Liquorice, Liddle, Bartter or Gitelman - how to differentiate?

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Abstract

Hypokalaemia with alkalosis can suggest excess aldosterone. Aldosterone stimulates the collecting duct mineralocorticoid receptor (MR) to upregulate the epithelial sodium channel (ENaC) and stimulate electrogenic sodium reabsorption, with secretion of potassium and protons. Gitelman, Bartter and Liddle syndrome, and liquorice ingestion all cause hypokalaemic alkalosis. This mini-review outlines the pathophysiology of these conditions as well as how to differentiate them.

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Bartter and **Gitelman syndromes** are recessively inherited salt-wasting disorders associated with secondary hyperaldosteronism and (usually) a low blood pressure.

Gitelman syndrome is caused by inactivating mutations of *SLC12A3* that encodes the thiazide-sensitive Sodium Chloride cotransporter (NCC) in the distal convoluted tubule (DCT) (1). Diagnosis can be incidental following the finding of hypokalemia on routine blood testing. The hallmark of hypocalciuria can be associated with ectopic calcification (chondrocalcinosis, sclerochoroidal calcification); urinary magnesium wasting can lead to hypomagnesemia (2).

Bartter syndrome includes several genetic defects that affect sodium transport in the thick ascending limb (see Figure1). The salt-wasting phenotype is generally more severe than in Gitelman, and the diagnosis is often made earlier in infancy. There is hypercalciuria, which can cause nephrolithiasis or nephrocalcinosis (3). Apart from Type 3 (see below), there is little magnesium wasting (4). The most widely used classification is based on the five known underlying gene defects (reviewed by Seyberth(5)):

Type 1 (*SLC12A1* encodes NKCC2) and Type 2 (KCNJ1 encodes ROMK) may present antenatally with polyhydramnios; children are prone to dehydration and growth retardation.

Type 3 (*CLCNKB* encodes one of the basolateral chloride channels ClC-kb) is the commonest form; the phenotype is often mild. ClC-kb is also present in the DCT and the phenotype can be similar to Gitelman.

Type 4 is caused by genetic inactivation of both basolateral chloride channels, usually by mutations of the chaperone barttin (*BSND*); it also causes sensorineural deafness.

Type 5 has been assigned to either a Bartter-like syndrome caused by gain-of-function mutations of the calcium sensing receptor (*CaSR*) or X-linked polyhydramnios and transient infantile salt-wasting (*MAGED2*).

The mainstay of treatment in Gitelman and Bartter is sodium, potassium and magnesium supplementation.

Liddle syndrome and **chronic liquorice ingestion** also cause hypokalaemia, but with hypertension and aldosterone suppression.

Liddle syndrome is due to autosomal dominant *ENaC* gain-of-function mutations(6), leading to suppression of renin and aldosterone (7). It presents early in life with hypertension, hypokalaemia and alkalosis, although presentation in adulthood has been reported. Liddle is responsive to amiloride or triamterene; spironolactone is ineffective.

Liquorice contains glycyrrhizinc acid (GZA), which inhibits the enzyme that prevents cortisol from activating the MR, 11-beta-hydroxysteroid dehydrogenase (11βHSD) (8). Since cortisol levels are 1000x greater than aldosterone, 11βHSD inhibition

leads to MR over-stimulation, causing hypokalaemia, metabolic alkalosis and hypertension (9). The syndrome of Apparent Mineralocorticoid Excess is caused by recessive loss-of-function mutations in 11βHSD and has the same phenotype (10).

Liquorice is a popular European confectionary; the Dutch consume an estimated 2 kg/person/year. Carbenoxolone is a derivative of GZA that also inhibits gastric and intestinal prostaglandin breakdown, and was a popular treatment for peptic ulcers, but has similar blood pressure and electrolyte complications to liquorice excess. Reduced 11βHSD activity can be detected by an increase in the cortisol to cortisone ratio in blood or urine.

These hypokalaemic metabolic alkaloses can be differentiated by blood pressure, age of onset, serum and urinary biochemistry (Table 1). Appreciation of the molecular basis of these syndromes helps in understanding their diagnosis and treatment.

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Figure Legends

Figure 1

This is a simplified cartoon of a single nephron. Inset panels show diagrams of renal tubular cells showing significant membrane transport proteins in (from bottom left, going clockwise), a thick ascending limb cell of the loop of Henle, a distal convoluted tubular cell and a principal cell in the cortical collecting duct.

Na+,K+,ATPase is the ubiquitous sodium potassium pump present in all cells. In the distal convoluted cell, potassium can exit the cell via the potassium channels ROMK (renal outer medullary potassium channel) and KCNJ10. Magnesium enters the cell via the (transient receptor potential channel) TRPM6 and calcium enters the cell via TRPV5 and exits via the sodium calcium exchanger NCX.

Table 1: The differentiating features of liquorice ingestion, Gitelman, Bartter and Liddle syndromes.

Disorder	Onset	Inheritance	Potassium	Blood pressure	Aldosterone	Other features
Liquorice	-	-	Low	High	Suppressed	
Liddle's	Children	Autosomal dominant	Low	High	Suppressed	
Bartter's	Children (90% neonatal)	Autosomal recessive	Low	Normal to Low	Elevated	Hypercalciuria (possibly nephrocalcinosis)
Gitelman's	Adults	Autosomal dominant	Low	Low	Elevated	Hypocalciuria, low serum magnesium

CoI statement:

None of the authors (E.M, R.J.U, S.B.W) declare any conflict of interest in authoring this manuscript.

Funding:

The authors have no funding to disclose.

Keywords:

Hypokalaemia, Gitelman, Bartter, Liddle, Liquorice