Liddle's syndrome variant: a diagnostic and therapeutic conundrum

Introduction

Liddle's syndrome is a rare inherited disease characterized by abnormal sodium reabsorption in the distal renal tubule leading to severe hypertension and hypokalaemia. This article reports the case of a 43-year-old hypertensive woman who presented with ventricular fibrillation following acute myocardial infarction. In this case the hypertension, which was associated with hypokalaemia but without any other accompanying endocrine abnormalities, proved refractory to conventional pharmacotherapy including spironolactone. However, treatment with amiloride resulted in prompt normalisation of serum potassium levels and blood pressure and, importantly, sustained maintenance of a stable cardiac rhythm. Although genetic analysis for known Liddle's syndrome mutations was unyielding in this case, the likely diagnosis is Liddle's syndrome variant.

Discussion

Sodium transport across epithelial cells occurs through the epithelial sodium channel (Snyder et al, 1994). This channel is therefore critical for Na^+ homeostasis and blood pressure control, and defects in epithelial sodium channel regulation and function are known to cause inherited forms of hypertension. The channel is made up of α, β and γ subunits – all three are required for normal activity. The channel is highly selective for Na^+ over K^+, and is selectively blocked by the diuretic amiloride.

Liddle's syndrome was first described in 1963 (Liddle et al, 1963) as a familial condition causing hypertension and hypokalaemia, but with low levels of aldosterone. Mutations causing Liddle's syndrome have been mapped mostly to the gene encoding the β-subunit of the epithelial sodium channel, the SCNN1B gene, but also to the SCNN1G gene encoding the γ-subunit (Cotton and Scriver, 1998; Wang et al, 2006; Kryukov et al, 2007; Rossi et al, 2008). The defects all seem to increase cell surface expression of the epithelial sodium channel at the apical membrane, thus increasing Na^+ ion flux from the tubular fluid into the epithelial cell, either by increased epithelial sodium channel trafficking to the membrane or more likely by decreased rates of endocytosis.

Dr Amit KJ Mandal, Consultant, Departments of Cardiology and Medicine, Wexham Park Hospital, Frimley Health NHS Foundation Trust, Slough, Berkshire

Dr Kyriacos Mouyis, Specialist Registrar, Departments of Cardiology and Medicine, Wexham Park Hospital, Frimley Health NHS Foundation Trust, Slough, Berkshire

Dr Ian AL Walker, Consultant, Departments of Clinical Chemistry and Cardiology, Wexham Park Hospital, Frimley Health NHS Foundation Trust, Slough, Berkshire

Professor Constantinos G Missouris, Consultant and Professor, Departments of Cardiology and Medicine, Wexham Park Hospital, Frimley Health NHS Foundation Trust, Slough, Berkshire SL2 4HL, and University of Cyprus Medical School, Nicosia, Cyprus

Correspondence to: Professor CG Missouris (dinos.missouris@nhs.net)

CASE REPORT

A 43-year-old hypertensive woman who was taking propranolol 80 mg daily presented to the authors' service in 1996 with acute inferior myocardial infarction. Her hypertensive mother and grandfather had died from myocardial infarction at the ages of 61 years and 50 years respectively. Her sister suffered with pre-eclampsia, and her brother had been diagnosed with hypertension at the age of 19 years.

On admission her blood pressure was 164/102 mmHg. Biochemical investigations revealed creatinine kinase-myocardial band (CKMB) 69 IU/litre (reference <25 IU/litre), serum potassium (K^+) 2.8 mmol/litre, sodium (Na^+) 138 mmol/litre and creatinine 59 µmol/litre. Left heart catheterization demonstrated an occluded posterior descending coronary artery and the rest of the coronary tree was unobstructed. Owing to the small calibre of the culprit vessel, the patient was managed medically with optimal risk factor control.

Four years later she re-presented with acute anteroseptal myocardial infarction, again in the context of uncontrolled hypertension. She was on treatment with diltiazem SR 120 mg twice daily, atenolol 25 mg daily, perindopril 4 mg daily, in addition to aspirin 75 mg daily and pravastatin 40 mg daily. Biochemistry results were as follows: Na+ 141 mmol/litre, K+ 3.3 mmo/litre and creatinine 60 µmol/litre. During coronary reperfusion therapy with thrombolyis she developed ventricular fibrillation requiring emergency cardioversion which was successful in restoring sinus rhythm.

Two months later the patient returned for review at which point her blood pressure was 180/102 mmHg. Plasma renin activity and aldosterone levels taken in the morning while the patient was ambulant, after a 2-week drug-free period with no variation in dietary sodium balance (and no liquorice ingestion), were 0.3 pmol/ml/hr (normal range 0.5–3.1 pmol/ml/hr) and 149 pmol/litre (normal range 100–800 pmol/litre) respectively, thereby excluding a diagnosis of primary hyperaldosteronism. Dexamethasone suppression test, urinary free cortisol, stimulated serum 17-hydroxyprogesterone, urine catecholamine excretion and urinary calcium excretion were within normal limits. 24-hour urine collection for adrenal steroid metabolites was normal, thereby excluding hypertensive forms of congenital adrenal hyperplasia, glucocorticoid resistance and the syndrome of apparent mineralocorticoid excess (11β-hydroxysteroid dehydrogenase II deficiency). Genetic analysis for Liddle's syndrome mutations was negative (performed by Professor Richard Lifton, Yale University, USA).

The patient's blood pressure was resistant to polypharmacy and her hypokalaemia failed to respond to treatment with spironolactone (25 mg daily for 4 weeks followed by 50 mg daily for a further 4 weeks). However, empirical treatment with amiloride (initially at 5 mg daily and increasing by 5 mg daily up to 20 mg daily) resulted in normalisation of both serum potassium levels and blood pressure within 1 week.

In this patient none of the recognized mutations known to cause Liddle's syndrome were found. However, the normal urinary steroid excretion profile and the response to amiloride but not to spironolactone is highly suggestive of unregulated activation of the renal tubular Na+ transport, caused by an as-yet unidentified mutation in this family which is likely to have been transmitted with autosomal dominant inheritance.

This report demonstrates that patients with hypertension and hypokalaemia, without associated endocrine abnormalities, who respond to treatment with amiloride but not to spironolactone, are likely to have a diagnosis of Liddle's syndrome or its variant. Treatment with amiloride is safe, effective and likely to reduce arrhythmic events following acute myocardial ischaemia and infarction in these patients. **BJHM**

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LEARNING POINTS

- Early onset, resistant hypertension with hypokalaemia should prompt investigation for Liddle's syndrome and exclusion of other secondary causes of hypertension.
- Genetic analysis for Liddle's syndrome is indicated in patients with a family history of hypertension suggestive of autosomal dominant expression.
- Targeted treatment involves potassium-sparing diuretics, such as amiloride, which selectively block epithelial sodium channel activity. Conventional antihypertensive agents are ineffective.
- Response to amiloride without recurrence of hypertension and hypokalaemia supports a diagnosis of Liddle's syndrome.
- By normalizing blood pressure and correcting potassium levels, amiloride afforded a membrane-stabilizing effect, therefore reducing further arrhythmias.

A surprising chest radiograph

A 97-year-old woman's routine admission chest radiograph showed a peculiar undulating tubular structure overlying the cardiac shadow in the upper to mid thoracic zone. Clinical examination was unremarkable. The patient was noted to be producing copious amounts of white phlegm and was reported to have a reduced oral intake with no symptoms of dysphagia or regurgitation. A collateral history confirmed the diagnosis of achalasia.

Achalasia is a rare gastroenterological condition (Schlottmann and Patti, 2018), and this case highlights an uncommon incidental finding of achalasia on a chest radiograph. **BJHM**

Dr Ryian Mohamed, ST1, Department of Ophthalmology, Central Middlesex Hospital, London NW10 7NS

Dr Rakesh Dattani, ST3, Department of Renal Medicine, Hammersmith Hospital, London

Dr Charles Cayley, Consultant, Department of Care of the Elderly, Central Middlesex Hospital, London

Correspondence to: Dr R Mohamed (m0601207@gmail.com)

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Figure 1. Chest radiograph showing achalasia. The abnormality is in the upper and mid zones; its course is mapped by the red arrows.