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ORIGINAL ARTICLE

Hypokalemic rhabdomyolysis in congenital tubular disorders: a case series and a systematic review

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Abstract Hypokalemia is a recognized cause of rhabdomyolysis but very few reports document its association with inborn renal tubular disorders. We report our experience with hypokalemic rhabdomyolysis in 5 pediatric patients affected by inborn renal tubular disorders and the results of a careful review of the literature disclosing 9 further cases for a total of 14 patients (8 male and 6 female subjects, aged between 1.6 and 46, median 16 years). The inborn renal tubular disorders underlying rhabdomyolysis were classic distal renal tubular acidosis (n =7), Gitelman syndrome (n=5), classic Bartter syndrome (n=1), and antenatal Bartter syndrome (n=1). In 8 patients rhabdomyolysis followed an acute intestinal disease, an upper respiratory illness or the discontinuation of regular medication. Five patients experienced two or more episodes of rhabdomyolysis. In 10 patients the underlying renal tubular disorder was recognized concurrently with the episode of rhabdomyolysis or some weeks later. In conclusion some congenital renal tubular disorders predispose to hypokalemic rhabdomyolysis. Prevention of discontinuation of regular medication and electrolyte repair in the context of acute intercurrent illnesses might avoid the development of hypokalemic rhabdomyolysis.

Keywords Bartter syndrome · Distal renal tubular acidosis · Gitelman syndrome · Hypokalemia · Rhabdomyolysis

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Introduction

Rhabdomyolysis is the abrupt breakdown of skeletal muscle fibers resulting in the release of muscle content into the circulation [1–4]. The increased blood concentration of creatine kinase to more than five times the upper normal limit permits this condition to be diagnosed. Rhabdomyolysis originates from a wide range of diseases and circumstances. Muscular trauma is the most traditional cause. Further causes include excessive physical exertion, inherited metabolic diseases such as defects in the glycogen metabolism and mitochondrial fatty acid oxidation, infectious diseases, endocrinopathies, medical drugs, illicit drugs, and alcohol. Finally, electrolyte abnormalities, including hypophosphatemia, hypocalcemia, hypernatremia, hyponatremia, and especially hypokalemia have all been associated with rhabdomyolysis [5, 6].

We report our experience with 6 episodes of hypokalemic rhabdomyolysis in 2 Swiss and 3 Italian patients

affected by inborn renal tubular disorders and the results of a careful review of the literature.

Case series

Between November 2002 and December 2006, 2 patients with a previously recognized renal tubular disorder (patient I, affected with antenatal Bartter syndrome; and patient II, affected with classic primary renal tubular acidosis) presented with a total of three episodes of both mild to moderate rhabdomyolysis and hypokalemia (Table 1). In 3 further patients (patients III, IV, and V; Table 1) each with 1 acute episode of mild to moderate rhabdomyolysis concomitantly associated with hypokalemia (patients III and V), but without any previously recognized renal tubular disorder, rhabdomyolysis was surprisingly followed by persisting normal anion gap metabolic acidosis (patient III) and hypokalemia (patients IV and V) prompting further diagnostic testing.

In the 5 patients the main symptoms of acute rhabdomyolysis were widespread muscular weakness or "aches and pain". In patients I, II, III, and V urine was normal in color, but + to ++ positive for "blood" on a dipstick; however, microscopic urinalysis failed to disclose hematuria. In patient IV urinalysis was negative for "blood" both on a dipstick as well as on microscopy. The course of rhabdomyolysis was never complicated by acute kidney injury (>25 μmol/L rise or increase by ≥50 percent in circulating creatinine) or hyperkalemia (>5.0 mmol/L).

In patient II and, some weeks after the acute episode of rhabdomyolysis, in patient III as well, the diagnosis of distal renal tubular acidosis based on at least two separate evaluations concurrently detecting metabolic acidosis (bicarbonate <18.0 mmol/L), urinary pH >6.20 and impaired urinary ammonium excretion, as indicated by the sum of urinary sodium and potassium greater than chloride [7, 8]. In patient III the diagnosis of distal renal tubular acidosis was further confirmed during maximal urinary alkalization after sodium bicarbonate load: a urinary pH of 7.78 was associated with a reduced urine-to-blood carbon dioxide tension gradient of 3 mmHg (reference: ≥20 mmHg) and a reduced fractional bicarbonate excretion of 2.53×10^{-2} (reference: $\geq5.00\times10^{-2}$). In both patient II and patient III the blood levels of calcium and phosphate were normal, and tandem mass spectrometry failed to demonstrate elevated free and short chain acylcarnitine levels with low long-chain acylcarnitine levels, the characteristic biochemical features of carnitine palmitoyl transferase 1 deficiency. In both patients long-term oral management with alkaline agents was followed by normalization of the acid-base balance and normal growth.

In patient I the diagnosis of antenatal Bartter syndrome was based on a history of maternal polyhydramnios and prematurity and at least two separate evaluations detecting normal blood pressure, hyperbicarbonatemia (>27.0 mmol/L), and hypokalemia (<3.6 mmol/L) of renal origin (fractional chloride excretion $>1.50\times10^{-2}$) [9]. In patients IV and V the diagnosis of Gitelman syndrome was made some weeks after the acute episode of rhabdomyolysis based on at least two separate evaluations detecting normal blood pressure, hyperbicarbonatemia, hypokalemia of renal origin, hypomagnesemia (<0.70 mmol/L) of renal origin (fractional magnesium excretion $>4.00\times10^{-2}$), urinary calcium/creatinine ratio after overnight fasting <0.10 mol/mol, and fractional chloride excretion increase by $<2.00\times10^{-2}$ in response to a single oral dose of hydrochlorothiazide of 1 mg/kg body weight [9, 10]. Blood levels of calcium and phosphate were normal in the patient with antenatal Bartter syndrome and in the patients with Gitelman syndrome. In patients I, IV, and V the urinary excretion of organic acids, which is mostly pathologically increased in mitochondrial cytopathies, was found to be within normal ranges.

In the 5 patients audiological evaluation excluded hearing impairment.

No molecular biology studies have been so far made in the patient with antenatal Bartter syndrome and in those with distal renal tubular acidosis. Furthermore, no biallelic mutations in the thiazide-sensitive sodium chloride co-transporter have been so far identified in the 2 patients with Gitelman syndrome.

Systematic review: data sources

Between January and February 2009 we performed a thorough computer-based search of the terms rhabdomyolysis, hypokalemia, renal tubular acidosis, renal tubular disorder, tubulopathy, Bartter, and Gitelman. Pertinent secondary references were also considered. Using this research technique, we were able to accumulate 9 cases (5 male and 4 female subjects, ranging in age between 4.0 and 46, median 21 years) of congenital renal tubular disorders complicated by hypokalemic rhabdomyolysis that have been published in peer-reviewed English-language scientific journals [11–19] between 1983 and 2008. One patient who was reported twice in the literature was considered only once [12, 13].

Results

The 5 patients included in the present case series and the 9 patients published in the scientific literature consisted of 8 male and 6 female subjects and ranged in age between 1.6 and 46 years, median 16 years (Table 2). Ten of the 14 patients (71%) were ≤18 years of age. The renal tubular

Table 1 History, clinical presentation, and acute management of 6 acute episodes of rhabdomyolysis in 5 pediatric patients (3 boys and 2 girls) included in the present report. Rhabdomyolysis originates from many medical or illicit drugs (including alcohol), but none of the patients had a corresponding history. In the 5 patients who were developmentally normal, rhabdomyolysis was not accompanied by altered mental status, hepatomegaly or hypoglycemia

	Patient I	Patient II		Patient III	Patient IV	Patient V
Age, years	4.0	7.2	7.6	1.6	18	15
Gender	Female	Male		Female	Male	Male
Recognized pre-existing tubular disease	Antenatal Bartter syndrome	Classic primary distal renal tubular acidosis		None	None	None
Trigger	Acute disease with diarrhea and vomiting; discontinuation of medical treatment	Upper respiratory illness; discontinuation of medical treatment		Upper respiratory illness; vomiting, fever	"Flu-like" disease, poor fluid intake	Unknown
Presentation	Severe widespread muscular weakness	Widespread muscular weakness		Widespread muscular weakness	Widespread "aches and pains", difficulty walking; benign acute myositis initially suspected	Severe, widespread muscular weakness and muscular cramps
Blood levels						
Sodium, mmol/L	125	142	140	141	134	140
Potassium, mmol/L	<1.5[b]	1.9	1.2	1.4	3.7	2.1
Bicarbonate, mmol/L	32.8	15.8	14.6	14.9	Not assessed	28.7
Creatinine, μmol/L	34	51	59	24	68	63
Creatine kinase, ratio[a]	11	18	13	14	83	7.7
Acute management	Parenteral volume expansion with intravenous isotonic saline and parenteral potassium chloride (up to 18 mmol/kg body weight daily)	Parenteral potassium chloride 4 mmol/kg body weight daily and potassium sparing diuretics	Parenteral potassium chloride 5 mmol/kg body weight daily and oral potassium chloride	Parenteral potassium chloride 5 mmol/kg body weight daily. Later correction of acidosis with potassium citrate and sodium bicarbonate	Liberal fluid intake, paracetamol	Liberal fluid intake and oral potassium chloride
Pre-existing tubular disease recognized after acute rhabdomyolysis				Primary distal renal tubular acidosis	Gitelman syndrome	Gitelman syndrome

[a] Measured creatine kinase level divided by the upper normal limit (ratio is calculated in order to compare results obtained using different laboratory techniques)

[b] Lower limit of detection for the laboratory

Table 2 Clinical and laboratory features in 14 patients with hypokalemic rhabdomyolysis complicating the course of an inborn renal tubular disorder (8 male and 6 female subjects, ranging in age between 1.6 and 46, median 15 years)

	Number of patients
Underlying renal tubular disorder	
Classic distal renal tubular acidosis	7[b]
Gitelman syndrome	5
Classic Bartter syndrome	1
Antenatal Bartter syndrome	1
Possible trigger	
Present[a]	8
Upper respiratory illness (with or without fever)	5
Intestinal disease (diarrhea or vomiting)	3
Discontinuation of regular medication	3
Unknown	6
Two or more episodes of rhabdomyolysis	5
Circulating potassium level	
≤2.1 mmol/L	11
2.2–3.5 mmol/L	2
≥3.6 mmol//L	1

[a] More than one trigger in some cases

[b] In one case associated with deafness

disorders underlying hypokalemic rhabdomyolysis were alkalotic renal hypokalemia and classic distal renal tubular acidosis in each of 7 cases. In 10 out of the 14 patients the underlying inborn renal tubular disorder was recognized concurrently with the acute episode of rhabdomyolysis or some weeks later. In 8 patients rhabdomyolysis followed an acute disease with diarrhea and vomiting, an upper respiratory illness (with or without fever) or the discontinuation of regular medication. In 5 patients recurrent episodes of rhabdomyolysis were noted. Severe hypokalemia (≤2.1 mmol/L) was noted at presentation in 11 patients. Circulating potassium was less severely reduced or even normal in the remaining patients. Characteristic electrocardiogram abnormalities without cardiac arrhythmias or respiratory muscle weakness were noted in severe hypokalemia.

In patients with distal renal tubular acidosis potassium chloride in a dose up to 5 mmol/kg body weight by mouth or, in the presence of conditions limiting its intake or absorption, by an intravenous route, rapidly normalized circulating levels of this ion. However, in Gitelman syndrome, classic Bartter syndrome, and especially in antenatal Bartter syndrome the correction of hypokalemia sometimes required the simultaneous administration of high dose intravenous potassium chloride (up to 20 mmol/kg body weight daily) combined with either a non-steroidal anti-inflammatory agent or a potassium-sparing diuretic. The course of hypokalemic rhabdomyolysis was complicated by the transient development of moderate to severe acute kidney injury in one patient [15]. Mild hyperkalemia (5.3 mmol/L) was noted in one case [11].

Discussion

Rhabdomyolysis is a recognized complication of severe hypokalemia [5, 6]. The most common conditions underlying hypokalemic rhabdomyolysis are diarrhea, abuse of laxatives, celiac disease, eating disorders, use of diuretics, eating liquorice, and excessive mineralocorticoids. The present case series and systematic reviews indicate that inborn renal tubular disorders, such as distal renal tubular acidosis, Gitelman syndrome, and the various forms of Bartter syndrome may cause hypokalemic, often recurrent rhabdomyolysis. Furthermore, the present data indicate that in inborn renal tubular disorders acute diseases that tend per se to decrease circulating potassium and short-term discontinuation of regular medication may trigger hypokalemic rhabdomyolysis. Finally, since rhabdomyolysis may elevate the concentration of potassium in blood, hypokalemia as a cause of rhabdomyolysis sometimes goes unrecognized. This observation is of paramount importance, considering that inborn tubular disorders often cause hypokalemic rhabdomyolysis before they have been appropriately diagnosed.

The consequences of rhabdomyolysis include acute kidney injury and hyperkalemia, which may cause fatal cardiac dysrhythmia [1–4]. The mainstay of treatment is aggressive intravascular volume expansion to promote diuresis and the elimination of the muscle content, including potassium, released into the circulation [1–4]. In hypokalemic rhabdomyolysis repairing hypokalemia to prevent the aggravation of rhabdomyolysis is a further treatment modality. However, considering that potassium administration is a common cause of threatening hyper-

kalemia, this treatment modality appears at first glance hazardous in the context of rhabdomyolysis. The present analysis, though, indicates that in hypokalemic rhabdomyolysis secondary to inborn renal tubular disorders management of hypokalemia with potassium chloride rarely leads to potentially life-threatening hyperkalemia. Furthermore, significant acute kidney injury rarely occurs. Actually, in most instances of hypokalemic rhabdomyolysis secondary to an alkalotic renal hypokalemia, repairing the potassium deficit requires large amounts of potassium chloride. Hence, close monitoring of potassium, creatinine, and urea levels is crucial in this setting.

Hypokalemia is the most recognized laboratory feature in Gitelman syndrome and in the various forms of Bartter syndrome. The defect underlying these conditions, an impaired tubular reabsorption of sodium chloride, leads to volume depletion, resulting in activation of the renin–angiotensin–aldosterone system and enhanced urinary potassium elimination [9]. Patients with classic distal renal tubular acidosis may be normo- or hypokalemic. In this condition the impairment in the proton pump results in inappropriate potassium secretion in the cortical collecting duct. In addition, metabolic acidosis diminishes proximal fluid reabsorption leading to increased distal salt delivery and secondary hyperaldosteronism with increased urinary potassium losses [7, 20].

The differential diagnosis of carnitine palmitoyl transferase 1 deficiency [8, 21] deserves consideration in patients presenting with both rhabdomyolysis and disturbed renal tubular acidification and that of Kearns–Sayre syndrome [22] in those with both rhabdomyolysis and renal dysfunction resembling Bartter and related syndromes.

Calf pain, weakness of the lower extremities, inability or refusal to walk in the context of an influenza-like illness and elevated creatine kinase levels are the features of benign acute myositis. This condition, which typically affects children and adolescents and resolves within 3 to 10 days [2], had been initially suspected in one of our patients. On the other hand, medical drugs, including among others antipsychotics and statins, illicit drugs and alcohol have been implicated as a cause of rhabdomyolysis [1–4]. We speculate that in patients affected by the renal tubular disorders mild to moderate hypokalemia, benign acute myositis, medication with the mentioned drugs, illicit drugs or alcohol might concur to cause rhabdomyolysis.

In Gitelman syndrome and in the various forms of Bartter syndrome intercurrent illnesses or discontinuation of regular medication sometimes exacerbate hypokalemia and therefore may cause severe cardiac arrhythmias [23]. The present observations indicate that congenital renal tubular disorders predispose to hypokalemic rhabdomyolysis as well. It behoves us to alert physicians caring for patients with renal tubular disorders to this complication. The challenges with this complication are the prevention of short-term discontinuation of regular medication and early referral for prompt electrolyte repair in the context of acute intercurrent illnesses, even if apparently benign. A set of rules that patients could be educated to follow has been proposed [24].

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