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CLINICAL CASE

A case of Gitelman's syndrome with severe hypokalemia and pseudoischemic ECG changes

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Summary

A case of Gitelman's syndrome with severe hypokalemia and pseudoischemic ECG changes is presented. A brief review on this kind of primary tubulopathy is also given. Clinical significance of possible difficulties for cardiologist is indicated (pseudoischemic ECG changes, QT-interval prolongation with life-threatening ventricular arrhythmias, risk of myopathy and rabdomyolisis development after statin administration, hypokalemia worsening due to prescribing diuretics).

Key words

Gitelman syndrome, hypokalemia, tubulopathy.

Hypokalemia that appears if serum K+ levels are less than 3/5 mmol/Ll is one of the most frequent electrolyte abnormalities and it occurs in more than 20% of patients admitted to hospital [1]. The most often cause of it is the adverse action of drugs, in particular – diuretics. The role of primary abnormalities of kidney tubular function (tubulopathy) is quite modest, and quite often it affects their opportune diagnostics and treatment.

We describe our observation of one of tubulopathy variants that manifested as severe hypokalemia with pseudoischemic changes on electrocardiogram (ECG).

29 years old female was presented with complaints on severe weakness, weight loss, occasional syncope, dry skin. These symptoms appeared at first 2 years ago and since then developed gradually. During last

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2 months the symptoms have been aggravating. Was examined by physician, neurologist, endocrinologist. Underwent fibrogastroduodenoscopy (FGDS), abdominal ultrasonography (US), head magnetic resonance imaging (MRI). Laboratory tests: cortisol, adrenocorticotropic hormone (ACTG), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH) – normal levels. Diagnosis remained unclear, for further diagnostics was admitted to hospital. No burdened family history. No bad habits. Her occupation is a teacher.

Physical examination revealed evident body mass deficiency: height – 161 cm, weight – 41 kg; signs of connective tissue dysplasia like joint hypermobility; dry skin. Thyroid gland, peripheral lymphatic nodes are not enlarged. Respiratory rate is 18 breaths per minute. Lung auscultation: vesicular breathing, no rales. Heart rate (HR) is 60 beats per minute, blood pressure (BP) is 90/60 mm Hg. Tongue is moist, with white coating. Stomach is soft, no pain during palpation. The lower margin of liver is at the right costal margin, spleen is not palpable. No peripheral edema.

Blood tests: general blood count: normal (hemoglobin – 153 g/L, platelets – 255*10^9/L, leucocytes – 6,1*10^9/L, stab – 4, segmentonuclear – 59, eosinophils – 1, lymphocytes – 33, monocytes – 3, ESR – 10 mm/hour. Biochemical analysis: evident hypokalemia, hypomagnesemia, alkalosis, levels of other markers are normal: glucose – 3 mmol/L, total protein – 16 μmol/L, blood urea – 4.2 mmol/L, creatinine – 73 μmol/L, bilirubin – 16 μmol/L, conjugated bilirubin – 0, alanine-aminotransferase (ALT) – 34 E/L, aspartate-aminotransferase (AST) – 32 E/L, K^+ – 2,0 mmol/L, Mg^{2+} – 0,53 mmol/L (reference levels – 0,66-1,07 mmol/L), Na^+ – 137 mmol/L, Ca^{2+} – 2,5 mmol/L, blood plasma pH – 8,0. Urinalysis: hyposthenuria (1004), protein – negative, leucocytes – 2-3 in visual field. Zimnitsky test: urine's specific gravity: 1006-1008, daily dieresis – 800 ml, nocturnal dieresis – 900 ml. 24-h Ca2+ urine excretion – 0.302 mmol (reference levels – 1.,7 – 3,3, mmol/day).

ECG: evident abnormal repolarization manifested as "pseudoischemic" ST depression in V_4-V_6 leads (Figure 1).

Patient was precisely investigated in order to exclude oncological pathology. Chest X-ray, abdominal and thyroid gland US, abdominal computer tomography (CT). Both US and CT revealed non-homogenous kidney structure and normal kidney size (Figure 2, 3)

The diagnostic version of tubulopathy was raised because of low urine's specific gravity, hypokalemia,

Figure 1. «Pseudoischemic» ECG changes as horizontal ST segment depression in V_4-V_6 lead registered at the time of admission to hospital.

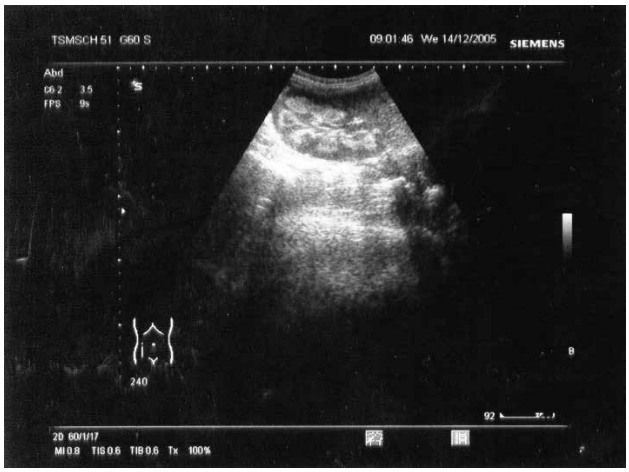

Figure 2. Kidney US (normal dimensions of the kidney, renal pyramids have hyperechoic contour with blurred boundary of different intensity)

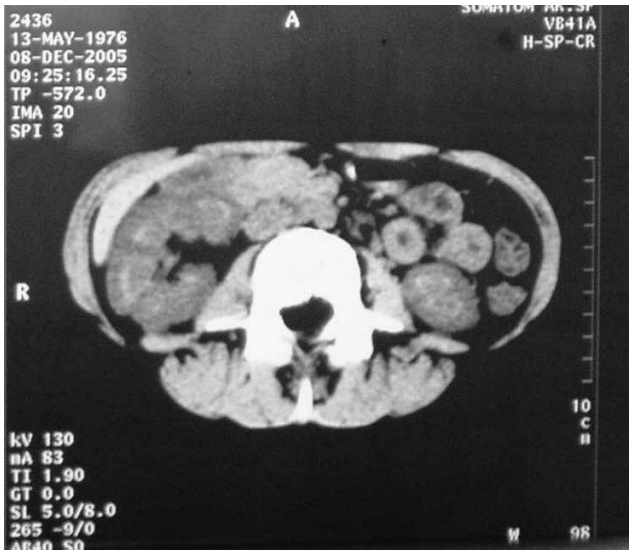

Figure 3. Kidney CT (normal shape, dimensions and position of kidney with distinct boundary. No concrements. No dilation of renal collecting system. Parenchymal structures density is non-homogenous, varies from 35 to 47 Hounsfield units.

hypomagnesemia. Additional tests revealed serum alkalosis, so differential diagnosis of hypokalemic alkalosis was made between Bartter and Gitelman syndromes. But sharply decreased 24-hour Ca2+ urine expression and manifestation of the disease at adult age allowed to establish the diagnosis of Gitelman syndrome, one of distal tubulopathy – distal tubular alkalosis. Not common US and CT signs are considered to be manifestations of nephrocalcinosis, some authors describe calcium deposits in other organs in case of this syndrome. Patient was administered with K+ medications: potassium chloride 3% 50 ml per 10 days intravenously dropwise, after it 3g/day per os, spironolactone 100 mg/day, short course of nimesulide 100 mg/day and magnesium salts with distinct clinical effect: weakness was relieved, work efficiency was restored, patient started to gain weight (after 1 month of therapy she gained 2 kg), no syncope was reported, BP raised up to 110/70 mm Hg, serum pH was normalized. Intravenous potassium chloride administration increased serum K^+ concentration up to intermediate level of 3,0 mmol/L, but it led to adverse reactions: weakness, paresthesia, pain in knee joints. After starting oral administration of potassium containing drugs K+ serum concentration decreased again to 2,3 mmol/L. Because of this spironolactone dose was increased up to 150 mg/day. Patient is under continuous observation.

Discussion

Hypokalemia when levels of serum K+ is <3,5mmol/L is one of the most frequent electrolyte abnormality in clinical practice. Its occurrence in general population is less than 1%, but this pathology can be found in >20% of hospital admitted patients [1].

Since the most frequent cause of hypokalemia is pharmacological therapy, in particular diuretics and laxatives, differential diagnosis should be started from taking precisely patient's history, gaining information about all received drugs, and it is reasonable to subdivide hypokalemia into pharmacological and non-pharmacological one.

Since the patient refused administration of any drugs, it was clear that this hypokalemia was non-pharmacological one. The list of non-pharmacological causes of hypokalemia is big enough [1-3] and includes insufficient intake of electrolyte with food that occurs very rarely because even in case of total starvation organism usually have sufficient compensatory mechanisms that allow to stabilize normal serum K^+ levels; loss of K^+ through gastrointestinal tract (GIT) and kidney, various endocrinological diseases, metabolic alkalosis, hypomagnesemia and some other causes like chronic alcoholism[4] and alcoholic delirium. Patient underwent precise investigation for endocrine pathology in outpatient setting, there were no signs indicating GIT pathology, good social status allowed to exclude dietary and alcoholic causes of potassium deficiency and additional diagnostic techniques that were performed after patient's admission to hospital made it possible to exclude paraneoplastic cause of hypokalemia. Therefore, the diagnostic search was reduced to primary renal causes and in particular to tubulopathies.

Tubulopathies (or tubular dysfunctions) are group of nephropathies that are characterized by partial or generalized loss of renal tubular functions with normal or slightly decreased glomerular filtration. There are primary and secondary tubulopathies, secondary ones appear as a consequence of another systemic disorder like Sjogren's syndrome, Wilson-Konovalov disease, multiple myeloma, paroxysmal nocturnal hemoglobinuria and others.

Primary tubulopathies are classified according with the localization of the lesion (proximal, distal), major clinical syndrome, between them metabolic acidosis or alkalosis have particular importance, main mechanism of transport abnormalities.

Between tubulopathies that are characterized with hypokalemia and metabolic alkalosis the most important ones are Bartter's syndrome and Gitelman's syndrome. Bartter's syndrome is a severe form that manifests very early even during antenatal period and has bad prognosis. Gitelman's syndrome has milder and sometimes asymptomatic course and often it manifests for a first time not only in children and adolescents but also in adults and elderly people [5-7].

There are two hereditary pathological conditions that are related to anomalies of ion transporters in renal tubules (Liddle's syndrome and 11ß-hydroxysteroid dehydrogenase deficiency) that can also cause hypokalemia and metabolic alkalosis, but they are characterized with early development of arterial hypertension and that's why they are excluded in this case.

The first description of Gitelman's syndrome was made in 1966 [8] and because it was considerably different from Bartter's syndrome it got the name of its founder. This inherited tubulopathy with autosome-recessive inheritance mechanism associated with SLC12A3 gene mutation that leads to impaired function of thiazide-sensitive Na^+Cl^- cotransporter in dis-

tal tubules. To date around 100 mutations of SLC12A3 gene have been identified, and occurrence of this pathology can be 1:40000 in Caucasian population [5,6] and even higher occurrence between Japanese [9].

Gitelman's syndrome is characterized with hypokalemia, hypomagnesemia, metabolic alkalosis, hypocalciuria, increased level of renin and aldosterone, weakness, muscle cramps and normal or low BP, with possible polyuria and nocturia. There are evidences of rhabdomyolisis development in case of severe hypokalemia up to formation of acute renal failure [10], cases of statins' intolerance with development of myopathy in patients in whom Gitelman's syndrome wasn't identified on time [11], recurrent syncope [12], possible development of chronic nephropathy with the outcome of chronic renal failure (CRF) [13], choroid and sclerotic calcification [14], paresthesia, depression [15], hypokalemic periodic paralysis [16]. There are many evidences of the combination of Gitelman's syndrome and chondrocalcinosis (pyrophosphate arthropathia) with typical joint syndrome and possible termination of acute arthritis attacks after prescription of magnesium containing drugs [17]. Since both hypokalemia and hypomagnesiema can cause QT interval prolongation, it is expectable that patients with Gitelman's syndrome are prone to more frequent registration of prolonged QT interval [18], development of paroxysmal ventricular arrhythmias [19] and sudden death [20].

Gitelman's syndrome therapy is consisted of several classes of drugs and is enough affordable and easy [5]:

• administration of potassium-containing drugs, preferably potassium chloride per os because this way of administration is more safe, since intravenous administration of potassium chloride is not always well tolerated by patients due to fast increase of potassium serum concentration;

• administration of magnesium-containing drugs (magnesium chloride or magnesium sulphate);

• if the therapeutic effect of mentioned above drugs is not sufficient, potassium-sparing diuretics (spironolactone, triamterene) are prescribed; there are evidences of effective use of eplerenone, antagonist of metalcorticoid receptors [21], and direct rennin inhibitor aliskiren [7].

• non-steroid anti-inflammatory drugs are less effective than in Bartter's syndrome therapy, but there are some evidences of their effective use [5].

Talking about our clinical case, we suppose that although genetic verification of diagnosis has not been performed, relatively late onset of the disease, distinct hypocalciuria together with resistant hypokalemic alkalosis and tendency to hypotension allows to set the diagnosis of Gitelman's syndrome and not a variant of Bartter's syndrome or other primary tubulopathy. Non-homogenous structure of kidney according with US and CT is likely to be the sign of nephrocalcinosis because of deposits of excessively reabsorbed calcium.

As a conclusion it is necessary to notice that, although up to recent times Gitelman's syndrome was considered to be a rare pathology, one of studies made in 1988 demonstrated that occurrence of this syndrome in Sweeden was estimated as 19 per 1 mln of people [22], Japanese researchers [9] investigated the frequency of corresponding genes mutations in 1852 persons on the continent and found out that suppose that occurrence of Gitelman's syndrome should be 10,3 per 10000 people or 1030 per 1 mln. If we assume that real occurrence of this syndrome in Russia is by a factor of ten lower, even in this case there is a big group of people who trying to apply for medical aid with complaints of weakness, fatigability, paresthesia, tendency to hypotension and are discharged with the wrong stereotypic diagnosis of "vegetovascular dystonia", although they could have been diagnosed properly since the diagnostic tactic is not complicated and the treatment is affordable. It is important to notice that, although Gitelman's syndrome is characterized with tendency to hypotension, some patients, especially elderly ones, can be presented with hypertension [23].

The aim of this publication is to attract the attention of doctors to this not very well known and underestimated pathology. Diagnostic algorithm of Gitelman's syndrome requires biochemical proving of resistant hypokalemia, exclusion of such its causes like pharmacological, endocrine, gastrointestinal loss of potassium, evaluation of serum pH (alkalosis is expected), levels of serum magnesium (decrease is expected), calciuria levels (diagnosis is proved with reduced calcium excretion with urine). Diagnosis can be proved with estimation of SLC12A3 gene mutations.

It is necessary to keep in mind such comorbid pathology like Gitelman syndrome. In cardiological practice it is important to remember it during interpretation of pseudoischemic ECG changes, QT interval prolongation, risk of rhabdomyolisis development after statin administration and hypokalemia aggravation after diuretics prescription.

Conflict of interest: None declared.

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