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Case Report:
Liddle's-Like Syndrome Associated With Nephrotic Syndrome in a Pediatric Patient

Nisreen Sinada[1*], **Rajendra Bhimma**[1]

1. Department of Paediatrics and Child Health, Nelson R Mandela School of Medicine, College of Health Sciences, University of KwaZulu-Natal, Durban, South Africa.

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Corresponding Author:
Nisreen Sinada
Address: Department of Paediatrics and Child Health, Nelson R Mandela School of Medicine, College of Health Sciences, University of KwaZulu-Natal, Durban, South Africa.
E-mail: nisreensinada@gmail.com

ABSTRACT

Nephrotic syndrome, especially the steroid-resistant form, is often complicated by hypertension in childhood. The syndrome is common in black children. However, the histopathological finding of membranous nephropathy in children with nephrotic syndrome is rare. Liddle's syndrome is a rare genetic abnormality that presents with salt-sensitive hypertension caused by constitutive activation of the amiloride-sensitive epithelial sodium channel. The epithelial sodium channel comprises homologous α, β, and γ subunits that share similar structures. Gene mutations associated with Liddle's syndrome occur in either the β or γ subunits and disturb or truncate a conserved proline-rich sequence (i.e., PY motif), leading to constitutive activation of the epithelial sodium channel. The association of nephrotic syndrome with Liddle's syndrome has only been described in an adult patient. We present here the first case of these two syndromes (nephrotic syndrome and Liddle's-like syndrome) co-existing in a child with membranous nephropathy in his histopathological finding on kidney biopsy.

Keywords: Children, Liddle's syndrome, Nephrotic syndrome, Hypertension

Introduction

Liddle's syndrome is a rare genetic abnormality that presents with salt-sensitive hypertension. It is a monogenic form of hypertension presenting with hypokalaemia, metabolic alkalosis, and decreased circulating levels of renin and aldosterone. The disease is caused by an increased function of the collecting tubule sodium channel with activation of the amiloride-sensitive Epithelial Sodium Channel (ENaC). This syndrome results from truncating or missense mutations in the C termini of the ENaC β or γ subunits due to mutations in the *SCNN1A, SCNN1B,* or *SCNN1G* gene [1]. The disease is autosomal dominant, although rare sporadic cases caused by de novo *ENaC* mutations have been reported [2-4]. Traditional diagnostic criteria include young age of presentation, hypokalaemia, metabolic alkalosis, hypertension, low renin, low aldosterone, normal cortisol, insensitivity to dexamethasone and spironolactone but sensitivity to triamterene or amiloride.

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Therapy consists of potassium-sparing diuretics, which directly close the sodium channels, such as amiloride or triamterene, together with a low sodium diet to inhibit sodium transport through the ENaC that mitigates sodium-sensitive hypertension [5, 6]. The syndrome was first described in 1963 by Liddle et al., who postulated a primary abnormality of renal sodium transport [7].

To date, the only case of Liddle's syndrome with nephrotic syndrome has been reported in a 65-year-old Japanese man. We present here the first reported case of a child with Liddle's-like syndrome associated with steroid-resistant nephrotic syndrome. In both cases, the nephrotic syndrome was membranous nephropathy on histopathology.

Case Presentation

An 11-year-old African boy presented with a history of long-standing headache and generalized edema for three weeks. He was previously well. There was no family history of hypertension, kidney disease, or similar conditions and no history of using traditional medication or illicit drugs. On examination, he was found to have anasarca and hypertensive emergency with a blood pressure of 211/147 mm Hg (consistent with stage II hypertension) with evidence of target organ damage. Urinary dipsticks analysis showed proteinuria 1+, no haematuria, normal pH of 6.0, and specific gravity of 1020 without other abnormalities. His urine protein:creatinine ratio on initial examination was 0.233 g/mmol with dipsticks urinalysis of 1+ protein. Following a dose of 20% albumin infusion, his urine protein:creatinine ratio increased to 2.18 g/mmol and dipsticks urinalysis of 4+ protein consistent with nephrotic range proteinuria (>0.3 g/mmol). He had serum albumin of 17 g/L (normal 35-50 g/L) with high cholesterol of 8.87 mmol/L (normal <4.4mmol/L), confirming the diagnosis of nephrotic syndrome. Additional biochemical testing showed a low serum complement C3 level of 0.72 g/L (normal 0.9-1.6 g/L), normal serum complement C4 of 0.13 g/L (normal 0.10 to 0.45 g/L) with hypokalaemia 2.7 mmol/L (normal 3.5-5.4 mmol/L) and a high serum bicarbonate of 31 mmol/L (normal 21-29 mmol/L). His serum sodium was normal (135 mmol/L; normal 135-145 mmol/L). He had normal kidney function based on normal blood urea and serum creatinine level corrected for age and a normal estimated glomerular filtration rate using the modified Swartz formula [8]. Screening for secondary causes of nephrotic syndrome was negative. The screening included serology tests for the following infections viz. hepatitis B, hepatitis C, human immune deficiency virus, cytomegalovirus, Epstein-Barr virus, human parvovirus B19, syphilis, and antistreptolysin antibodies. His autoimmune screen (antinuclear antibody, anti-dsDNA, anti-neutrophil cytoplasmic antibody) was negative, and there was no history of drugs, malignancy, or known allergens. Ultrasound of the abdomen showed the kidneys' normal morphology and contour, with the right kidney 12 cm and left kidney 14 cm in length, above the normal size limit (> the 95th percentile for his age), and hyperechoic. There was gross ascites. The liver, gallbladder, spleen, and bladder were normal.

Ophthalmology evaluation showed bilateral grade IV hypertensive retinopathy, consistent with chronic hypertension. His chest x-ray showed a normal-sized heart with bilateral pleural effusions, greater on the right side. Echocardiology examination showed moderate left ventricular hypertrophy and a sliver of pericardial effusion around the posterior ventricular walls. There were no features of cardiac tamponade. There was normal left ventricular contractility with a fractional shortening of 45%.

Initial management included labetalol infusions for control of his blood pressure together with albumin and furosemide infusions for control of edema and oral potassium supplementation to maintain serum potassium around 3.5-5.4 mmol/L. His blood pressure was difficult to control and required polypharmacy, including amlodipine 10 mg given every 12 hours (0.5 mg/kg/d), hydralazine 75 mg mane, 50 mg at noon and 75 mg nocte (5 mg/kg/d), enalapril 10 mg given 12 hourly (0.5 mg/kg/d), and doxazosin 4 mg daily (0.1 mg/kg/d). Triamterene and amiloride were unfortunately not available for treatment.

A kidney biopsy on light microscopy showed glomerular basement membrane thickening, perpendicular spikes, holes within the glomerular basement membrane, and a "rosary-like" glomerular basement membrane with mild tubular atrophy. There was mild tubulointerstitial nephritis with mild interstitial fibrosis highlighted on the Masson trichrome stain (Figure 1 A-E). On immunofluorescence examination, patchy PLA2R positivity on glomeruli (Figure 2). On electron microscopy, numerous subepithelial dense deposits were found, with intramembranous dense deposits (Figure 3). These findings on histopathology favored membranous nephropathy.

On receipt of the biopsy findings, prednisone (60 mg daily) was started for the patient. His blood pressure remained above the 95th percentile, corrected for his sex, height, and age. However, his edema resolved. He was discharged for follow-up in two weeks.

He unfortunately defaulted treatment and presented to the emergency department three weeks later with massive anasarca, severely impaired vision, hypertensive encephalopathy with generalized convulsions, ptosis of the right eye, and right-sided hemiplegia, with upper limb affectation more than the lower limbs. Besides these clinical finding, he had hypokalaemia (serum potassium 2.6 mmol/L), metabolic alkalosis (serum bicarbonate 30 mmol/L), hypoalbuminemia (serum albumin 27 g/L), with a urine protein:creatinine ratio of 3.1 g/mmol. His transtubular potassium gradient was 5, suggesting renal potassium wasting (transtubular Potassium gradient TTKG normally <3 in the presence of hypokalaemia). A computerized tomogram of the brain showed a bleeding above the corpus callosum, consistent with a left parenchymal bleeding and a possible sagittal venous thrombosis with posterior reversible encephalopathy syndrome. A stroke workup showed normal protein S, protein C, anti-thrombin III, and factor V, normal international normalization ratio of 1.09, normal platelet count of 266 $\times 10^9$/L, hematocrit of 0.341, and negative lupus anticoagulant. His serum renin activity showed a low normal value of 3.9 mIU/L (normal range 2.8-39.9 mIU/L) and low serum aldosterone 74.5 pmol/L (normal 111-1219 pmol/L), supporting the diagnosis of Liddle's-like syndrome.

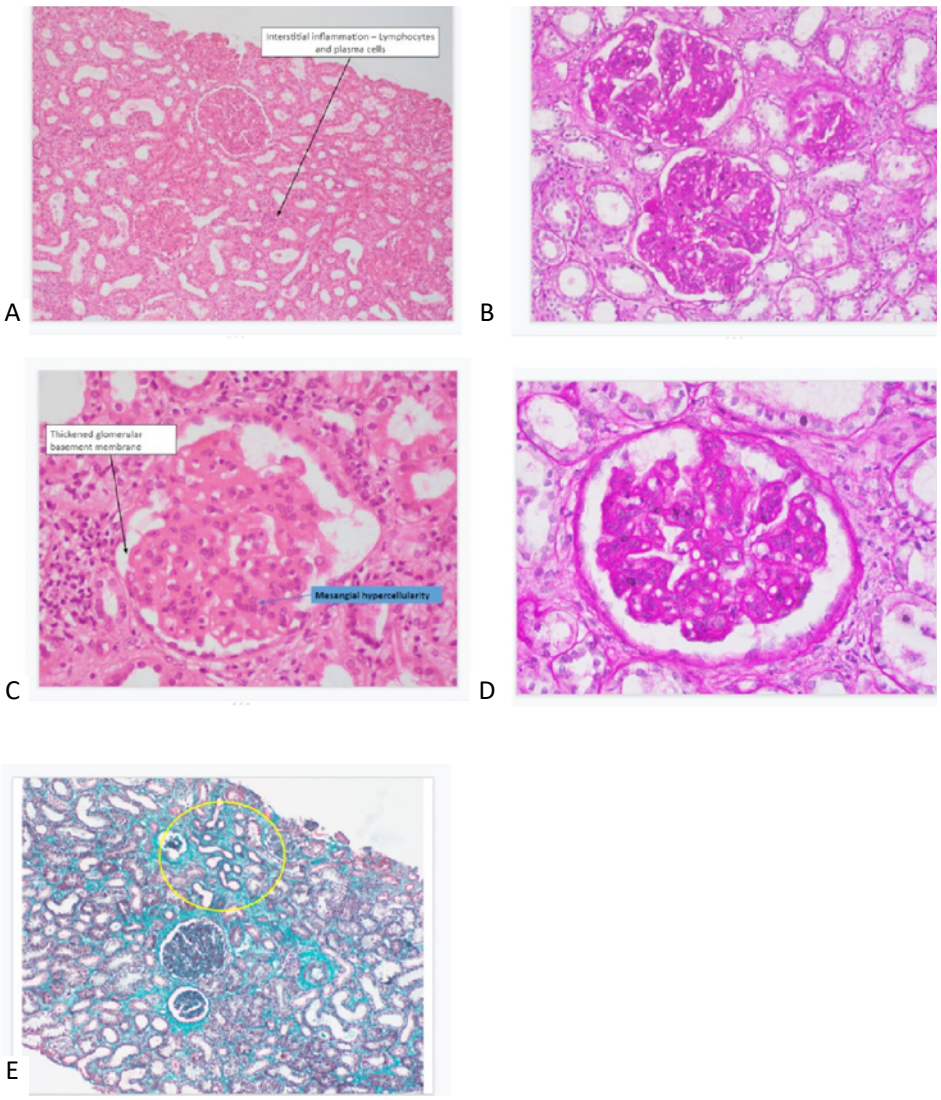

Figure 1 A-E. Light microscopy A. Global glomerular basement membrane thickening and tubulo-interstitial nephritis. All glomeruli and the entire glomerular capillary surface show thickened basement membranes.)H&E100-X(B. Global glomerular basement membrane thickening. (PAS 200X) C. Glomerulus showing basement membrane thickening. (H&E 400X(D. PAS stain highlighting glomerular basement membrane thickening. (PAS 400X) E. Glomerular basement membrane thickening, mesangial matrix expansion, adjacent tubular atrophy and periglomerular fibrosis (circled area). (Masson trichrome 100X)

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Table 1. Blood pressure and laboratory findings on admissions and follow-up

	First admission	Following oral potassium supplementation	Second admission	Last hospital visit
BP (mmHg)(95th percentile of blood pressure corrected for height, age and sex: (121/76)	211/147	162/106	161/111	118/70
Serum sodium (normal 135-145mmol/l)	135	138	147	142
Serum potassium (3.4-5-5.3 mmol/l)	2.7	3.1	2.6	3.7
Serum chloride (normal 98-107 mmol/l)	112	108	112	114
Serum albumin (normal 35-50 g/l)	17	24 (given 20% albumin infusion)	27	29
Urea (1.8-6.4 mmol/l)	7	8	4.7	5.6
Creatinine (normal 37-63umol/l)	51	38	39	41
eGFR mls/1.73m^2/min	117	157	153	168
Serum Bicarbonate levels (normal 21-29 mmol/l)	31	22	30	22
Serum cholesterol (normal <4.4 mmol/l)	8.87	-	6.81	5.95
Urine protein creatinine ratio (normal <0.015g/mmol and nephrotic range >0.2g/mmol)	2.18	0.635	3.117	0.88

A magnetic resonance imaging combined with brain angiography showed features in keeping with posterior reversible encephalopathy syndrome with an associated vasculopathy and left high parietal lobe parenchymal hemorrhage (Figure 4).

He was treated with a labetalol infusion initially to decrease blood pressure gradually to the 90th percentile, corrected for age, sex, and height over three days. The oral antihypertensive medication that he was on previously was reintroduced, and spironolactone 25 mg every 12 hours (1.25 mg/kg/d) given orally was added to his antihypertensive treatment regimen. For his nephrotic

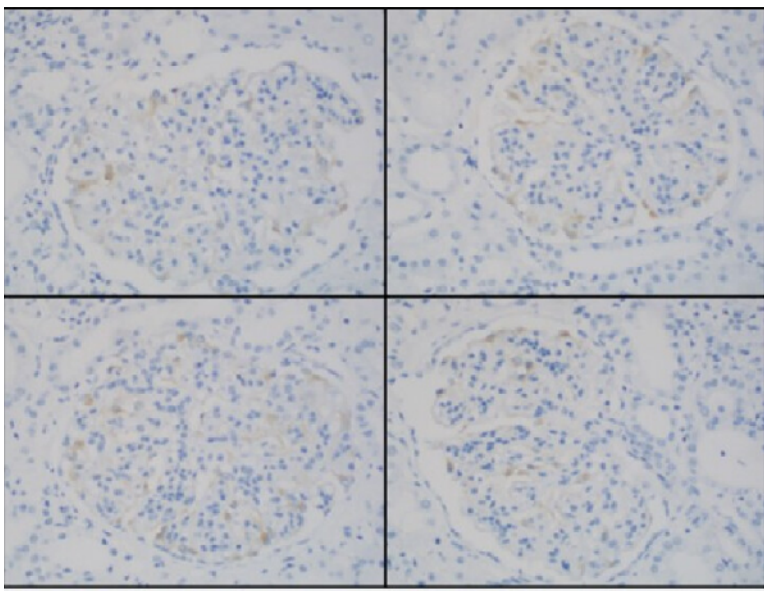

Figure 2. Immunohistochemisty

Various glomeruli showing patchy PLA2R positivity but reported as negative for PLA2R staining

(PLA2R IHC 400X)

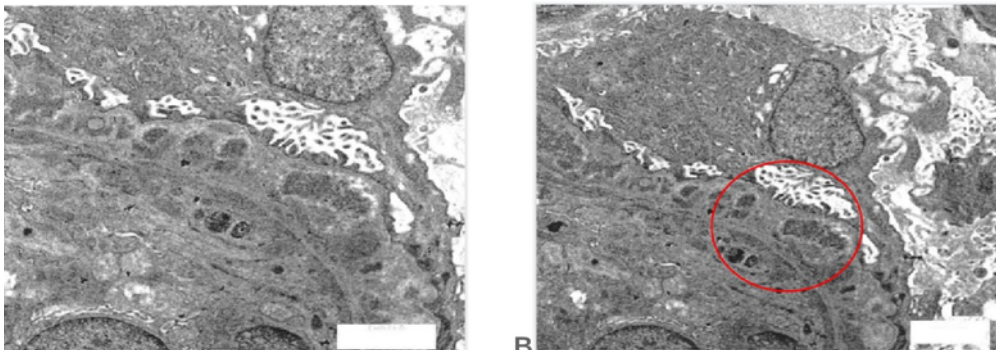

Figure 3. Electron microscopy A. Glomerular basement membrane thickening and subepithelial electron dense deposits. (EM8 21A) B. Glomerular basement membrane thickening, subepithelial and intermembranous electron dense deposits. (EM8-21B)

syndrome, prednisone (60 mg daily) was reintroduced for six weeks and, after that, reduced. On his last hospital visit, his blood pressure was normal, and his nephrotic syndrome was in partial remission with proteinuria decreased by more than 50% of baseline with a protein:creatinine ratio of 0.88 mg/mmol, serum albumin of 29 g/L, serum potassium 4.1 mmol/L, and serum bicarbonate 22 mmol/L (Table 1). A motivation was sent to the Department of Health of KwaZulu-Natal to have either triamterene or amiloride made available.

Discussion

We present the first pediatric case of a Black African child with nephrotic syndrome—membranous nephropathy on histopathology—and features of Liddle's-like syndrome with a complication of a cerebrovascular accident following a hypertensive crisis. To date, the only other report of nephrotic syndrome associated with Liddle's syndrome was a 65-year-old Japanese male also associated with primary membranous nephropathy on histopathology [9].

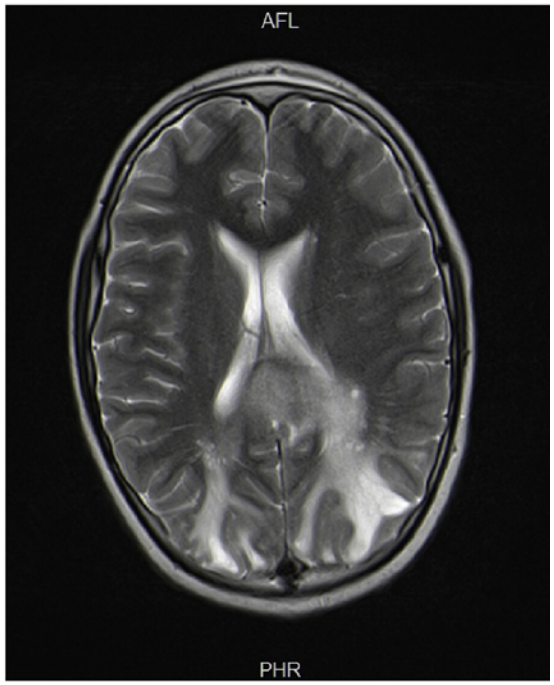

Figure 4. Magnetic resonance image (MRI) brain T2 weighted MRI image showing hyperintensity (oedema) of the parietal and occipital lobes bilaterally involving both white and grey matter. This is suggestive of posterior reversible encephalopathy syndrome (PRES). The mechanism of the vasogenic oedema seen is hyperperfusion due to a failure of auto-regulation which causes a disruption of the blood brain barrier. Other images (not shown), showed a lesion in the left superior parietal lobe which was hyperintense on the T1 weighted image (suggesting blood), with restricted diffusion on the diffusion weighted scans (suggestive of a recent infarct) and succeptability artefact on the GRE scans (indicative of blood products). This finding were compatible with a recent haemorrhagic infarct. AFL

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Liddle's syndrome was first described by Grant Liddle et al. in 1963 with the following clinical and biochemical findings: young age, hypertension, hypokalaemia, metabolic alkalosis, low renin, low aldosterone, normal cortisol, insensitivity to dexamethasone and spironolactone, and sensitivity to triamterene and amiloride [7]. Our patient had all the above biochemical findings, except we did not have triamterene or amiloride to treat the patient as this is not available in our region. In addition, we could not do genetic testing for mutations of the β or γ subunits of *ENaC* gene due to financial constraints and unavailability of these genetic tests in our country.

Since the original report by Liddle et al., only a few cases have been reported in the literature. A report by Vania et al. of a 10-month-old female child is to date the youngest age in which this syndrome has been reported. The authors had a long follow-up of 14 years. They were thus able to describe additional features of suppression of the renin-aldosterone circadian rhythm and occurrence of a normal blood pressure circadian rhythm under effective treatment [10]. Unfortunately, we did not have access to ambulatory blood pressure monitoring and a long enough follow-up in our patient to confirm these additional findings.

To differentiate Liddle's syndrome from other hypokalaemia, hyporeninaemic, and hypertensive syndromes in childhood, such as apparent mineralocorticoid excess, Liddle et al. proposed that this disorder was due to excess avidity in the ascending limb of Henle's loop for intraluminal sodium, causing volume-mediated atrophy of the juxtaglomerular apparatus [10]. Notably, the defective sodium transport mechanism was found to be more extensive. Helbock and Reynolds [11] suggested an increase in sodium influx with a secondary high intracellular sodium concentration. Later, Gardner et al. [12], Hyman et al. [13], and Assadi [14] observed that the fractional sodium efflux and influx were both increased while the intracellular sodium concentration was normal. Additionally, Wang et al. [15] and Noblins et al. [16] examined the potassium flux in erythrocytes, concluding that the cellular disorders in electrolyte transport may show a different degree of severity, which in turn can reflect a clinical evolution in the pathophysiological expression of the disease. The main defect in apparent mineralocorticoid excess syndrome is due to inactivating mutations in the 11ß-hydroxysteroid dehydrogenase type 2 gene (*11ß-HSD-2*). This enzyme is usually expressed in the kidneys and converts the biologically active cortisol into the receptor inactive form cortisone. This effect is important in physiological aspects, because cortisol usually binds as avidly as aldosterone to the mineralocorticoid receptor. Although cortisol has a much higher plasma concentration than aldosterone, it does not have a mineralocorticoid activity, as it is converted locally to cortisone. In apparent mineralocorticoid excess, however, the reduced activity of 11ß-hydroxysteroid dehydrogenase allows normal levels of cortisol to induce a marked mineralocorticoid activity. Treatment of this disorder most commonly includes spironolactone. The diagnosis of apparent mineralocorticoid excess is made by an increased ratio of urinary free cortisol to urinary free cortisone or by an increased ratio of urinary metabolites of cortisol (tetrahydrocortisol and 5α-tetrahydrocortisol) to the metabolite of cortisone (tetrahydrocortisone) [5, 6, 17].

Although the close association of high proteinuria with the activation of the *ENaC* was confirmed in vitro studies [18, 19], to date, there have been no reports in the pediatric literature of nephrotic syndrome associated with Liddle's syndrome. However, the former is one of the most common forms of glomerular disease in children. Hypertension may be present in children with nephrotic syndrome, especially steroid-resistant nephrotic syndrome; however, one should pay attention to serum potassium levels and the acid-base balance, not to miss the diagnosis of Liddle's syndrome. Also, it is important to note that triamterene or amiloride for intractable hypertension or edema is the treatment of choice in patients with Liddle's syndrome. Unlike spironolactone, the latter is more commonly used in children with nephrotic syndrome to control edema and hypertension in our region.

There are limitations to the confirmatory diagnosis of Liddle's syndrome in this report. The first is the lack of our ability to demonstrate an appropriate response to amiloride or triamterene. Our patient had recalcitrant hypertension and persistent hypokalaemia that corrected with the addition of an aldosterone antagonist (spironolactone) to his treatment regime. Usually, spironolactone has no therapeutic effect because, in Liddle's syndrome, the epithelial sodium channel is activated even in the presence of hypoaldosteronism [20]. This finding suggests a Liddle's-like syndrome as opposed to a firm diagnosis of Liddle's syndrome. While spironolactone is not helpful in Liddle's syndrome, it could be considered in low-renin hypertension (Liddle's-like syndrome) since the aldosterone excretion rates are "normal" despite suppression of plasma renin activity [21, 22]. Secondly, in the absence of genetic testing, we could not demonstrate an autosomal dominant inheritance, although rare sporadic cases of the disease caused by de novo *ENaC* mutations have been reported [2-4]. Thirdly, as we showed normal cortisol lev-

els, urinary testing for urinary free cortisol and cortisone and their metabolites to exclude the syndrome of apparent mineralocorticoid excess was not done, as this testing is not available at our center. Fourthly, another anomaly in our patient is the late age of presentation, as Liddle's syndrome is usually a disease of younger children, although Liddle's-like syndrome has been reported in elderly patients [23-26].

Conclusion

To the best of our knowledge and based on an extensive literature search, this is the first case of nephrotic syndrome associated with Liddle's-like syndrome in a child. The only other case has been described in an adult male, and in both cases, the histopathological findings were that of primary membranous nephropathy that is rare in childhood. Although nephrotic syndrome associated with hypertension is not rare, particularly in black children, the finding of a persistent metabolic alkalosis and hypokalaemia should alert one to the possibility of Liddle's syndrome, which should be confirmed on further testing.

Ethical Considerations

Compliance with ethical guidelines

Exemption from ethics review has been granted for this study with reference number: EXM002/2021.

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Authors' contributions

Data curation, resources, writing the original draft: Nisreen Sinada; Writing, review, and editing: Rajendra Bhimma.

Conflict of interest

The authors declared no conflict of interest.

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