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Case Reports

Gitelman's Syndrome: Asymptomatic Hypokalaemia in a Chinese Boy

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Abstract Gitelman's syndrome is a rare heritable primary renal tubular disorder, characterised by hypokalaemic metabolic alkalosis, hypomagnesaemia and hypocalciuria. Most of them run a benign course. If present, symptoms include fatigue and muscle weakness. Rarely serious symptoms like cardiac arrest have been reported. Treatment is by magnesium supplement, potassium supplement or potassium-sparing diuretics. This report reviews incidental finding of Gitelman syndrome in an asymptomatic teenager and emphasizes clinical, laboratory and molecular features of the disease.

Key words Gitelman's syndrome; Hypokalaemia; Hypocalciuria; Hypomagnesaemia

Case Report

A 9-year-old Chinese boy presented to the casualty department of a local hospital in Hong Kong for 3-day history of fever with cough and sputum sound, which were progressive in severity. All along he enjoyed good past health and did not report any muscle weakness, cramps or tetany. His history was unremarkable for vomiting, diarrhoea and diuretic or laxative use. He did not have any family history of muscle weakness or electrolyte disturbance. His parents were non-consanguineous.

Physical examination on admission showed normal blood pressure. He was not in respiratory distress or toxic looking. There were crepitations over bilateral lung bases. His thyroid gland was not enlarged. He had neither neurological deficit nor muscle weakness.

He was treated with one course of Azithromycin for pneumonia. His fever subsided 2 days after admission and his respiratory symptoms gradually resolved.

Laboratory investigations on admission (Table 1) showed mildly elevated white blood cells and C-reactive protein. Marked hypokalaemia (down to 1.9 mmol/L) was the most striking biochemical abnormality. He was at first replaced by high doses of syrup potassium chloride. However, this could only transiently maintain his serum potassium level. He had rebound hypokalaemia one day after initial normalisation, till a second bolus of syrup potassium chloride was given. Nonetheless, he remained asymptomatic and his electrocardiogram tracing showed normal sinus rhythm without features of hypokalaemia (i.e. no flattening of T wave, inverted T wave, U wave, depression of ST segment, decreased QRS voltage or prolonged PR or QT interval) throughout the hospitalisation period.

Further investigations (Table 1) in exploring the cause of hypokalaemia were proceeded.[1] His thyroid function was normal. His transtubular potassium gradient (TTKG), calculated by [urine/plasma potassium]/[urine/plasma osmolarity], when his urinary osmolality exceeded plasma osmolality, was 17.3. His urine potassium-creatinine (K-Cr) ratio was 19.6 mmol/mmol. Both of his TTKG and K-Cr ratio suggested renal loss of potassium. With

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metabolic alkalosis, hypomagnesaemia, normocalcaemia, hypocalciuria (spot and 24-hour urine collection) and elevated renin and aldosterone in this nomotensive patient, the clinical diagnosis of Gitelman's syndrome was made. His genetic analysis revealed three heterozygous mutations of SLC12A3 gene (c.488C>T (p.THr163Met), c2612G>A (p.Arg871His) and c.3053G>A (p.Arg1018G1n)). The first two mutations have been described in Chinese patients with Gitelman's syndrome, while the latter mutation has been reported in at least one patient with Gitelman's syndrome.

He was treated with potassium sustained release tablets, three times per day. His serum potassium level was normalised one week after gradual titration of medication. Daily supplement with magnesium lactate was later added.

Table 1 Laboratory investigations

Parameters	Value	Reference range (unit)
Blood		
Haemoglobin	10.3	11.5-15.5 (g/dL)
White blood cells	16.2	4.5-13.5 x 10^9 (/L)
Neutrophils	10.5	1.8-8.0 x 10^9 (/L)
Platelet	595	150-400 x 10^9 (/L)
Sodium	133	137-144 (mmol/L)
Potassium	1.9	3.5-5.0 (mmol/L)
Urea	4.0	3.1-7.8 (mmol/L)
Creatinine	57	34-65 (mmol/L)
C-reactive protein	99.8	<9.9 (mg/L)
Calcium (adjusted)	2.16	2.15-2.55 (mmol/L)
Phosphate	1.11	0.72-1.39 (mmol/L)
Magnesium	0.55	0.66-1.07 (mmol/L)
Chloride	106	98-107 (mmol/L)
Glucose, random	6.0	≤7.8 (mmol/L)
Blood gas, venous	pH 7.53	7.35-7.45
Base excess	+3	-2 to +3 (mmol/L)
Osmolarity	270	275-295 (mOsm/kg)
Renin	10.8	1.31-3.95
Aldosterone	990	111-862
TSH	2.0	0.28-4.3 (mIU/L)
Spot urine		
Potassium	55.6	N/A (mmol/L)
Calcium	<0.5	N/A (mmol/L)
Creatinine	2.84	N/A (mmol/L)
Osmolarity	331	50-1400 (mOsm/kg)
pH	7.1	4.5-8.0
K-Cr ratio	19.6	N/A (mmol/mmol)
TTKG	17.3	N/A
24-hour urine collection		
Calcium	<0.4	2.0-7.4 (mmol/day)
Creatinine	5.66	9.00-21.00 (mmol/day)
24-hour urine Ca/Cr	<0.07	<0.2 (mmol/mmol)

N/A: not applicable; TSH: thyroid stimulating hormone; K-Cr: potassium-creatinine; TTKG: transtubular potassium gradient; Ca/Cr: calcium/creatinine

He remained asymptomatic and normokalaemic after 2 months of follow up.

Discussion

Gitelman's syndrome, also known as familial hypokalaemia-hypomagnesaemia, is a rare primary salt-losing renal tubular disorder first reported by Gitelman et al in 1966.[2] It is inherited as autosomal recessive traits. The prevalence is estimated approximately at 1 in 40000 inhabitants. No gender difference is observed.

The clinical manifestations are caused by loss-of-function mutations in the solute carrier family, member 3 (SLC12A3) gene, which encodes thiazide sensitive NaCl co-transporter (NCCT) in the distal convoluted tubules.[3,4] To date, there have been more than 180 different NCCT mutations reported in the literature, but negative genetic screening may be encountered. Detection of large genomic rearrangement explains the negative genetic finding. Normally homozygous and combined heterozygous mutations are expected in Gitelman's syndrome as it is inherited in autosomal recessive trait. However, in a large cohort study of 448 patients in whom Gitelman's syndrome was suspected, by direct sequencing analysis, two affected alleles were only identified in 315 patients (70%). One affected allele was identified in 81 patients (18%). By identifying genomic rearrangement by multiplex ligation-dependent probe amplification (MLPA) and quantitative multiplex polymerase chain reaction of short fluorescent fragments (QMPSF), mutation detection rate has been improved to 91%.[5]

The inactivated NCCT can explain most, but not all, features of Gitelman's syndrome. Reduced sodium reabsorption leads to increased delivery of sodium to collecting ducts and secondary volume depletion. The intravascular volume contraction stimulates sodium reabsorption in the collecting duct via upregulation of renin-angiotension-aldosterone system, maintaining sodium homeostasis at the expense of increased potassium and hydrogen ion secretion. This results in hypokalaemia and metabolic alkalosis.

NCCT inactivation also contributes to reduced chloride absorption hence raised renal tubular calcium reabsorption, which is a discernible parameter from Bartter's syndrome (which often conversely has hypercalciuria). In addition to decreased urinary calcium excretion, majority of Gitelman's syndrome also has mild degree of hypomagnesaemia, which is not a constant finding in Bartter's syndrome.

However, the exact mechanism of hypocalciuria and hypomagnesaemia in Gitelman's syndrome is still not fully understood.

Clinical symptoms of Gitelman's syndrome include fatigue, cramps, muscle weakness, carpopedal spasms, salt craving and rarely serious symptoms such as paralysis and cardiac arrest. Growth retardation may also be seen in Gitelman's syndrome but not as frequent as in Bartter's syndrome. Ten percent of patients have prolongation of QT interval. Most symptomatic patients present during periods of fever or when extra magnesium is lost during vomiting or diarrhoea. However, many of the patients with Gitelman's syndrome remain asymptomatic during neonatal, infancy and preschool years.[4] Often hypokalaemia is only detected during routine blood taking for other reasons, as in our patient. Even so, one cohort study of 50 adult patients with Gitelman's syndrome showed a lower quality of life score compared with controls in terms of musculoskeletal, renal, paresthesia and palpitation.[6]

Antenatal/neonatal Bartter's syndrome, classical Bartter's syndrome and Gitelman's syndrome are three phenotypes of Bartter-like diseases that have now been recognised. Until its genetic background has been unraveled since 1996, previously Gitelman's syndrome is mistaken as a "milder form" of Bartter's syndrome, the site of defect in the latter is now recognised in the thick ascending limb of loop of Henle. Defective chloride transport leads to loss of sodium and calcium, activation of renin-aldosterone system and loss of potassium. Bartter's syndrome has been classified into 5 types.

Patients with Bartter's syndrome usually present early in childhood and the failure to thrive is more severe and with a greater degree of growth retardation. Gitelman's syndrome is associated with no or much milder failure to thrive and growth retardation. Nonetheless, they share similar physiologic derangements including hypokalaemic, hypochloremic metabolic alkalosis (except type II Bartter's syndrome which initially presents with transient hyperkalaemic metabolic acidosis), high renin and aldosterone with increased urinary excretion of Na+, Cl- and K+.[7] Table 2 summarises the clinical presentations, biochemical parameters and genetic mutations of Gitelman's and Bartter's syndrome.[7,8]

The diagnosis of Gitelman's syndrome in this patient was made from laboratory investigation findings including hypokalaemia, hypomagnesaemia, metabolic alkalosis and hypocalciuria. Molecular analysis further confirmed the diagnosis.

Treatment of Gitelman's syndrome is mainly symptomatic by supplementation of potassium chloride and magnesium chloride. Observation of chondrocalcinosis with persistent magnesium deficiency favours supplementation of magnesium. However, normalisation of serum magnesium is difficult since high dose of magnesium causes diarrhoea. Sometimes aldosterone antagonists are required to correct and maintain serum potassium level. Patients are encouraged to maintain a high-salt diet. The long-term prognosis of Gitelman's syndrome, in terms of growth and life expectancy, is favourable.

Conclusion

This case demonstrated a classical case of Gitelman's syndrome. He had fulfilled most of the diagnostic criteria for Gitelman's syndrome including normotensive

Table 2 Summary of genetic and clinical features of different subtypes of Bartter's and Gitelman's syndrome

	Gene locus	Gene	Gene product	Renal defect	Clinical features
Bartter's syndrome					
Type I	15q15-21	SLC12A1	NKCC2	TAL	Polyhydramnios, prematurity, polyuria, nephrocalcinosis
Type II	11q24-25	KCNJ1	ROMK	TAL	Polyhydramnios, prematurity, polyuria, nephrocalcinosis, transient hyperkalaemic acidosis
Type III	1p36	CLCNKB	CLC-Kb	TAL	No nephrocalcinosis
Type IV	1p31	BSND	Barttin	TAL	Sensorineural deafness, no nephrocalcinosis
Type V	3q13.3-q21	CASR	CASR	TAL	Hypocalcaemia, suppressed PTH
Gitelman's syndrome					
	16q13	SLC12A3	NCCT	Distal tubule	Hypocalciuria, hypomagnesaemia

TAL: Thick ascending limb of the loop of Henle; KCNJ1: K channel subfamily J member 1; NKCC2: furosemide-sensitive Na-K-Cl cotransporter; ROMK: renal outer-medullary K channel; CLCNKB: chloride channel Kb; BSND: Bartter's syndrome sensorineural deafness; CASR: calcium-sensing receptor); SLC12A3: solute carrier family 12 member 3; PTH: parathyroid hormone; NCCT: NaCl co-transporter.

hypokalaemic metabolic alkalosis, hypomagnesaemia and hypocalciuria. His age group with normal physical examination further confirms the diagnosis. Electrolyte disturbance was resolved with potassium and magnesium supplementation. Hypocalciuria and hypomagnesaemia are two parameters that distinguish it from Bartter's syndrome. In addition, diagnosis of Gitelman's syndrome is feasible by genetic analysis.

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