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Case Report

Rhabdomyolysis in diabetic ketoacidosis

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Abstract: Rhabdomyolysis is a potentially lethal disorder, characterized by elevated serum concentrations of creatine kinase (CK) due to skeletal muscle injury. In this paper a patient with diabetic ketoacidosis (DKA) is reported who developed rhabdomyolysis (maximum CK level, 37 700 U/L; normal, < 170 U/L), anemia (6.2 g/dL) and thrombocytopenia (16 000/μL). This combination of rhabdomyolysis with anemia and thrombocytopenia has not yet been reported in DKA. The pathogenic mechanism leading to rhabdomyolysis in DKA remains unsettled. From the literature it seems that those patients who develop rhabdomyolysis have very high glucose levels and a high osmolality on admission. Low phosphate levels can play a role as well. The etiology of anemia and thrombocytopenia in our patient remains obscure. Intravascular hemolysis could not be demonstrated but intramedullar hemolysis, due to osmolar shift or hypophosphatemia, cannot be excluded. A review of the literature data revealed that rhabdomyolysis is not so uncommon in DKA. However, to obtain incidence data in children, prospective studies are necessary.

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Rhabdomyolysis is a potentially lethal disorder, characterized by elevated serum concentrations of creatine kinase (CK), lactate dehydrogenase (LDH), and alanine aminotransferase (ALT) due to skeletal muscle injury. Various etiologies are known, such as excessive muscular activity, trauma, drugs, infections, metabolic disorders, genetic or immunologic diseases. This report describes the occurrence of rhabdomyolysis in association with diabetic ketoacidosis (DKA) in a 15-month-old boy.

Case report

A 15-month-old boy presented with lethargy and vomiting for the past 3 d. He was afebrile. On admission he was severely dehydrated and comatose. His lungs were clear to auscultation, the heart sounds were normal but peripheral pulses were weak. Blood pressure was 85/55 mmHg. There was no hepatosplenomegaly. Tendon reflexes were symmetrical. Admission laboratory values indicated severe hyperglycemia (1600 mg/dL), a serum sodium concentration of 155 mmol/L and acidosis (HCO_3^-, 13.9 mmol/L). Diabetes with ketoacidosis was diagnosed. His HbA1c was 10.7% (normal, 4–6%). There was no family history of diabetes. Before transportation to our hospital the patient received sodium bicarbonate (1.5 mEq/kg) and an infusion of normal saline (10 mL/kg). Regular insulin (two units per kg body weight) was given subcutaneously before insulin infusion (0.05 U/kg/h) was started. Six hours later glycemia had dropped to 580 mg/dL and the serum sodium concentration increased to 179 mmol/L (Table 1). Glucose infusion was progressively introduced (NaCl 0.45%/Gluc 5%). Serum sodium concentration remained high and was normalized over 12 h by an infusion with glucose 5%. Hereupon the boy developed unilateral seizures during 1.5 min. Ophthalmologic examination did not reveal papilledema and a CT of the brain was normal. Over the next 24 h the boy's circulation and consciousness improved but it was noted that he was very quiet and

immobile. Every manipulation seemed to be painful. Thereupon serum CK was determined and was found to be greatly increased with a maximum of 37 700 U/L on day 7 (normal < 170 U/L). Serum concentrations of aspartate aminotransferase (AST), ALT and LDH were elevated as well [LDH, 3597 U/L (normal, 240–480 U/L); AST, 658 U/L (normal, 5–37 U/L); ALT, 282 U/L (normal, 5–40 U/L)]. The serum potassium and phosphate concentrations are reported in Table 1. Phosphate decreased on day 3 to a level of 1.84 mg/dL, which is very low for a 15-month-old boy, but he responded promptly to treatment. Concomitant with the increase in CK, a drastic fall in hemoglobin and thrombocytes was noted: hemoglobin fell from 10.5 to 6.3 g/dL on day 7. The peripheral platelet count decreased and reached a nadir of 16 000/μL on day 6. Renal function remained normal. The patient received a packed cell and platelet transfusion and during the following days, all the laboratory values recovered progressively. The patient could be discharged after 3 weeks. Genetic analysis revealed that he had a high-risk genotype (HLA-DQA3-DQB3.2/DQA4-DQB2). Furthermore, it was demonstrated that all autoantibodies were positive [protein tyrosine phosphatase (IA2A), insulin autoantibodies (IAA), islet cell antibodies (ICA) and glutamic acid decarboxylase antibodies (GADA)]. When last seen, 10 months after discharge, the boy was in good, general health and his psychomotor development was normal. Neurological examination was completely normal. Therefore, no additional imaging has been performed until now. His treatment consisted of insulin given twice daily (total dose: 0.8 U/kg/d) and his HbA1c was 7.1%.

Discussion

The patient described in this case report had the characteristic clinical features of DKA but, in addition, his clinical course was characterized by some complications. On day 3 he developed seizures. These are a well-known complication of DKA but usually develop 4–12 h after the initiation of therapy (1). Here, the seizures were most probably caused by the osmolar shifts induced by the rapid correction of hypernatremia with hypotonic (0.45) saline solution (2).

Our patient also developed some unusual complications: rhabdomyolysis, anemia and thrombocytopenia. Well-known causes of rhabdomyolysis, such as drugs (statins, clarithromycin, neuroleptics…), toxins, muscle-enzyme deficiencies, metabolic diseases and bacterial or viral infections were investigated with negative results except for a positive throat swab for influenza A virus.

Viral infections, such as influenza virus (especially B), can cause rhabdomyolysis. However, infectious rhabdomyolysis is most often associated with high fever, and CK levels are lower than in non-infectious rhabdomyolysis (3). Moreover, bacterial cultures were negative and serum amylase and lipase concentrations were normal. Therefore we wondered whether the rhabdomyolysis in our patient could be directly related to the diabetes; hence, the literature was reviewed. The literature provided strong arguments for a direct relationship between DKA and rhabdomyolysis.

In 1962 Rainey et al. (4) described the first case of myoglobinuria in DKA: a 36-year-old black man who developed muscle weakness and myoglobinuria on the second day after diagnosis of DKA. Clinical and laboratory manifestations were reviewed and speculating on the physiopatholgy, the authors concluded that 'diabetes has heretofore not been reported as causing myoglobinuria and it seems unlikely that such a relationship would have gone unrecognized'. In 1981, Buckingham et al. (5) described a 2-year-old boy with DKA and rhabdomyolysis and Koh et al. (6) reported on an 11-year-old boy with very similar clinical and biochemical features. Three other patients who developed acute renal failure due to rhabdomyolysis during DKA are described in the literature (7–9).

To get more insight into the frequency of this complication, Møller-Petersen et al. (10) investigated serum levels of myoglobin and serum activity of CK isoenzyme MM in 12 patients admitted with DKA. In five patients, hypermyoglobinemia and elevated

Table 1. Laboratory results and fluid therapy of our patient (from day 1 until day 6)

	Admission	6 h	18 h	Day 3	Day 4	Day 5	Day 6
Glucose (mg/dL)	1600	580	171	182	183	258	179
Na (mmol/L)	155	179.0	184.1	146.9	145.5	138.2	137.9
K (mmol/L)	3.97	3.5	3.48	3.57	3.47	5.01	4.44
P (mg/dL)	–	–	3.95	1.84	2.73	3.55	3.61
HCO_3 (mmol/L)	13.9	22.5	26.1	27.0	24.2	16.9	21.9
Creatinine (mg/dL)	1.96	1.16	0.79	–	0.48	0.53	0.44
Hb (g/dL)	–	–	10.5	10.3	9.9	6.3	10.8
Platelets (10^9/L)	–	–	191	136	62	16	81
CK (U/L)	–	–	–	–	–	19 209	37 700
Fluids	NaCl 0.9%	NaCl 0.45% Gluc. 5%	Gluc. 5%	TPN	TPN	TPN	TPN

TPN, total parenteral nutrition; CK, creatine kinase.

activity of CK isoenzyme MM was found. This group had significantly higher median blood glucose levels and higher median serum osmolality on admission (10). These findings were confirmed by another study in which 41 patients with DKA and rhabdomyolysis were compared with 36 patients suffering from DKA without rhabdomyolysis (11). The values for serum potassium, bicarbonate, phosphate and calcium did not differ between the two groups. However, the mean serum sodium level, the mean blood glucose level and the osmolality on admission were higher ($p < 0.001$) in those patients with rhabdomyolysis than in those without. Wang et al. (12) encountered 44 cases of rhabdomyolysis in 265 diabetic emergencies and found that the patients who developed rhabdomyolysis had higher levels of serum sodium, serum creatinine, blood urine nitrogen and osmolarity on admission.

The pathogenic mechanism leading to rhabdomyolysis in DKA remains unresolved. Zierler (13) has shown that alteration of electrolytes and glucose in the incubation medium in the presence of insulin can lead to leakage of intracellular enzymes from an isolated *in vitro* muscle preparation. In streptozotocin-diabetic rats, the soleus muscle showed a 48% increase in intracellular Na^+ content, and such an increase is usually associated with an increase in intracellular Ca+ (14, 15). Persistently high intracellular calcium may result in activation of neutral proteases and subsequent leakage of muscle enzymes (11). In experiments using rat thymocytes, it was demonstrated that cells regain their normal volume after shrinking in hypertonic solution, via activation of Na^+/H^+ antiport which operates in parallel to a Cl^-/HCO_3^- exchanger (16). This volume-induced activation of Na/H exchange may potentiate an increase in intracellular calcium, possibly via activation of kinases. Thus, the diabetic as well as hyperosmolal state may have an additive effect in causing an elevation of intracellular calcium. Other factors that could play a role in the development of rhabdomyolysis in DKA are potassium and phosphate depletion (due to renal loss and the intracellular shift during insulin treatment) (17, 18). In our patient, all these factors might have played a role in the induction of rhabdomyolysis.

The combination of rhabdomyolysis with anemia and thrombopenia has not been described previously in DKA. In the literature, two patients with acute hemolytic anemia secondary to severe hypophosphatemia after treatment for DKA are reported (19). Our patient did have a low concentration of phosphate on day 3. Intravascular hemolysis could not, however, be demonstrated (normal reticulocytes, normal haptoglobin). Intramedullar hemolysis (due to osmotic shifts or hypophosphatemia) is another possible mechanism and cannot be excluded since no bone marrow examination was performed.

In conclusion, rhabdomyolysis is not uncommon in adults with DKA. However, prospective studies are necessary to obtain incidence data in children. Once rhabdomyolysis has occurred, protective measures should be taken to preserve renal function and diminish the morbidity and mortality of this complication.

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