MEGA JOURNAL OF CASE REPORTS

Case Presentation

Compiled Date: May 06, 2023

Gitelman Syndrome without Activation of Renin-Angiotensin-Aldosterone System (RASS) - A Case Report

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Abstract

Gitelman syndrome (GS) is a rare autosomal recessive hereditary disorder, presented as salt-losing tubulopathy. The clinical manifestations of the disease are various and the severity of clinical symptoms correlates with the degree of hypokalemia and hypomagnesaemia, although there are inter-individual variations. We present the case of a 65-year-old Chinese woman with genetically confirmed GS and atypical clinical manifestation with normal plasma aldosterone and renin levels. The patient with hypokalemia-induced metabolic alkalosis, normal blood magnesium, increased excretion of both urinary calcium and urinary potassium, in spite of non-significant activation of the Renin-Angiotensin-Aldosterone System (RASS). The diuretic loading tests of Thiazide loading test and Furosemide loading test were performed, of which showed a weaker response to thiazide and a good response to furosemide. On the basis of genetic testing, one pathogenic mutation related of c.2891G>A (p.R964Q) and the other uncertain significance mutation of c.505+58C>T in the SLC12A3 gene were confirmed the diagnosis of GS. We presented a case of genetically confirmed GS manifested as non-activation of RAAS in a Chinese female. Therefore, the heterogeneity of the clinical manifestations of GS is currently thought to be related not only to the type of mutation and modified genes, but also to environmental factors such as the gender of the patient and dietary habits. We presumed that whether RASS activated or not may paralleled with the severity of GS, the extent of potassium loss may contribute to the degree of activation of RASS.

Keywords: Gitelman syndrome; Hypokalemia; The diuretic loading test; Non-activation of RAAS

Abbreviations: GS: Gitelman Syndrome; RASS: Renin-Angiotensin-Aldosterone System; SLC12A3: Solute Carrier Family 12 Member 3; KDIGO: Kidney Disease: Improving Global Outcomes; BS Bartter syndrome; NCC: Sodium-Chloride Co-transporter; PRA: Plasma Renin Activity; DCT: Distal Convoluted Tubule

Introduction

Gitelman Syndrome (GS) is a rare autosomal recessive hereditary disorder, presented as salt-losing tubulopathy. The disease is characterized by renal potassium wasting, hypokalemia, metabolic alkalosis, hypocalciuria, hypomagnesemia, and hyperreninemic hyperaldosteronism, with normal or low blood pressure **[1].** The disease is caused by loss-of-function mutations in Solute Carrier Family 12 Member 3 (SLC12A3) gene, which encodes the renal thiazide-sensitive Sodium-Chloride Co-transporter (NCC) located in the apical membranes of cells in the first part of the Distal Convoluted Tubule (DCT) cells **[2,3].** The clinical manifestations of the disease are various and the severity of clinical symptoms correlates with the degree of hypokalemia and hypomagnesaemia, although there are inter-individual variations **[4,5].** According to the consensus developed by KDIGO experts and the consensus conducted by Chinese experts for the diagnosis and treatment of GS in China, genetic diagnosis is required to confirm the diagnosis of the disease. GS is treated with symptomatic treatment and electrolyte replacement therapy with the aim of achieving symptomatic relief, improving quality of life and avoiding serious complications **[6,7].** We present, a case of Chinese woman with genetically confirmed GS and atypical clinical manifestation with normal plasma aldosterone and renin levels.

Case Presentation

A 65-year-old female patient was admitted to our hospital in November, 2021 due to recurrent limb fatigue for six years and aggravating for 12 days. Six years ago, after taking amoxicillin for a cold, the patient developed a generalized rash with fever, cold sweats, palpitations, fatigue of the limbs, numbness and dizziness, without unconsciousness or syncope. Hypokalemia was revealed in a local hospital during the hospitalization. The symptoms disappeared after treatment with anti-allergic drugs and potassium supplementation, the amount of which was not known. Over the past 6 years, the patient has had recurrent symptoms of limb fatigue at a frequency of once a year, which was relieved by potassium supplementation. The patient suffered from limb fatigue and palpitation again after dinner 12 days ago. She was admitted to the cardiology department of our hospital of whom blood potassium level was 3.5 mmol/L with oral potassium supplementation taken. In the medical history so far, the patient denied the presence of hypertension; the patient denied taking diuretics, laxatives, glucocorticoid, unidentified Chinese herbal medicines, licorice and its preparations; the patient denied significant change in weight, significant change in food taken, recurrent diarrhea, recurrent episodes of urinary frequency, urgency or pain, fever, significant change in urine output. The patient had little significant weight loss recently. The patient was diagnosed with paroxysmal atrial fibrillation for 3 years, who was not treated by standardized treatment protocols of sinus rhythm control and ventricular rate control. The patient presented with palpitations with complete ECG findings suggestive of atrial fibrillation, which lasted for about 1 day and resolved after treatment with cardioversion and potassium supplementation. The patient's family history was not burdened with kidney and genetic diseases. Her parents were passed away and non-consanguineous marriage; Her father was diagnosed with hypertension. Physical examination revealed normal status with a BMI of 21.56 kg/m2, without signs of cushingoid features. Blood Pressure (BP) values were 113/76 mmHg. The results of

laboratory test regarding urinalysis and blood serum are presented in the following **Table 1.1, 1.2 and 2.** A Computed Tomography (CT) revealed normal anatomy of adrenal glands.

Table 1.1: The results of biochemical tests of serum and blood gas analysis at the baseline.

Laboratory parameter	Value or range	Normal range
Serum biochemistry		
Potassium (mmol/L)	3.1	3.5-5.3
Magnesium (mmol/L)	2.20	1.12-2.16
Calcium (mmol/L)	1.96	2.11-2.52
Sodium (mmol/L)	144.9	137-147
Chloride (mmol/L)	107.9	99-110
Phosphate (mmol/L)	1.20	0.85-1.51
Creatinine (μmol/L)	53.40	41-81
Estimated Glomerular filtration (eGFR) according to CKD-EPI (mL/min/1.73m2)	95.44	>90
Albumin (g/L)	39.7	35-55
Cholesterol (mmol/L)	2.86	2.8-5.2
Triglycerides (mmol/L)	0.85	0.56-1.7
AST (IU/L)	26	13-35
ALT (IU/L)	28	7-40
Alkaline phosphatase (IU/L)	94	35-135
Glucose (mmol/L)	3.79	3.9-6.1
HbA1c (%)	5.4	4-6
Cortisone (8am) (nmol/L)	543.4	171-536
Cortisone (4pm) (nmol/L)	334.2	64-327
Cortisone (0am) (nmol/L)	49.13	-
ACTH (pg/ml)	19.20	ND-46
Arterial blood gas analysis		
PH value	7.49	7.35-7.45
Base excess (mmol/L)	3.70	-3.0-3.0
HCO3– (mmol/L)	26.90	22.0-26.0
PaCO2 (mmol/L)	35.10	35.0-45.0
PaO2 (mmol/L)	77.40	80.0-100.0

Table 1.2: The results of biochemical tests of serum after oral supplementation with potassium chloride.

Potassium (mmol/L)	3.8-4.3	3.5-5.3
Upright plasma renin (ng/ml/hr)[#]	0.13	0.10-5.56
Upright plasma aldosterone (pg/ml)[#]	119.00	70.00-300.00

Upright angiotensin II[#]	55.00	50.00-120.00
Supine plasma renin (ng/ml/hr)[#]	0.05	0.15-2.33
Supine plasma aldosterone (pg/ml)[#]	93.00	30.00-160.00
Supine angiotensin II[#]	72.00	25.00-60.00
Upright plasma renin (pg/ml)[*]	17.05	4.00-38.00
Upright plasma aldosterone (pg/ml)[*]	177.56	40.00-310.00
Upright angiotensin II[*]	68.35	49.00-252.00

Testing methods

[#] Radioimmunoassay

[*] Chemiluminescence

Table 2: The results of urinary analysis.

Laboratory parameter	Value or range	Normal range
Urinary analysis		
Sodium excretion (mmol/24h)	146.60	130-260
Potassium excretion (mmol/24h)	41.40	25-100
Calcium excretion (mmol/24h)	2.14	2.5-7.5
Chloride excretion (mmol/24h)	139.80	170-250
Phosphate excretion (mmol/24h)	16.00	23-48
24h-urine volume (ml)	2000	-

Combining the patient's clinical manifestations with laboratory test results followed as: hypokalemia-induced metabolic alkalosis, higher blood magnesium, increased excretion of both urinary calcium and urinary potassium, in spite of non-significant activation of the Renin-Angiotensin-Aldosterone System (RASS), based on Chinese Expert Consensus on the Treatment of Gitelman Syndrome 2021 edition, Gitelman Syndrome (GS) was considered a possibility **[7].**

Moreover, the diuretic loading tests of Thiazide loading test and Furosemide loading test were performed, according to the protocol described in the previous study by Colussi **[3]** and Peng **[8],** as important clinical function tests to help identify the site of tubular injury, to confirm the clinical phenotype in terms of tubular function and to reflect the functional status of the renal Sodium and Chloride Cotransport protein (NCC), of which could also as method of differential diagnosis for Gitelman Syndrome (GS) and Bartter syndrome (BS) on the basis of genetic mutations **[3,9,10].** The results of diuretic loading tests are presented in the following **Table 3.**

Table 3: The results of diuretic loading tests.

	Thiazide loading test	Furosemide loading test
FE_{CLb} (%)	1.02	0.78
FE_{CLMAX} (%)	4.26	23.157
ΔFE_{CL} (%)	3.24	22.377

ΔFE_{CL} (%) = FE_{CLMAX} (%)-FE_{CLb} (%)

b: basal clearances; Δ: maximal increase; Max: maximal clearances.

The Thiazide loading test didn't show a blunted response of the net increase in chloride fractional excretion (ΔFECL) below 2.86%, which was the cut-off value for diagnosis of GS founded by Peng and her group in Chinese GS patient, with a maximum change from baseline of 3.24% after administration of hydrochlorothiazide orally. The sensitivity and specificity of the diagnosis of GS in the Chinese population was 95.7% and 95.8% for ΔFECL below 2.86%, respectively [8]. The Furosemide loading test revealed a responsive increase in chloride fractional excretion(ΔFECL) that the maximum change from baseline after administration of furosemide intramuscularly was 22.38%, which showed significantly increased reaction to the Furosemide loading test. Eventually, genetic testing was carried out by company Shanghai WeHealth BioMedical Technology Co., Ltd. The results of genetic testing are presented in the following Table 4.

Table 4: The results of genetic testing.

Gene	Chromosome location (GRCh37/hg19)	Gene location	Reference sequence	cDNA level	Protein level	Validation result	Classification of variation
SLC12A3	chr16:56938314	Exon25	NM_000339.3	c.2891G>A	p.R964Q	Heterozygosis	Pathogenic
SLC12A3	chr16:56902342	Intron	NM_000339.3	c.505+58C>T	-	Heterozygosis	Uncertain significance

A suspicion of tubulopathy was done based on the results of laboratory and imaging tests as well as a clinical manifestation. On the basis of gene sequencing using the Sanger method, Heterozygous variants were detected in one allele of the SLC12A3 gene **(Figure 1).** One pathogenic mutation related to GS was detected: heterozygous rs202114767 Exon25 missense mutation c.2891G>A (p.R964Q) (reference sequence: NM_000339.3); the other uncertain significance mutation related to GS was detected: heterozygous rs1400026397 Intron missense mutation c.505+58C>T (reference sequence: NM_000339.3), both of which were included in the dbSNP database, confirming the diagnosis of GS **(Figure 1).** Unfortunately, due to the lack of consent of the patient's parents to conduct genetic tests, it was not possible to determine the exact mechanism of inheriting the mutation.

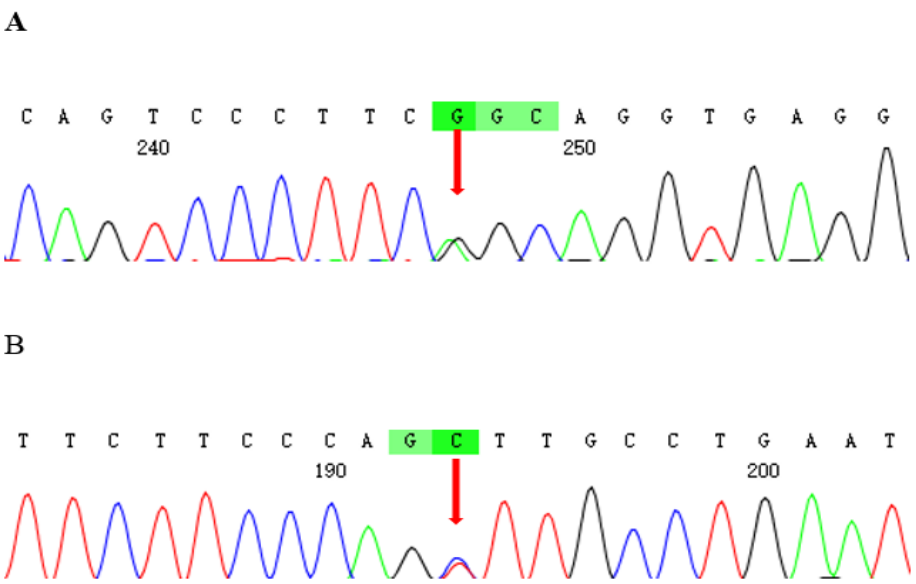

Figure 1: Variation Description: SLC12A3: NM_000339.3: exon25: c.2891G>A: p.R964Q (A). SLC12A3: NM_000339.3:505+58C>T (B).

The patient was recommended an oral supplementation of potassium chloride (1 packet of granules of 1500 mg every 8h) as well as a potassium-rich diet. She was also advised to avoid diarrhoea, vomiting, overindulgence, sweating, overexercising and alcohol consumption [7]. The results of biochemical tests of serum after a year oral supplementation with potassium chloride are presented in **Table 5.**

Table 5: The results of biochemical tests of serum after a year oral supplementation with potassium chloride.

Potassium (mmol/L)	3.8	3.5-5.3
Upright plasma renin (ng/ml/hr)[#]	0.24	0.10-5.56
Upright plasma aldosterone (pg/ml)[#]	156.00	70.00-300.00
Upright angiotensin II[#]	58.00	50.00-120.00
Supine plasma renin (ng/ml/hr)[#]	0.12	0.15-2.33
Supine plasma aldosterone (pg/ml)[#]	114.00	30.00-160.00
Supine angiotensin II[#]	47.00	25.00-60.00

Testing methods

[#] Radioimmunoassay

Discussion

The patient was a middle-aged woman who had been suffering from general weakness and palpitations with sweating for six years. The patient's hypokalemia was diagnosed locally as low in potassium and was treated with potassium supplements, but the symptoms recurred when the potassium supplements were discontinued; Hypokalemia could cause limb weakness and fatigue, as well as life-threatening or unexpected cardiac arrhythmias and respiratory paralysis. Regarding the cause of hypokalemia, there was no evidence of hypokalemia due to inadequate intake or excessive loss, as the patient had no significant reduction in intake or

recurrent diarrhoea; the patient denies any history of use of diuretics, licorice preparations or other potassium-removing drugs, so drug-induced hypokalemia is not considered for the time being. Although the patient has symptoms such as episodic weakness of the limbs, the potassium is still low during asymptomatic episodes. The patient, who was a female, with normal function of thyroid, had no clinical manifestations of hyperthyroidism. The patient's blood potassium level was monitored below 3.5 mmol/L after discontinuation of potassium supplementation, while a complete 24-hour urine electrolyte test indicated a 24-hour urine potassium level of 41.40 mmol/L. It was clearly considered the loss of nephrogenic potassium. The patient's urinary analysis indicated a urine pH of 5.5 and a urine specific gravity concentration of 1.024. Venous blood gas analysis which was showing metabolic alkalosis did not suggest evidence of acidosis, so the diagnosis of hypokalemia due to renal tubular acidosis was considered insufficient. There were no significant abnormalities in the CT of the adrenal glands. Additionally, the patient's blood potassium level was monitored from 3.8 - 4.3 mmol/L after continuation of potassium supplementation (Oral supplementation with potassium chloride), whichever the method of Radioimmunoassay and Chemiluminescence, upright plasma renin has been found with the simultaneous normal upright plasma aldosterone, while the supine plasma renin was lower than the normal range, the supine plasma aldosterone was normal by Radioimmunoassay. On supine position, angiotensin II was slightly higher than the normal range by Radioimmunoassay, but the level of it were normal on upright position by Radioimmunoassay and Chemiluminescence. Current laboratory findings did not show significant evidence of the activation of the Renin-Angiotensin-Aldosterone System (RASS). Although the patient had hypokalemia, there was no history of elevated blood pressure. On this basis, primary hyperaldosteronism was excluded. A normal circadian rhythm of ACTH and cortisol secretion was also demonstrated, the 24-hour urine cortisol level was not significantly ascended, further supporting the diagnosis of non-hypercortisolism.

The results of the perfected genetic test also suggested the SLC12A3 mutation. The diagnosis of GS was considered definite by the above analysis and potassium supplementation therapy was continued and changes in blood potassium levels were monitored. Moreover, the results of biochemical tests of serum after a year oral supplementation with potassium chloride also presented the similar plasma level compared with previous aldosterone and renin plasma level on upright and supine position. In typical cases of BS and GS, assessing response to diuretics (furosemide and thiazide), which known as the diuretic loading tests may be used to diagnose the type by detecting which part of the renal tubule is not functioning correctly. We describe a case of GS diagnosed through genetic analysis which was showed a weaker response to thiazide and a good response to furosemide. In other words, that produced the diuretic loading tests' results apparently correspond to the genetic mutations. The kidney's processing of ions, such as sodium, chloride, magnesium, calcium, and potassium, is a complex process that is relied on the molecular activity of numerous renal tubular channels [11-13]. Nevertheless, most of the patients have subtle clinical findings or unremarkable physical examinations, the medical literature describing the GS cases without activation of the Renin-Angiotensin-Aldosterone System (RASS) are sparse. It is believed that renal tubular ion exchange channel mutations are found in GS patients, and this may induce the proliferation of juxtaglomerular cells and the elevation of renin secretion, followed by increased aldosterone secretion. Compared with the primary hyperaldosteronism patients of higher aldosterone and lower renin levels, patients with GS have higher renin and higher aldosterone levels. Therefore, GS was considered as secondary hyperaldosteronism [14-18]. As for the pathophysiology of GS, the renal loss of sodium is associated with volume depletion that activates RAAS: the final effect of aldosterone signaling is the

increase of sodium reabsorption at the collecting ducts by up-regulation of the epithelial sodium channel. Sodium reabsorption induces an electrogenic gradient that promotes potassium and hydrogen secretion. The final result is induction of hypokalemia and metabolic alkalosis **[19].** In addition , scientists believe that hypovolemia and salt wasting in GS are responsible for stimulation of increased levels of serum renin and aldosterone. Mariusz Flisiński found that the results of th eir patient confirmed a normal aldosterone concentration despite significantly increased level of renin. It has been proven that serum aldosterone may not be as high as expected for the degree of hyperreninemia in BS and GS due to a low total body potassium content **[20].** Whereas, on spine position, our patient's plasma results showed a degraded renin concentration with normal aldosterone concentration; on upright position, our patient's plasma results didn't show an elevated aldosterone concentration with simultaneous normal renin concentration by the method of Radioimmunoassay and Chemiluminescence. On supine position, angiotensin II was slightly higher than the normal range by Radioimmunoassay, but the level of it were normal on upright position by Radioimmunoassay and Chemiluminescence. The results of our patients showed the non-activation of RASS, slightly higher serum magnesium concentration, both of the two clinical manifestation was contradicted with the previous studies and findings. We hope there will be more studies to explore the concrete mechanism in the future. Moreover, studies that analyzed the effect of diet on RAAS axis of GS patients showed that the concentration of aldosterone and plasma renin activity (PRA) increased during the low-sodium and high-potassium diets **[20,21].** From what we investigated, whether diets of the low-sodium and high-potassium may contribute to the elevated aldosterone and renin level for our patient without the activation of RAAS would be a thought-provoking question.

Conclusion

In conclusion, we believe that in the presented case of a patient with Gitelman's syndrome, whether the Renin-Angiotensin-Aldosterone System (RASS) activated or not may paralleled with the severity of GS. In other words, the less severe the disease, the less likely activated of RASS, of which the extent of potassium loss may contributed to the degree of activation of RASS. Additionally, as far as we know, the heterogeneity of the clinical manifestations of GS is currently thought to be related not only to the type of mutation and modified genes, but also to environmental factors such as the gender of the patient and dietary habits. Further, studies in larger groups of patients with GS are necessary to confirm this observation and it's necessary to investigate the level of aldosterone and renin after potassium supplements intake by patients with GS.

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Citation of this Article

Yanan S, Fang J, Haitao W, Yujun L, Ning W, Aiyu J and Yang J. Gitelman Syndrome without Activation of Renin-Angiotensin-Aldosterone System (RASS) - A Case Report. Mega J Case Rep. 2023; 6: 2001-2009.