Journal of the American Society of Hypertension ■(■) (2017) 1–4

Clinical Cases

The importance of genetic counseling and genetic screening: a case report of a 16-year-old boy with resistant hypertension and severe hypokalemia

Ze-Min Kuang, MD, PhD[a,1], Ying Wang, MM[b], Jia-Jie Wang, MM[c], Jing-Hua Liu, MD[a], Rong Zeng, MD[a], Qi Zhou, MD[a], Zhen-Qiu Yu, MD[a], and Long Jiang, MD, PhD[d,*]

[a]*Department of Hypertension, Beijing Anzhen Hospital of Capital Medical University, Beijing, China;*
[b]*Department of Cardiology, The Chenzhou City First People's Hospital Affiliated to University of South China, Chenzhou, Hunan, China;*
[c]*Department of Cardiology, The Second Clinical Hospital Affiliated to University of South China, Hengyang, Hunan, China; and*
[d]*Department of Cardiovascular, The Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi Province, China*

Manuscript received July 19, 2016 and accepted January 24, 2017

Abstract

Liddle's syndrome, an autosomal dominant form of monogenic hypertension, is characterized by salt-sensitive hypertension with early penetrance, hypokalemia, metabolic alkalosis, suppression of plasma rennin activity and aldosterone secretion, and a clear-cut response to epithelial sodium channel blockers but not spironolactone therapy. Here, we describe the case of a 16-year-old boy patient with resistant hypertension (maintain 170–180/100–110 mm Hg after administration four kinds of antiypertensive drugs) and severe hypokalemia. After a series of checks, we exclude primary aldosteronism and renal artery stenosis and other diseases. Finally, the Liddle syndrome was diagnosed because of the DNA sequencing found that the proband's mother and himself had mutations P616L (c.1847 C>T) in the SCNN1B gene. Liddle syndrome should be considered as a cause of hypertension in children or adolescents particularly with suppressed renin activity. Early diagnosis and appropriately tailored treatment avoid complications of long-term unrecognized or inappropriately managed hypertension. Genetic testing has made it possible to make accurate diagnoses and develop tailored therapies for mutation carriers. The role of genetic testing and genetic counseling in establishing the early diagnosis of Liddle's syndrome is important. J Am Soc Hypertens 2017;■(■):1–4.

Keywords: Genetic diagnosis; Liddle's syndrome; precision medical.

Introduction

Hypertension continues to be one of the leading causes of morbidity and mortality among adults worldwide. Fewer than 20% of cases have a secondary (ie, nonessential) etiology. However, it is important to diagnose and treat secondary hypertension at an early stage because most forms of secondary hypertension are highly responsive to properly directed treatment.[1] The incidence of secondary hypertension among children is estimated to be between 1% and 5%.[2] Hyperaldosteronism (primary or secondary) is one potential cause of secondary hypertension, particularly in cases that are associated with severe hypokalemia.[3] Low potassium levels can induce a variety of cardiac conduction blocks and arrhythmias. Potassium deficiencies also play a role in delayed long-term growth and development.[3] Here, we report the case of a 16-year-old boy with resistant hypertension and severe hypokalemia.

Case Presentation

A 16-year-old male from Shandong province, China, was admitted to our facility complaining of weakness. His blood

Conflict of interest: This case report was not funded. The authors have received no payment in preparation of this article.

Ethical standard: The patient gave his informed consent before publication. No violation of ethical standards was committed.

*Corresponding author: Long Jiang, MD, PhD, Department of Cardiovascular, Institute of Cardiovascular Disease, The Second Affiliated Hospital of Nanchang University, Nanchang 330006, Jiangxi Province, China. Tel: +86-18301378271; Fax: +86-0791-86262262.

E-mail: skyiadx@hotmail.com

[1] First authors: Ze-Min Kuang, deputy chief physician, Beijing AnZhen Hospital, Affiliated to Capital Medical University, Hypertension Division, 2 Anzhen Road, Chaoyang District, Beijing 100029, China. E-mail: kuangzemin@outlook.com.

1933-1711/$ - see front matter
http://dx.doi.org/10.1016/j.jash.2017.01.012

pressure was severely elevated at 190/110 mm Hg. He was first noted to have severely elevated blood pressure at age 13 years and was treated with a combination tablet consisting of hydrochlorothiazide 12.5 mg, triamterene 12.5 mg, dihydralazine sulfate 12.5 mg, and reserpine 0.1 mg given once daily. He reported a family history of hypertension in his mother who was diagnosed at age 40 years. Laboratory testing revealed a very low blood potassium level of 1.8 mmol/L. He denied a history of vomiting, diarrhea, or use of medications associated with hypokalemia. His potassium was restored to a normal level, and he was started on antihypertensive therapy with a combination of nifedipine sustained release 20 mg twice daily, enalapril 20 mg twice daily, spironolactone 40 mg three times daily, and terazosin hydrochloride 2 mg once daily. Despite this therapy, blood pressure remained significantly elevated ranging from 150 to 160/100 to 110 mm Hg and he noted a return of generalized weakness. Repeat blood potassium was again very low at 1.93 mmol/L. Blood pressure further increased to 260/160 mm Hg, and his treatment program was changed to include nifedipine sustained release 30 mg twice daily, telmisartan 40 mg twice daily, terazosin 2 mg once daily, and spironolactone 40 mg three times daily. Blood pressure remained severely elevated ranging from 170 to 180/100 to 110 mm Hg. Because of the early onset of severe hypertension and unexplained hypokalemia, a secondary form of hypertension was considered. Cushing's syndrome was excluded because of normal serum cortisol levels (midnight, 1.04 μg/dL, 8 AM 11.12 μg/dL, and 4 PM 7.67 μg/dL) and a lack of physical findings consistent with this disorder. There was no history of exogenous mineralocorticoid use; 11-beta-HSD deficiency was excluded based on normal cortisol and aldosterone levels and no findings of premature puberty. Renal artery stenosis was excluded based on a normal renal artery color Doppler ultrasound and a low plasma renin activity. Pheochromocytoma was excluded on the basis of normal plasma catecholamine levels and a negative CT scan of the adrenal glands. The aldosterone-to-renin ratio (ARR) was noted to be elevated, and further evaluation for primary aldosterone was carried out with a captopril suppression test which was interpreted as negative (Table 1). The normal CT scan of the adrenal glands and lack of blood pressure response or hypokalemia to spironolactone were also considered to be inconsistent with primary aldosteronism.

Because of the patient's low blood potassium level, low renin level, and the ineffectiveness of spironolactone treatment, Liddle's syndrome was suspected. Genetic analysis to confirm this diagnosis involved DNA sequencing of two pathogenic genes (SCNN1B and SCNN1G[4]). We found a heterozygous missense mutation (c. 1847 C>T, P616L) in the SCNN1B gene. The frequency of this mutation in the population is very low, and an in vivo study has shown that this mutation may lead to sustained sodium channel activation, thus resulting in sodium retention.[5]

DNA analysis of the patient's first-degree relatives (his parents) showed that his mother had an identical heterozygous mutation. The patient's mother had hypertension without hypokalemia. Extended release nifedipine tablets (30 mg/qd) were used to maintain her blood pressure at 120/80 mm Hg. The family history further revealed that the maternal grandmother, who had hypertension and died suddenly at 50 years of age of a cerebral hemorrhage, may have been a mutation carrier. Other relatives, including his maternal grandfather and uncles, had no history of hypertension (Figure 1). After considering the results from the genetic analysis and his family history, the patient was finally diagnosed with Liddle's syndrome.

Discussion

Liddle's syndrome is an autosomal dominant form of monogenic hypertension and exhibits a clear response to epithelial sodium channel (ENaC) blockers.[6] Little is known about the prevalence of Liddle's syndrome.[7] It is important to screen for this condition in patients with hypertension and hypokalemia because the treatment for Liddle's syndrome differs from treatment for other forms of essential or secondary hypertension. Potassium-sparing diuretics, such as amiloride and triamterene, which directly block sodium channels, are effective treatments for Liddle's syndrome.

The genetic basis of Liddle's syndrome is the mutation of the gene encoding ENaC, which included three homologous subunits: α, β, and γ. These subunits are encoded

Table 1
The result of captopril suppression test

Index	Seated (Before Interpretation)	Seated (After Interpretation)
Renin (ng/mL/h)	0.01 (0.93–6.56)	0.10
Angiotensin (pg/mL)	43.63 (55.30–115.30)	40.78
Aldosterone (ng/mL)	0.14 (0.065–0.296)	0.07
ARR (ng/dL ng/mL/h)	1400 (>30)	70

ARR, aldosterone to renin ratio.