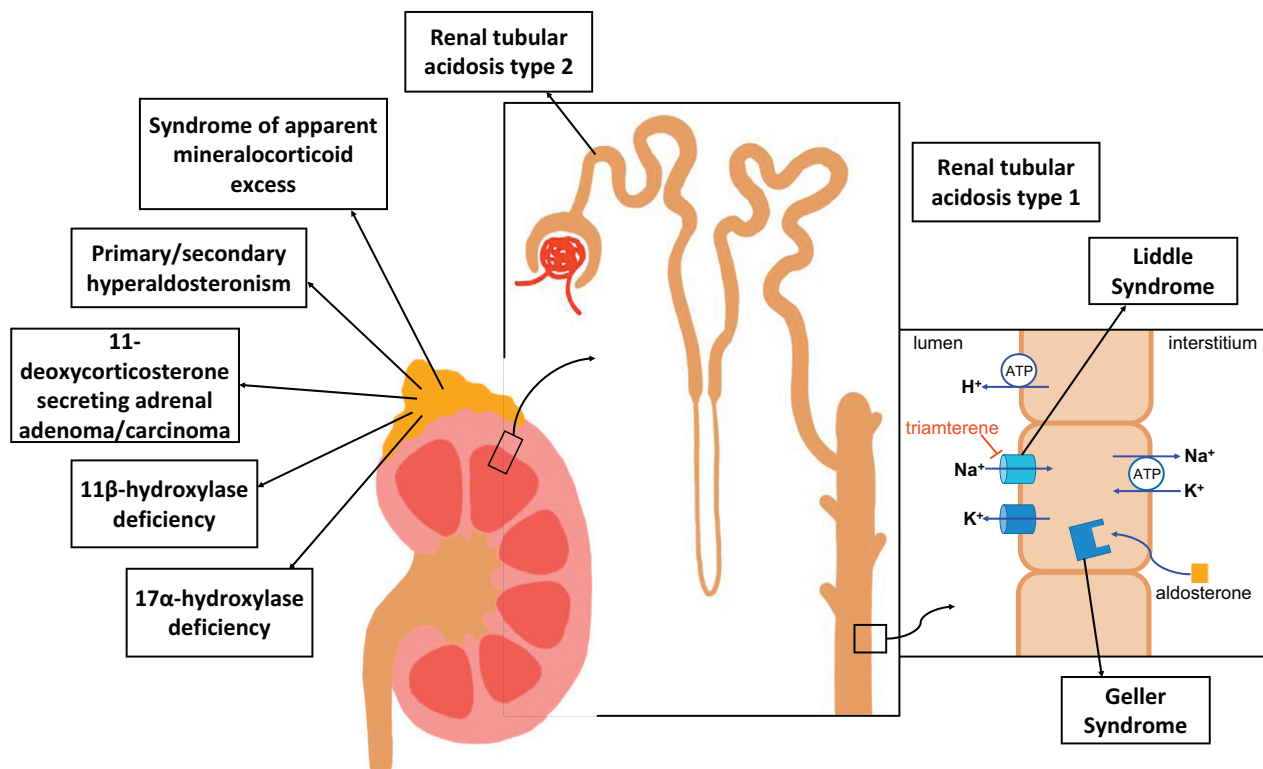


Fig. 1. Differential diagnoses in a patient with long-term hypokalemia.

to exclude such conditions should include urinary steroid profiling for metabolites of DOC and corticosterone. An increased cortisol-to-cortisone ratio is typical in AME. High levels of DOC with low aldosterone are seen in congenital adrenal hyperplasia secondary to 11β-hydroxylase deficiency, 17α-hydroxylase deficiency, and DOC-producing adrenal tumors.⁵⁻⁷ Conversely, a high aldosterone level is noted in patients with primary or secondary hyperaldosteronism.⁵ Renal tubular acidosis types 1 and 2 can present with hypokalemia without altered renin or aldosterone and classically present with metabolic acidosis.⁸ Geller syndrome is caused by mutation of the mineralocorticoid receptor gene, leading to hypertension and hypoaldosteronism, and can be ruled out with genetic testing.⁵ In LS, apart from hypertension and a strong family history of hypertension and hypokalemia, abnormal laboratory results typically include hypokalemia, low serum aldosterone levels, and decreased plasma renin activity.³

Current treatments for LS include potassium-sparing diuretics triamterene and amiloride, which block ENaCs. Spironolactone, another potassium-sparing diuretic, is ineffective in LS because it functions as a competitive inhibitor of aldosterone, and LS is characterized by aldosterone-independent hypertension.^{9,10} Incorporating a low-salt diet in daily life enhances the effectiveness of treatment.¹¹

To date, there are only approximately 70 families with a history of LS, and sporadic cases have been reported.^{3,12} We report a pediatric case of LS with a novel mutation in *SCNN1B* coding for ENaC and review the associated literature.

Case Report

A 16-year-old female presented to the pediatric endocrine service for evaluation of recurrent hypokalemia. The patient’s medical history revealed epigastric pain for 2-3 years, nausea with no vomiting, lightheadedness, drowsiness, worsening muscle cramps

and weakness, and a constant state of fatigue. She was previously evaluated by pediatric gastroenterologists, with unremarkable gastroenterological findings and normal endoscopic evaluation. Furthermore, she had been evaluated for the muscle cramps 18 months prior and was noted to be hypokalemic. She was prescribed potassium supplements, which failed to resolve her symptoms and hypokalemia. She had a strong family history of hypokalemia and hypertension spanning 3 generations, including her mother and maternal grandmother. The patient herself did not have a history of hypertension; however, she had been taking propranolol (80 mg daily) as migraine prophylaxis for an unspecified amount of time. It was unclear retrospectively whether hypertension may have triggered the headaches or if the headaches were of an unrelated etiology. Additional medications are listed in Table 1.

The physical examination was unremarkable, with no hyperpigmentation, muscle weakness, or fasciculations. Her vital signs were within normal limits, and her blood pressure was normal. A

Table 1 Patient Medications at Initial Visit

| Medication | Dosage |
|--|---|
| Norethindrone acetate, ethinyl estradiol, and ferrous fumarate tablets; 1-mg norethindrone acetate and 20-µg ethinyl estradiol (24) per tablet and 75-mg ferrous fumarate (7) per tablet | 1 tablet orally once daily |
| Omeprazole, 20-mg capsule | 1 capsule orally once daily |
| Potassium chloride, 10-mEq tablet | 2 tablets orally every morning with breakfast |
| Citalopram, 40-mg tablet | 1 tablet once daily |
| Ibuprofen, 800-mg tablet | 1 tablet orally every 8 h as needed for pain (menstrual cramps) |
| Dicyclomine, 20-mg tablet | 1 tablet orally 4 times per day |
| Propranolol, 80-mg tablet | 1 tablet orally once daily |

Table 2
Patient Laboratory Results at Initial Visit and Follow-up After Treatment with K⁺-sparing Diuretic Triamterene (50 mg twice daily) for 3 Months

| Laboratory test | Initial results (reference range) | Follow-up results |
|--|-----------------------------------|-------------------|
| Plasma renin | Undetectable | ... |
| Plasma aldosterone | Undetectable | ... |
| Na ⁺ (mmol/L) | 137 (135–145) | 138 |
| K ⁺ (mmol/L) | 3.2 (3.5–5.0) | 4.4 |
| Cl ⁻ (mmol/L) | 105 (96–106) | 105 |
| Co2, Total (mEqCO ₂ , total) (mmol/L) | 25 (23–29) | 27 |
| Anion gap (mmol/L) | 7 (3–10) | 6 |

Abbreviations: Cl⁻ = chloride; CO₂ = carbon dioxide; K⁺ = potassium; Na⁺ = sodium.

review of previous laboratory studies showed recurrent hypokalemia, with the lowest serum potassium measuring 2.9 mmol/L (reference range 3.5–5.0 mmol/L) 18 months prior. Her serum potassium was 3.2 mmol/L at the consultation visit (Table 2). Renin and aldosterone were also obtained and were unmeasurable. Based on her clinical presentation and further workup, differential diagnoses, including AME, congenital adrenal hyperplasia (11β-hydroxylase and 17α-hydroxylase deficiency), and Geller syndrome (Fig. 1) were ruled out.

Due to the patient’s clinical presentation and a strong family history of hypertension and hypokalemia, a diagnosis of LS was considered. Genetic consultation and testing were ordered for the

patient and her mother after obtaining their informed consent. This revealed a novel c.1713delC (p.Tyr571) mutation in *SCNN1B*, resulting in the premature termination of the *SCNN1B* protein product, ENaC β-subunit (Fig. 2). This sequence variant is expected to be pathogenic and likely the cause of LS in our patient. The patient was prescribed triamterene (50 mg, twice daily) and instructed to continue potassium chloride (20 mEq once daily) and showed good compliance and response based on her follow-up visit (Table 1). She remains normotensive and asymptomatic on her prescribed regimen, with no further episodes of hypokalemia.

Discussion

We present a case of LS with a novel c.1713delC deletion mutation affecting *SCNN1B*. This mutation results in the premature truncation of the β subunit of the ENaC protein. All known mutations that are associated with LS alter a specific region of ENaC, the tyrosine base near the C-terminus of *SCNN1B* or *SCNN1G* of the proline–tyrosine (PY) motif.¹³ In our case, we have a novel cytosine deletion that is suspected of causing LS in this patient.

ENaCs serve as one of the key regulators of sodium resorption.¹⁴ Point mutations in *SCNN1A*, *SCNN1B*, and *SCNN1G*, which, respectively, encode the α, β, and γ subunits of ENaC, lead to LS.¹⁴ All the subunits have a similar structure, consisting of an intracellular N- and C-terminus, 2 transmembrane domains, and an extracellular loop (Fig. 2).^{14,15}

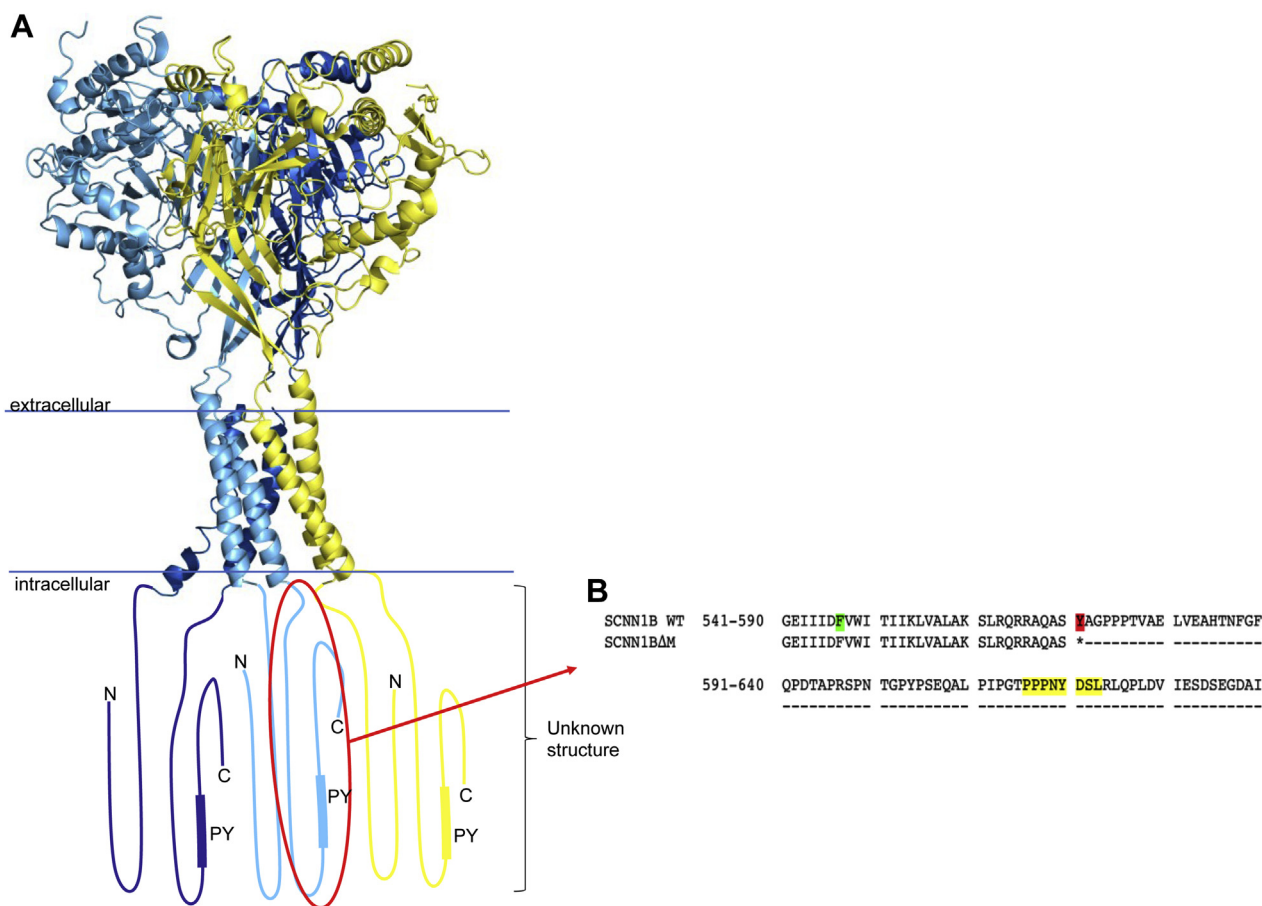


Fig. 2. Location of novel c.1713 deletion resulting in Liddle syndrome. **A**, The predicted organization of human epithelial sodium channels (ENaCs) created in PyMOL¹⁶ (Protein Data Bank 6BQN) and based on the cryo-electron microscopy of human ENaC.¹⁸ **B**, The amino acid sequence of the intracellular domain deletion in ENaC. The start of the intracellular segment is highlighted in green, our novel nonsense mutation in *SCNN1B* is highlighted in red, and the proline–tyrosine motif is highlighted in yellow.^{19,20}

A notable feature found near the C-terminus of all 3 subunits is a PY motif with the highly conserved consensus sequence PPPXYXXL.¹⁵ All reported mutations causing LS have alterations in the amino acids of this region, specifically in the β and γ subunits, leading to increased channel activity.^{1,16} These changes prevent the internalization and degradation of ENaC by proteins such as neuronal precursor cell-expressed developmentally down-regulated 4. As more channels escape degradation due to impaired binding of neuronal precursor cell-expressed developmentally down-regulated 4 to the mutated PY motif, ENaCs begin to accumulate in the apical membrane of the epithelial cells of the distal nephron, increasing the amount of sodium reabsorption from the lumen.^{1,3}

LS has variable penetrance and can also present with isolated hypertension or hypokalemia.³ It is, thus, important to screen for this condition in anyone presenting with refractory hypertension or isolated hypokalemia with suppressed aldosterone and renin and a strong family history of severe or refractory hypertension and/or hypokalemia. However, because there have only been sporadic cases of LS, the lack of family history should not exclude LS in the differential diagnosis.¹⁷ To date, most LS cases have presented with low plasma renin activity, low serum aldosterone, metabolic alkalosis, and early-onset hypertension that is unresponsive to standard blood pressure-lowering treatments, including spironolactone.^{3,11} Approximately 7% to 8% of patients diagnosed with LS are normotensive, like our patient.³ It is worth considering that our patient was on a β -blocker for migraine headaches and this might have masked hypertension.

Studies of the initial treatment of LS comparing spironolactone, triamterene, and dexamethasone for the treatment of hypertension and hypokalemia found LS to be most responsive to triamterene treatment.¹² With a better understanding of the mechanism underlying the condition, including ENaC accumulation in the distal nephron, management now includes utilizing ENaC antagonists, such as amiloride, in certain cases, as well as salt restriction, which enhances the effects of ENaC antagonists.^{12,17} Identification and treatment of LS is critical because of the well-known morbidities that are linked to long-term hypertension and hypokalemia, such as cerebrovascular events and arrhythmias.

In some cases, triamterene or amiloride as a stand-alone treatment, even with dietary changes, may be insufficient for treating hypertension in LS. In resistant LS cases, a vasodilator or β -blocker has been used as well.⁹ In our case, the patient had been using propranolol (80 mg once daily) for migraine prophylaxis, which may have contributed to her normotensive presentation at both her initial visit and subsequent follow-ups. Thus, no additional treatment apart from triamterene was considered.

Conclusion

In conclusion, we have described a novel deletion, c.1713delC (p.Tyr571) in *SCNN1B*, causing the premature truncation of the β -subunit of the ENaC protein. Additionally, the patient presented as normotensive with hypokalemia. This is not the classical clinical picture for LS, in which hypertension is present in >90% of cases. Because both hypokalemia and early-onset severe hypertension

have substantial morbidity and mortality associated with them, it is important to consider rare genetic syndromes like LS when investigating these patients. Further studies are needed to better understand the variable presentation of this condition and to delineate the long-term prognosis of patients with atypical presentations.

Author Contributions

R.K.B., I.A.G., and V.S. contributed equally.

Disclosure

The authors have no multiplicity of interest to disclose.

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