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A Rare Case of Liddle Syndrome Due To A Novel Mutation in A Normotensive Adult

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Abstract

Liddle syndrome (pseudoaldosteronism) is a genetically heterogenous autosomal dominant disorder. The key clinical characteristics of this syndrome are early onset salt-sensitive hypertension with hypokalemia, metabolic alkalosis, inhibition of renin activity and aldosterone secretion. Liddle syndrome is caused by mutations (missense or frameshift) in the genes of epithelial sodium channel (ENaC) subunits namely SCNN1A, SCNN1B or SCNN1G genes.

A normotensive adult diabetic male with CKD presenting with hypokalemic paralysis, was found to have Liddle syndrome after ruling out commoner causes. The genetic analysis revealed a novel mutation in α subunit of ENaC. This is likely the second SCNN1A mutation identified after the description of one case of germ line mutation in the α subunit in a Caucasian family affected by Liddle syndrome by Salih M.

Keywords: Liddle syndrome, Hyperkalemia, Hypertension, Chronic kidney disease, gene mutation

Introduction

Liddle syndrome (pseudoaldosteronism) is a genetically heterogenous autosomal dominant disorder. The key clinical characteristics of this syndrome are early onset salt-sensitive hypertension with hypokalemia, metabolic alkalosis, inhibition of renin activity and aldosterone secretion[1]. Liddle syndrome is caused by mutations (missense or frameshift) in the genes of epithelial sodium channel (ENaC) subunits. ENaC channels are present in the apical portion of epithelial cells of distal nephron, distal colon, lung and ducts of exocrine glands. These channels belong to the ENaC/DEG (degenerin) family of proton-gated cation channels which mediates transport of Na+ through the apical membrane from lumen into the epithelial cell[2]. By regulating Na+ ion balance in the extracellular fluid (ECF) and in the kidney, these channels are a significant part of ECF volume and blood pressure (BP) regulation [3].

Case report

A 58-year-old male, diabetic for 4 years, normotensive, known chronic kidney disease (CKD) for 4 years, presented to our OPD with symptoms of weakness on the lower limbs. There was no history of leg swelling, urine output was adequate, glycemic control was maintained. General examination did not reveal any positive finding except pallor. Neurological examination revealed diminished tone, diminished power (2/5) on both lower limbs with diminished deep tendon reflexes (flaccid paralysis). Other system examination was normal. Patient's BP was normal (126/70 mm Hg), no signs of peripheral edema. The patient was on oral antidiabetic drug linagliptin.

He didn't give any history of fever, diarrhea, vomiting, excessive urine volume or of any diuretic intake.

Routine testing revealed hypokalemia (K^+ 2.6 mmol/dl), S.creatinine 3.2 mg/dl, Hemoglobin 8.8 g/dl. The rest of the parameters were under normal limits. He was prescribed oral potassium supplementation and previous medications were continued. However, the serum potassium was persistently low despite intravenous correction. Further evaluation was planned, a battery of tests advised which is as follows.

Meanwhile, a Neurology consultation was taken, and the patient also underwent a nerve conduction study (NCS) to rule out peripheral neuropathy (diabetic neuropathy). The study revealed diminished cMAP with normal conduction velocities. There was no clinical or radiological evidence of myelopathy.

Laboratory evaluation revealed the following

Parameter	Observed value	Normal range
Blood parameters		
WBC	8600	4.00-11.00 x 10^3/µL
Hemoglobin	9.4	13-16.5 g/dl
Platelet count	231,000	150-400 x 10^3/ µL
RBS	146	74.0-106.0 mg/dl
Urea	70	14.98-36.38 mg/dl
Creatinine	3.4	0.52-1.05 mg/dl
Na	137	137-145 mmol/l
K	1.8	3.5-5.1 mmol/l

Ca	9.3	8.40-10.20 mg/dl
Mg	1.5	1.6-2.3 mg/dl
PO4	4.2	2.50-4.50 mg/dl
Uric acid	5.8	2.50-8.50 mg/dl
Albumin	4.5	3.5-5.0 g/dl
TSH	0.79	0.40-4.05 mIU/L
Urine routine		
Albumin	Trace	Negative
Glucose	Nil	Negative
Pus cells	5-6/hpf	1-5/hpf
Epithelial cells	2-3/hpf	Upto 20/hpf
RBC	Nil	Absent
Ultrasound Abdomen		
Bilaterally contracted kidneys RK - 7.8 cm, LK – 8.4 cm, corticomedullary differentiation blurred. Rest organs within normal limits.		
Urine electrolytes		
Na	58 mmol/L	
K	23.7 mmol/L	
Ca	3.7 mg/dl	
Cl	82 mmol/L	
ABG		
pH	7.57	7.35-7.45
pCO2	39.6	36.0-48.0 mmHg
HCO3	29.3	22-26 mmol/L

Repeated testing of serum electrolytes revealed persistent hypokalemia. A thorough drug history was taken and a review of medication which might lead to hypokalemia was done and ruled out. The thyroid function test was normal. ABG was suggestive of metabolic alkalosis.

To rule out urinary potassium loss, urine electrolytes were tested which showed higher than normal potassium excretion. Calculated TTKG was found to be 5.

Based on ruling out other causes of hypokalemia, a presumptive clinical diagnosis of a potassium-losing channelopathy was made. As the patient had hypokalemic metabolic alkalosis without hypertension, we suspected either Bartter or Gitelman syndrome. Further considering the age of the patient and low urinary Ca and concomitant hypomagnesemia, a diagnosis of Gitelman syndrome was more likely.

To confirm our case, we sent a gene panel test for hypokalemic disorders, which revealed, contrary to our clinical diagnosis, a likely pathogenic variant mutation of ENaC channel leading to Liddle syndrome.

Parents are non-consanguineously married.
There is no family history of similar complaints.

RESULT SUMMARY

Positive – Likely Pathogenic variant detected

VARIANT DETAILS

GENE/ REFSEQ	COORDINATE (GRCh37)	VARIANT* (107s)	EXON/ INTRON	VARIANT TYPE	ZYGOSITY/ INHERITANCE	OMIM/ PHENOTYPE	CLASSIFICATION* ACMG/AMP
SCNN1A / NM_001038.6	chr12: 6483916	c.32_33insT p.Ser12fs*1	Exon 2	Frameshift	Heterozygous/ AD	Liddle syndrome-3 (OMIM#618126)	Likely Pathogenic

**Clinical correlation Recommended*

IN SILICO PREDICTION PARAMETERS

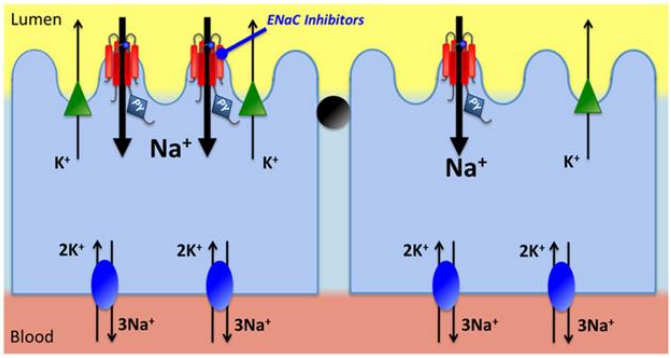
Variant	EFFECT
MutationTaster	Damaging

The patient was put on oral amiloride tablet 5 mg along with oral potassium supplements. Subsequently, potassium levels increased to normal range and the patient improved clinically with improvement in muscle power. Within a few days, the patient was off potassium supplements and maintained normal electrolytes with amiloride alone. The patient is doing well till now.

Discussion

ENaC is an amiloride-sensitive epithelial sodium channel, localized in the apical portion of epithelial cells of distal nephron[4]. Under physiological conditions, its expression and activity are positively regulated by aldosterone and antidiuretic hormone and are influenced by numerous extracellular factors, such as sodium, chloride, protons and proteases[5]. This channel is crucial, together with ROMK (renal outer medullary K^+) channels and Na^+/ K^+ ATPase, for Na^+ reabsorption and K^+ excretion and thus, for electrolytes homeostasis[5]. The channel is a heteromeric complex constituted of three homologous subunits, α, β, and γ[4,6,7], encoded by the SCNN1A (chr 12p13.31), SCNN1B (chr 16p12.2) and SCNN1G (chr 16p12.2) genes, respectively[5]. Within the C-terminus of all three ENaC subunits, there is a highly conserved sequence, named the PY (Proline Tyrosine) motif, which is a binding site for Nedd4 (Neural precursor cell expressed, developmentally down-regulated 4), that mediates internalization and proteasomal degradation of the channel[5,8-10].

Liddle syndrome results from germline mutations in SCNN1A, SCNN1B or SCNN1G genes. The germline mutations of the SCNN1B and SCNN1G genes cause loss or disruption of the PY sequence, resulting in gain-of-function and determine increased membrane density of ENaC and consequent increase in renal Na^+ reabsorption. The germline mutation of SCNN1A gene affects the extracellular domain, causing disruption of a disulfide bridge, leading to gain-of-function and increase of the open probability of the channel and consequent increase in Na^+ current, without affecting the PY motif.



The prevalence of Liddle syndrome across the general hypertensive population is unknown. In two recent studies, including 330 and 766 Chinese patients affected by arterial hypertension, the prevalence of Liddle syndrome resulted to be 1.52%[11] and 0.91%[12], respectively.

The typical clinical feature is resistant, early onset salt-sensitive hypertension, often associated with a family history of early onset hypertension and sudden death. Biochemically, the characteristic findings are hypokalemia, metabolic alkalosis, suppressed plasma renin activity (PRA) and low serum aldosterone levels.

Crosstalk between diabetes and ENaC:

Diabetes mellitus is the leading cause of a form of chronic kidney disease known as Diabetic Kidney Disease (DKD), which is the most common cause of end-stage renal disease (ESRD). DKD is associated with

significant changes in renal hemodynamics and electrolyte transport. Alterations in renal ion transport, triggered by pathophysiological conditions in diabetes, can exacerbate hypertension, accelerate renal injury, and are integral to the development of DKD. Some of the major renal ion transporters have altered expression and activity under diabetic conditions including SGLT2, ENaC, TRPC6, TRPM6, NHE, K_{ATP}.

ENaC activity in diabetes

Expressed primarily in principal cells of the distal nephron, ENaC plays a central role in maintaining salt and water homeostasis, regulating extracellular fluid volume, controlling blood pressure, and overall renal function[5]. Diabetes and DKD have been associated with increased ENaC activity and expression by multiple mechanisms, which may interfere with renal blood pressure control, exacerbate hypertension, and thereby contribute to the progression of DKD.

Studies have shown that insulin augments ENaC expression and activity[15,16,17]. As an example, single-channel analysis in freshly isolated, split-open tubules demonstrated that ENaC activity was acutely activated by insulin. Moreover, insulin receptor knockout mice have significantly lower activity compared to their wild-type littermates[18].

One proposed mechanism suggests that ENaC involvement with DKD is inexorably linked to the serum and glucocorticoid-regulated kinase (SGK1) protein. SGK1 is stimulated by insulin, which causes more ENaC to be translocated to the membrane (through the Nedd4–2 signaling pathway) increasing sodium reabsorption from the tubule. This may lead to excess renal sodium retention, hypertension, and ultimately renal damage associated with DKD[19]. In a rat model of streptozotocin (STZ)-induced T1DM, increased glucose was correlated with upregulation of all three ENaC subunits, attributed to elevations in aldosterone and vasopressin[20]. Another proposed mechanism of ENaC increases in DKD involves the serine protease, plasmin[21]. Dysfunction of the glomerular filtration barrier (GFB) in DKD causes plasmin to be filtered to the tubules where it activates ENaC and increases sodium reabsorption[22]. In a study of patients with T2DM, microalbuminuria, a hallmark of GFB breakdown, is associated with increased aberrant filtration of plasmin. This surge of filtered plasmin was shown to be sufficient to increase the open probability for ENaC and was proposed as a possible mechanism contributing to hypertension in diabetes[23]. Clinical studies have also found that amiloride, an ENaC blocker, may be protective in DKD as it significantly increased sodium excretion, and reduced blood pressure, albuminuria, and plasmin in urine of diabetic patients[24]. Recently a pilot randomized cross-over study comparing the effects of daily administration of either oral amiloride or the NCC inhibitor, hydrochlorothiazide (HCTZ), to patients with type 2 diabetes and proteinuria revealed similar effects with both drugs resulting in reduced systolic blood pressure[25].

In diabetes, prolonged hyperglycemia causes excess glucose to contact and react with proteins and lipids resulting in advanced glycation end-products (AGEs), with an especially pronounced elevation in the distal nephron where ENaC is highly expressed[26]. When applied to cultured tubular epithelial cells in concentrations comparable to what occurs in diabetes, AGEs increased ENaC mRNA and protein and stimulated ENaC activity by inhibiting catalase and increasing intracellular ROS production[27]. The effect on ENaC activity persisted for more than 72 hours after removal of AGEs. This sustained ENaC elevation may

be key to understanding why DKD often continues to progress despite adequate glucose control and provide key insights necessary for the development of more effective treatments.

From these studies, it is evident that diabetes creates pathophysiological conditions that affect ENaC via multiple pathways, causing a sustained increase in activity or expression, ultimately resulting in blood pressure elevation. As hypertension is one of the most important risk factors in the progression from diabetes to DKD, ENaC is a critical mechanistic and potential therapeutic target in DKD research.

Liddle syndrome and CKD

One of the hallmarks of Liddle syndrome is elevated blood pressure due to the overactive sodium channels in the kidneys. Chronic hypertension is a well-known risk factor for the development of CKD (hypertensive nephrosclerosis). Another mechanism of kidney damage in Liddle syndrome is prolonged hypokalemia. Over time, the chronic effects of high blood pressure, electrolyte imbalances, and kidney damage may contribute to kidney dysfunction, which could potentially progress to CKD.

Our case of Liddle syndrome

The patient of Liddle syndrome presented here is unique because unlike the most common presentation of early-onset resistant hypertension, our patient had a normal BP. It is seen that extremely severe phenotypes and mild forms can exist, with some patients carrying a causative mutation who are normotensive or in whom a clinical diagnosis of Liddle syndrome is made in old age[14]. Moreover, in this case there was no family history of young-onset hypertension or known monogenic disease. The only clue to a genetic basis of the disease was hypokalemic metabolic alkalosis, for which no known factor could be found.

Although the patient was diabetic, it was relatively short duration, and the glycemic control was maintained. Moreover, there were no clinical features of diabetic kidney disease like edema, visual disturbance etc, and paraparesis could not be attributed to diabetic neuropathy as tested by NCS study. A fundus examination was performed, and diabetic retinopathy was ruled out. To clinch the exact diagnosis of kidney dysfunction, we had planned for a renal biopsy but could not go ahead due to bilaterally small sized kidneys with altered cortico-medullary differentiation (CMD).

Based on these observations, we can presume that the chronic kidney dysfunction could be attributed to Liddle syndrome and associated dyselectrolytemia (chronic hypokalemia).

Another unique feature is the mutation described in the genetic analysis report. It is a novel heterozygous frameshift mutation c.32_33insT p.Ser12fs*1 in chr12 : 6483916 exon 2 of the SCNN1A (NM_001038.6) by NGS analysis. According to ACMG recommendation, this mutation is classified as likely pathogenic. This is a very rare entity, and this particular mutation has never been described before in literature.

Of all reported cases of Liddle syndrome, till date 24 different mutations of the β subunit and 6 different mutations of the γ subunit were identified in 72 families worldwide. Only one case of germ line mutation in the α subunit was identified in a Caucasian family affected by Liddle syndrome. This is likely the second mutation identified in α subunit of ENaC[13].

Conclusion

This is the first case of Liddle syndrome reported by our center. A normotensive adult diabetic male with CKD

presenting with hypokalemic paralysis, was found to have Liddle syndrome after ruling out commoner causes. Our results expand the mutational spectrum of Liddle syndrome, this likely being the second α-subunit mutation to be reported in literature. The rare syndromes, owing to variants of the same gene mutation, may have varied clinical presentation, therefore it is utmost important to have a high degree of suspicion for these uncommon diagnoses. The role of genetic testing in appropriate clinical setting cannot be overemphasized.

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