Clinical Analysis of a Hypokalemic Salt-losing Tubulopathy Case

Wei Zheng, Quan Hong, Xue-Guang Zhang, Xiao-Dong Geng, Guang-Yan Cai, Xiang-Mei Chen, Di Wu
Department of Nephrology, Chinese People's Liberation Army General Hospital, Chinese People's Liberation Army Institute of Nephrology, State Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Diseases, Beijing Key Laboratory of Kidney Disease, Beijing 100853, China

Key words: Diagnosis; Gene Screening; Hypokalemia

Clinical Experience

Hypokalemia is among the most common electrolyte disorders in clinical practice and severe condition is life-threatening and has received extensive attention in clinical practice. Genetic diagnosis remains the gold standard for the diagnosis and identification of hereditary renal tubular diseases. Below is the report of genotyping and diagnosis of a case of secondary Gitelman syndrome (GS) based on next-generation sequencing.

Medical Records

A 39-year-old female patient was admitted to the hospital due to “intermittent upper limb and perioral numbness for 7 years and elevated serum creatinine for 1 year.” The patient had intermittent numbness of both hands and perioral numbness in 2008 and thereafter developed gradual weakness of breath and talk. The patient sought treatment in 2009, her blood potassium was low (the data have been lost), and she was treated with a potassium supplement. The patient later sought treatment in January 2015. Her blood biochemistry results presented the following: potassium 3.1 mmol/L, urea nitrogen 12.17 mmol/L, and creatinine 175.5 mmol/L. In the past, the patient had intermittently taken a variety of oral weight-loss drugs from 2002 to 2007. The specific components including Aristolochia fangchi (Guang Fang Ji). The patient denied having a history of taking diuretics and the family members did not have a history of any similar diseases. The blood pressure of this patient was 95/60 mmHg. The laboratory examination data are shown in Tables 1 and 2. Urinary tract ultrasonography did not show any obvious abnormality.

Renal biopsy light microscopy resulted in the following pathological description: renal tubules exhibited granular degeneration, vacuolar degeneration, focal renal tubular lesions, and moderate atrophy. In addition, focal interstitial lesions, moderate fibrosis, moderate focal inflammatory cells, and moderate infiltration were observed. Renal arterial wall thickening and small arterial hyalinization were present. Immunofluorescence results were as follows: IgA(−), C3(−), IgG(−), Fib(−), IgM(−), C4(−), and C1q(−). Pathological diagnosis showed renal tubulointerstitial damage and renal arteriosclerosis [Figure 1].

The gene analysis report showed that there was no clear meaningful disease-causing mutation and no abnormality was found in a copy number variation analysis.

Discussion

This case describes a 39-year-old woman who sought treatment mainly because of “intermittent upper limb and perioral numbness for 7 years and elevated serum creatinine for 1 year.” Blood biochemistry results suggested obvious hypokalemia and metabolic alkalosis. The common causes of hypokalemia include the following: 1. Insufficient potassium intake: This patient had normal diet; therefore, this cause was not considered. 2. Excessive mobilization of extracellular potassium into cells. a. Alkalosis: She did not have a history of diuretic use or aldosteronism-related diseases. Therefore, hypokalemia caused by alkalosis was excluded. b. Increased β-adrenal activity: This patient did not experience stress factors that would cause the increased secretion of catecholamines and did not use β-adrenal agonists; therefore, increased β-adrenal activity was excluded. c. Hypokalemic periodic paralysis: Periodic paralysis is characterized by
Table 1: Laboratory examination data

| Test indicators | Test results | Normal adult reference range |
|-----------------|--------------|-----------------------------|
| Hb (g/L)        | 93           | 137–179 (men) 116–155 (women) |
| ALT (U/L)       | 8.3          | 0–40                        |
| AST (U/L)       | 13.9         | 0–40                        |
| BUN (mmol/L)    | 6.52         | 1.8–7.5                     |
| Cr (µmol/L)     | 140.1        | 30–110                      |
| UA (µmol/L)     | 535.9        | 104–444                     |
| Ca (mmol/L)     | 2.22         | 2.09–2.54                   |
| P (mmol/L)      | 0.99         | 0.89–1.60                   |
| K⁺ (mmol/L)     | 2.74         | 3.5–5.5                     |
| Na⁺ (mmol/L)    | 139.4        | 130–150                     |
| Cl⁻ (mmol/L)    | 76.7         | 94–110                      |
| Mg²⁺ (mmol/L)   | 0.74         | 0.6–1.4                     |
| Urine specific gravity | 1.014 | 1.003–1.030 |
| Urine pH        | 8.5          | 4.0–8.0                     |
| 24-h urinary aldosterone detection (mmol/24 h) | 36.6 | 2.77–22.2 |
| Plasma aldosterone (standing) (pmol/L) | 430.1 | 180.1–819.9 |
| Plasma aldosterone (lying down) (pmol/L) | 315.1 | 163.4–481.9 |
| Plasma renin activity (standing position) (µg L⁻¹·h⁻¹) | 7.7 | 0.93–6.56 |
| Plasma angiotensin II (lying down) (ng/L) | 260.6 | 55.3–115.3 |
| Plasma renin activity (lying down) (µg L⁻¹·h⁻¹) | 7.7 | <0.79 |
| Plasma angiotensin II (lying down) (ng/L) | 159.2 | 28.2–52.2 |
| Urinary potassium (mmol/24 h) | 86.83–108.33 | 25–100 |
| Urinary sodium (mmol/24 h) | 125.04–182.4 | 130–260 |
| Urinary chloride (mmol/24 h) | 16.32–47.5 | 170–250 |
| Urinary calcium (mmol/24 h) | 0.38–0.48 | 2.5–7.5 |
| Urinary magnesium (mmol/24 h) | 1.68–2.66 | 2.1–8.2 |

BUN: Blood urea nitrogen; ALT: Alanine transaminase; AST: Aspartate transaminase.

Table 2: Arterial blood gas analysis

| Test indicator             | Test result | Normal adult reference range |
|---------------------------|-------------|-----------------------------|
| pH                        | 7.44        | 7.35–7.45                   |
| Oxygen partial pressure measurement (mmHg) | 106.4 | 80–100 |
| Carbon dioxide partial pressure (mmHg) | 55.3 | 35–45 |
| Actual bicarbonate concentration (mmol/L) | 36.9 | 20–26 |
| Base excess (mmol/L)      | 11.4        | −3–3                        |

periodic episodes of muscle weakness or paralysis combined with hypokalemia. The thyroid function of this patient exhibited normal, and her symptoms did not conform to the clinical features of periodic paralysis. d. Significantly increased erythrocyte production: this condition is commonly observed after the use of folic acid, Vitamin B12, and granulocyte-macrophage colony-stimulating factor. The patient did not have a history of using the above drugs; In addition, this patient did not have chloroquine and barium poisoning and did not have a history of encountering a low-temperature environment. Therefore, hypokalemia caused by the excessive mobilization of extracellular potassium into cells was excluded. 3. Excessive potassium loss: a. The patient did not exhibit vomiting, diarrhea, ostomy drainage, or digestive tract tumors; therefore, gastrointestinal loss of potassium was excluded. The patient did not exhibit great potassium loss after excessive sweating. b. Loss by kidney: (1) diseases related to mineralocorticoid increases mainly include adrenocortical tumor or hyperplasia, juxtaglomerular cell tumor, ectopic aldosterone-producing tumor, Cushing syndrome, and pseudohypaldosteronism. Patients with these conditions mainly present increased blood pressure. However, this patient exhibited low blood pressure. Therefore, hypokalemia caused by diseases related to mineralocorticoid increase was not considered. (2) Hereditary diseases or secondary injury of renal tubular dysfunction. Moreover, the common identifications include the following:

**Bartter syndrome**

Bartter syndrome (BS) is an autosomal recessive hereditary diseases. These patients may present with growth retardation. According to clinical presentations, the major symptoms include the following: (1) Hypokalemia (2) hyperkalaemia (3) metabolic alkalosis (4) hyperreninemia (5) hyperaldosteronemia (6) exogenous vasopressin insensitivity (7) juxtaglomerular hyperplasia (8) hypochloremia (9) normal blood pressure, and (10) clear family history. Gene screening is the gold standard of diagnosis for this syndrome.[1] This patient experienced disease onset in mid-life, normal growth and development, and no family history of BS.

**Liddle syndrome**

Liddle syndrome (LS) is a single-gene disorder that is characterized by autosomal dominant inheritance. The clinical characteristics are early onset of hypertension, hypokalemia, reduced plasma renin activity, and hypoaldosteronemia.[2] Except for hypokalemia, this patient did not exhibit the above clinical presentation. Therefore, the possibility of LS was low.

**Gitelman syndrome**

GS is an autosomal recessive hereditary disease. The onset of GS mainly occurs in late adolescence or in adulthood. The most typical laboratory test abnormalities include hypokalemia, hypochloremic metabolic alkalosis, hypomagnesemia, hypocalciuria, and renin-angiotensin-aldosterone system activation.[3] The main characteristic of GS is normal low-limit blood pressure or low blood pressure. Urinary protein is normal or slightly elevated with mainly low-molecular-weight proteins. The diagnosis of GS is based on clinical symptoms and abnormal biochemistry test results.
results. However, the gold standard of diagnosis remains gene analysis. This patient exhibited disease onset during middle age. Laboratory examination showed obvious hypokalemia, hypochloremia, hyperkaluria, hypocalciuria, increased plasma renin activity and angiotensin II, metabolic alkalosis, and low blood pressure. These findings were consistent with the clinical characteristics of GS. Therefore, GS was highly suspected.

To confirm the diagnosis, we performed a renal biopsy and used next-generation sequencing to perform gene analysis and screen for renal tubular diseases.

In summary, the described patient was a woman, whose disease onset began during middle age. The laboratory tests result exhibited obviously low urine specific gravity, increased urine pH, hypokalemia, hypochloremia, hyperkaluria, hypocalciuria, metabolic alkalosis, increased plasma renin activity and angiotensin II, and low blood pressure. The patient did not have a history of taking diuretics. The renal biopsy pathology report showed renal tubulointerstitial injury and renal arteriosclerosis. The genetic diagnostic analysis did not reveal any abnormality. Although the diagnosis of GS was not valid, a review of the medical history showed that the patient exhibited the long-term use of a variety of weight-loss drugs. The main components include Guang Fang Ji. Guang Fang Ji belongs to Aristolochia. Aristolochic acid nephropathy resulting from its use as an additive in weight-loss drugs was first reported in Belgium. Many studies since have confirmed that aristolochic acid is a nephrotoxic drug and a human carcinogen that can cause progressive renal interstitial fibrosis and urothelial carcinoma. The patient exhibited low specific gravity urine and urine acidification function impairment, and these presentations of renal pathology were also consistent with the pathological changes in aristolochic acid nephropathy. Therefore, the possibility of renal tubular disease caused by drug-related damage should be considered. Although, the gene screening for hereditary diseases that present renal tubular dysfunction was negative. However, the clinical presentations of this patient were consistent with GS. Therefore, the patient was finally diagnosed with (1) secondary GS and (2) chronic renal insufficiency (CKD stage 3).

The treatment of this patient was relief of symptoms and the correction of electrolyte disorders. After supplementation with potassium and treatment with a high-salt diet, the patient no longer exhibited upper extremity and perioral numbness. Hypokalemia, hyponatremia, hypochloremia, and metabolic alkalosis were all improved during re-examination, and blood pressure was stable.

The main feature of this study was the use of advanced next-generation sequencing to perform gene diagnosis; this technique can precisely distinguish diseases that are easily confused and present similar clinical symptoms, thus achieving precise medical treatment.

Financial support and sponsorship
This work was supported by a grant from the major State Basic Research Development Program of China (No. 2014CBA02005).

Conflicts of interest
There are no conflicts of interest.

References
1. Fremont OT, Chan JC. Understanding Bartter syndrome and Gitelman syndrome. World J Pediatr 2012;8:25-30. doi: 10.1007/s12519-012-0333-9.
2. Botero-Velez M, Curtis JJ, Warnock DG. Brief report: Liddle’s syndrome revisited – A disorder of sodium reabsorption in the distal tubule. N Engl J Med 1994;330:178-81. doi: 10.1056/nejm199401203300305.
3. Knoers NV, Levchenko EN. Gitelman syndrome. Orphanet J Rare Dis 2008;3:22. doi: 10.1186/1750-1172-3-22.
4. Gökmen MR, Cosyns JP, Arti VM, Šiborová M, Phillips DH, Schmeiser HH, et al. The epidemiology, diagnosis, and management of aristolochic acid nephropathy: A narrative review. Ann Intern Med 2013;158:469-77. doi: 10.7326/0003-4819-158-6-201303190-00006.
5. Pozdzik AA, Berton A, Schmeiser HH, Missoum W, Decaestecker C, Salmon IJ, et al. Aristolochic acid nephropathy revisited: A place for innate and adaptive immunity? Histopathology 2010;56:449-63. doi: 10.1111/j.1365-2559.2010.03509.x.