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Differential Diagnosis of a Female Young Adult with Generalized Weakness, Hypokalemia, Hypomagnesemia and Inappropriate Kaliuresis and Clinical Diagnosis of Gitelman's Syndrome

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Abstract

We present the case of a 23-year-old female patient referred to the emergency department due to persistent generalized muscle weakness and whole-body fatigue, gradually deteriorating during the last three months. The patient's medical history as well as family history was unremarkable. Detailed physical examination did not reveal any specific signs of disease. Her blood pressure, which was measured twice daily, was within the normal range. Biochemical blood testing revealed hypokalemia, hypomagnesemia, metabolic alkalosis, increased plasma renin activity and increased plasma aldosterone levels. The patient's age, the clinical manifestations and the results of the laboratory tests led as to include Gitelman syndrome in our differential diagnosis. Gitelman syndrome is a very rare autosomal recessive inherited tubular disorder, usually affecting young adults. Gitelman syndrome is typically characterized by hypokalemia, metabolic alkalosis, hypomagnesemia, hypocalciuria, increased serum renin and aldosterone levels and normal arterial blood pressure. The patient was treated with spironolactone and oral potassium supplements with restoration of normal serum potassium levels and resolution of her symptoms and thus the final diagnosis of Gitelman syndrome was established.

Keywords: Gitelman syndrome; Hypokalemia; Metabolic alkalosis; Hyperreninemic hyperaldosteronism

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Introduction

Hypokalemia is a common disorder of electrolyte balance and is often the result of patients' treatment with non-potassium sparing diuretics, such as thiazides and loop diuretics and gastrointestinal losses, as a result of persistent vomiting and/or diarrheas. Other less frequent causes of hypokalemia include secondary hyperaldosteronism as a result of cardiac or hepatic failure. Nevertheless, other rare causes of hypokalemia can render it a major problem of patient's differential diagnosis and a challenge for the physician who is in charge of resolving it.

Depending on the degree of hypokalemia clinical symptoms may vary from asymptomatic (usually when serum potassium levels range between 3 mmol/l - 3.5 mmol/l) to mildly or overt symptomatic (when potassium levels are well below 3 mmol/l. Symptoms of hypokalemia may include generalized muscle weakness, muscle cramps, limb paralysis, respiratory failure due to respiratory muscle paralysis, as well as cardiac arrhythmias, culminating to life-threatening ventricular fibrillation, with progressive worsening of the degree of hypokalemia.

In this case report we present the case of a 23 year old woman that was admitted to the emergency department of our hospital with generalized weakness and hypokalemia and no other overt signs of disease.

Case Presentation

A 23 year-old woman was admitted to the emergency department of our hospital with imminent

Table 1: Laboratory tests at admission.

General Blood Count		Biochemical tests	
WBC	7300/μl (3,8-10,5)	AST	18 U/l (10-31)
NEUT	65,8% (45-75)	ALT	19 U/l (10-34)
LYMPH	25,7% (20-51)	ALP	72 U/l (30-120)
MONO	8,2% (2-11)	LDH	95 U/l (0-248)
Hct	41,9% (37-47)	Total Bilirubin	0,9 mg/dl (0,3-1,2)
Hb	13,6 gr/dl (11,6-16,4)	CPK	66 U/l (0-145)
MCV	90,6 fl (80-99)	Total proteins	6,8 gr/dl (6,6-8,3)
PLT	190.000/μl (150000-450000)	Albumin	4,2 gr/dl (3,5-5,2)
Urinalysis		Glucose	84 mg/dl (75-110)
SW	1015	Urea	36 mg/dl (17-43)
pH	Alkaline	Creatinine	0,94 mg/dl (0,66-1,1)
Glucose	(-)	**K^+**	**2,8 mmol/l (3,5-5,1)**
Oxone	(-)	Na^+	142 mmol/l (136-145)
Protein	(-)	Ca^{+2}	10mg/dl (8,8-10,6)
RBC	0-1	**Mg^{+2}**	**1,8 mg/dl (1,9-2,5)**
WBC	0-2	Cl^-	93 mmol/dl (95-108)

generalized muscular weakness and fatigue of progressive intensity during the last three months.

Patient and family history was unremarkable, whereas no intake of pharmaceutical or OTC preparations was reported. Detailed physical examination was unremarkable with the exception of mild bilateral muscle weakness of the upper and lower extremities. Multiple measurements of the patient's blood pressure were within the normal range. Laboratory blood tests revealed hypokalemia (K+: 2.8 mmol/l), mild hypomagnesemia ($Mg+^2$: 1.8 mg/dl), mild hypochloremia (Cl-: 93 mmol/l) whereas the rest of the blood tests performed were within the normal range (Table 1). ECG performed did not reveal abnormalities related to hypokalemia.

It was decided that the patient should be transferred to the department of internal medicine for admission, in order to further investigate the cause of hypokalemia. Differential diagnosis of the latter included unreported use of diuretics (thiazides or loop diuretics), gastrointestinal losses of potassium by unreported use of laxatives or other OTC substances as well as primary hyperaldosteronism.

In the internal medical department the patient's ECG was monitored on a 24h basis by the use of Holter monitoring device.

Further detailed general blood tests and general hormonal measurements performed were within the normal range. CA125, CA15-3, CA19-9, CEA and α-FP measured in blood were also normal.

Acid-base balance was measured by the use of arterial blood gases, whereas full measurement of plasma electrolyte concentrations, plasma osmolality, measurement of plasma renin activity (in the supine and upright position) and plasma aldosterone, as well as collection of 24h urine samples for the measurement of urine creatinine, urea, electrolytes and osmolality were performed. Results of the above tests are summarized in Table 2.

Radiological examination subsequently performed included chest X-ray, kidney-ureter-bladder X-ray, upper/lower abdomen ultrasound and kidney ultrasound, triplex ultrasound of renal vessels and renal scintigraphy, renal-adrenal CT/MRI and CT/MRI of the pituitary gland and the sella turcica. All above examinations did not reveal any abnormal finding.

Arterial blood gases measurements revealed metabolic alkalosis with pH: 7.54, HCO3: 26.9 mmol/l and PCO2: 33.7 mmHg. Urinalysis testing and electrolytes measurements of 24h urine collections were within the normal range. Plasma osmolality was 285 mOsm/kg, whereas urine osmolality was 680 mOsm/kg. Plasma renin activity and plasma aldosterone measurements were well above the upper normal limit.

Based on the above laboratory results gastrointestinal losses, diuretic use, cystic fibrosis, were all excluded from the differential diagnosis of hypokalemia, since all of the above states involve intense urine hypochloremia (urine Cl- < 20 mmol/l).

Moreover, renal artery stenosis and primary hyperaldosteronism were also excluded as potential causes of hypokalemia with high renin activity and high plasma aldosterone because of the lack of concomitant hypertension in our patient's setting.

Laboratory investigation of patient's hypokalemia, diagnosis and treatment

In the diagnostic setting of hypokalemia, potential inappropriate kaliuresis has to be verified. Accordingly, we measured the Fractional Excretion of Potassium (FEK) which is determined as the ratio [(Urine K+ x Plasma creatinine) / (Plasma K+ x Urine creatinine)] × 100, the ratio Urine K+/ Urine creatinine and The Transtubular Potassium Gradient (TTKG), which gives a crude estimate of renin activity in the kidney and potassium sparing at the site of the collective tubules, by measuring the concentration of K+ secreted at the end of the distal nephron cortex (major site of potassium kidney secretion) [1,2]. TTKG is determined as the ratio (Urine K+ x Plasma Osmolality)/ (Plasma K+ x Urine Osmolality). Above indices determine kidney origin of hypokalemia and were subsequently determined in our patient's diagnostic setting.

By applying above measurements in our patient's case we estimated a TTKG > 2 and FEK > 9% thus establishing the setting

Table 2: Laboratory tests performed in the setting of hypokalemia investigation.

ARTERIAL BLOOD GASES	
PO_2 : 112,5 mmHg	
PCO_2 : 33,7 mmHg	
pH : 7,54	
SO_2 : 98,5%	
$HCO3^-$: 26,9 mmol/l	
SERUM ALDOSTERONE : 41,3 ng/dl	**PLASMA OSMOLALITY:** 285 mOsm/kg
Normal Range Supine position : 1-16 ng/dl	
Upright position: 3,5 - 30 ng/dl	
PLASMA RENIN ACTIVITY: 14,58 ng/ml	
Normal Range Supine position : 0,2 - 2,7 ng/ml	
Upright position : 1,7 - 5,2 ng/ml	
24H URINE COLLECTION TEST (Vol: 2250ml)	**URINE OSMOLALITY:** 680 mOsm/kg
Urea : 24,28 gr/d (15 - 34,2 gr/d)	
Creatinine: 25,32 mg/Kg/d (14-26 mg/Kg/d)	
K^+ : 122,75 mmol/d (25-125 mmol/d)	
Na^+ : 153,46 mmol/d (40-220 mmol/d)	
Ca^{+2} : 83,55 mg/d (50-150 mg/d)	
Mg^{+2} : 136,22 mg/d (25-290 mg/d)	
Cl^- : 132,64 mmol/d (110-250 mmol/d)	

of inappropriate kaliuresis. Therefore, identification of renal causes of hypokalemia was the next step in the differential diagnosis. The latter may include the use of nephrotoxic drugs and substances, renal tubular acidosis I and II and the rare Bartter, Gitelman and Liddle syndromes. Since our patient presented with hypochloremic metabolic alkalosis renal tubular acidosis was excluded from the differential diagnostic setting. Moreover, use of nephrotoxic drugs and substances was excluded on the basis of patient's records and history. Liddle syndrome, an autosomal dominant inherited mutation of Na+ channels that gives rise to increased potassium reabsorption and is manifested by hyporeninemic hypoaldosteronism was also excluded on the basis of our patient's documentation of the presence of hyperreninemic hyperaldosteronism and the absence of arterial hypertension as well [2-4]. Classical Bartter syndrome, which is a syndrome clinically evident from the second year of life to the adolescence and usually involves growth retardation, mental retardation and deafness, is manifested by hypokalemia, sometimes with concomitant hypomagnesemia (20% of the cases), hypochloremic metabolic alkalosis, inappropriate kaliuresis, hypercalciuria and hyperreninemic hyperaldosteronism. The same laboratory features are found in antenatal/neonatal Bartter syndrome. The latter syndrome could also be excluded in the clinical setting of our patient. Gitelman syndrome usually becomes clinically evident during puberty or early adulthood and is manifested by hypokalemia, sometimes with concomitant hypomagnesemia, hypochloremic metabolic alkalosis, inappropriate kaliuresis, sometimes with concomitant hypocalciuria and hyperreninemic hyperaldosteronism. We, therefore, concluded that Gitelman syndrome was the final diagnosis in our patient and treatment with spironolactone was subsequently inititiated.

Discussion

Gitelman syndrome is a very rare hereditary disorder of the renal tubules that should be included in the differential diagnosis of a young normotensive patient with persistent hypokalemia of unknown origin. The prevalence for Gitelman syndrome is 1 in 40,000 as compared with 1 in 1,000,000, in Bartter syndrome [5].

Our patient presented with generalized muscle weakness whereas laboratory tests revealed hypokalemia, hypomagnesemia, hypochloremic metabolic alkalosis and inappropriate kaliuresis. Further endocrine workup performed revealed increased plasma renin activity and hyperaldosteronism thus indicating secondary hyperaldosteronism should be considered in the differential diagnosis. Since patient's blood pressure was normal, as was the case with our patient's phenotype and patient's age (23 years old), classical Bartter syndrome could be ruled out and the diagnosis of Gitelman syndrome was established [3,4,6]. Treatment with a daily dose of spironolactone 25mg was started and the patient was prescribed a dietary program rich in potassium and was discharged at the 7th day from admission to the hospital. A follow-up visit was scheduled after one month, in order to verify patient's serum potassium levels and the appropriate dose of spironolactone. During the latter visit serum K^+ levels were 3.2 mmol/l and it was therefore decided that the dose of spironolactone should be increased to 50 mg per day and a potassium supplement should also be given per os. In the next monthly follow-up visit, patient's serum K^+ levels were between 3.5 and 3.6 mmol/l, serum Mg^{+2} levels were 1.9 mg/dl (lower normal levels) and the patient was free of symptoms. Her treatment regimen remained unchanged and the patient was instructed to have one follow-up visit after three months and then yearly follow-up visits. Three years now the patient remains asymptomatic and serum K^+ levels remain between 3.5 mmol/l and 3.7 mmol/l and serum Mg^{+2} levels between 1.8 mg/dl and 1.9 mg/dl. Serum electrolytes measured in the parents of the patient were within the normal range and since the patient does not have siblings no further genetic testing was considered necessary.

Bartter syndrome and Gitelman syndrome were considered

variants of a single disorder, on clinical grounds. Yet, molecular biology testing and genetic testing, performed during the last decade, revealed that they are distinct entities of ion channel disorders of the renal tubules, sharing common phenotypical features [7,8]. They comprise a group of rare renal tubular disorders with autosomal recessive inheritance, which share the common features of hypokalemia with inappropriate kaliuresis, hypochloremic metabolic alkalosis and hyperreninemic hyperaldosteronism with normal blood pressure [8].

Three main phenotypes can be differentiated on the basis of age of onset, severity of the symptoms, severity of hypokalemia, reduced or increased urinary calcium and reduced or increased urinary prostaglandins. Above clinical entities comprise classical Bartter syndrome, antenatal/neonatal Bartter syndrome and Gitelman syndrome [8,9].

Classical Bartter syndrome, which is a syndrome clinically evident from the second year of life but is usually manifested during childhood or adolescence and usually involves growth retardation, mental retardation and deafness, is manifested by hypokalemia, sometimes with concomitant hypomagnesemia (20% of the cases) and hypercalciuria as well as kidney stone formation [8-10]. A variant of it is Bartter syndrome III, which presents with normal or slightly increased urinary calcium excretion but without kidney stone formation [9]. Bartter syndrome is caused by mutations of genes coding the sodium-potassium-chlorine co-transporter (NKCC2) (type I), the inward rectifying ATP-dependent potassium K+ channel (ROMK) in the thick ascending limb of the loop of Henle (type II), the kidney-specific basolateral chloride channel (CIC-Kb) (type III), or barttin, the β-subunit of the kidney basolateral chloride channel, (type IV) or by mutations of the gene coding the calcium-sensing receptor [3,4,8,9,11]. Defects of above transport systems result in increased loss of salt and water, consequent stimulation of renin-angiotensin-aldosterone system with increased secretion of potassium and hydrogen cations and increased production of renal prostaglandin E_2 (PGE_2) as well as juxtaglobular apparatus hyperplasia [8,11]. The latter can be revealed by renal biopsy. Treatment consists of potassium sparing diuretic use (Spironolactone, Eplerenone, Triamterene, Amiloride), oral potassium supplements and Non-Steroid Anti-Inflammatory (NSAIDs) drugs [3,4,7,8,11]. Antenatal/neonatal Bartter syndrome is the most severe clinical entity and is manifested by hydramnion, prematurity of the newborn, growth and mental retardation, hypercalciuria, nephrasbestosis and increased urinary PGE_2. As is the case with classical Bartter syndrome, post-partum Bartter syndrome is also caused by mutations of the genes coding for sodium-potassium-chlorine co-transporter (NKCC2) or ATP-dependent potassium channel (ROMK) in the ascending limb of the loop of Henle [3,4,8,11].

Gitelman syndrome usually becomes clinically evident during puberty or early adulthood but the patient may remain asymptomatic for many years, thus making its diagnosis extremely difficult [6,7,12,13]. Main symptoms consist of fatigue, generalized muscle weakness, muscle cramps and, rarely, tetania. Serum electrolyte disorders consist of hypokalemia and hypomagnesemia [14-17]. Serum magnesium levels may be just under the lower normal range [21,22]. Hypocalciuria is usually present but is not always reported as a consistent finding [14,17-20]. It is caused by biallelic inactivating mutations in the *SLC12A3* gene encoding the thiazide-sensitive sodium-chloride co-transporter (NCC) expressed in the apical membrane of the distal convoluted tubules [6,12,23]. There are also several reports of defective function in the γ-subunit of Na-K-ATPase or of chlorine ion channel of the distal convoluted tubules [14-16]. A Gitelman syndrome-like phenotype, including hypomagnesemia and hypocalciuria, has also been associated with mutations in the *CLCNKB* gene encoding the chloride channel ClC-Kb, the cause of classic Bartter syndrome. It should be noted, however, that hypovolemia is not as severe as it is in classical Bartter syndrome and, therefore, renal PGE_2 production is unequivocal. That is the reason why NSAIDs are not considered particularly useful in the syndrome's treatment setting [3,4,6,13].

Our patient's laboratory workup revealed mild hypomagnesemia and normal 24h urinary calcium excretion. Treatment with spironolactone 50 mg daily and daily oral supplementation with potassium led to total resolution of her symptoms. No magnesium supplementation was considered necessary for her treatment. Potassium-rich dietary regimen was also considered part of the treatment.

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