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Brief report

Rhabdomyolysis and acute renal failure in a child with influenza A infection

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Abstract. A 13-year-old previously healthy girl developed rhabdomyolysis and acute renal failure during influenza A infection. The patient recovered renal function completely with supportive therapy. This complication has been described in adult patients, but progression to acute renal failure in this context has not been reported previously in children. This diagnosis should be considered in the differential diagnosis of a pediatric patient presenting with acute renal failure and viral symptomatology.

Key words: Acute renal failure – Rhabdomyolysis – Myoglobinuria – Influenza

Introduction

Rhabdomyolysis with acute renal failure due to influenza infection is a rarely reported complication in adults [1–4]. Although rhabdomyolysis with myoglobinuria has been described in children [5, 6], acute renal failure in this context has been reported only once, in a child with carnitine palmityl transferase deficiency [7]. We report an otherwise well pediatric patient who developed rhabdomyolysis and acute renal failure in association with influenza A infection.

Case report

A 13-year-old African-American girl with a past medical history significant only for asthma presented to the Children's Hospital of Philadelphia with a 1-day history of "aching in the chest", emesis, and high fever. Physical examination at that time was notable for a temperature of 39.5 °C, erythematous oropharynx, and normal lung and cardiac examinations. She appeared well hydrated. Rapid streptococcus testing was negative. She was diagnosed with a presumed viral upper respiratory tract infection and discharged home on acetaminophen. Over the intervening week, the fever persisted in the range of 103–104 °F. She complained of myalgias, cough, and rhinorrhea. She had occasional emesis but no diarrhea. Her oral intake was reported to be poor. She had ingested 400 mg of ibuprofen daily for the 7 days prior to presentation (total cumulative dose 2.8 g). On the day prior to admission she developed abdominal pain and oliguria. She denied dysuria, dark urine, headache, vision changes, or rash. She had no prior history of urinary tract infection, macroscopic hematuria, polydipsia, or polyuria. The family history was noncontributory.

On repeat presentation to the emergency department, she appeared ill, but not toxic. Her pulse was 83/min, respirations 20/min, temperature 36.6 °C, and blood pressure 120/80 mmHg (supine), 92/53 mmHg (standing). Her weight was 49.5 kg. Pulse oximetry was 97% while breathing room air. Her mucous membranes were tacky and her lips were dry. Her throat was erythematous without exudates. Expiratory wheezes were present bilaterally. Cardiac examination was normal. Her abdomen was soft with mild periumbilical tenderness on palpitation, but no rebound, guarding, masses, or organomegaly. Muscles of the extremities were mildly tender on palpation; strength was grossly intact. There was no edema noted.

Laboratory studies included serum sodium 137 mmol/l, potassium 5.3 mmol/l, chloride 90 mmol/l, bicarbonate 19 mmol/l, urea 103 mg/dl, creatinine 9.7 mg/dl, calcium 7.3 mg/dl, and phosphorus 12.4 mg/dl. Serum albumin was 3.7 g/dl, alkaline phosphatase 59 U/l, alanine amino transferase 461 U/l, aspartate amino transferase 1,232 U/l, and total bilirubin 0.5 mg/dl. Urinalysis showed amber-colored urine with 4+ blood, 3+ protein, specific gravity 1.017, pH 6.0, and microscopy with 3–5 red blood cells/high-power field, 5–10 white blood cells/high-power field, and no casts. White blood cell count was 12.2/μl, hemoglobin 13.4 g/dl, and platelet count 294/μl. Creatine kinase was markedly elevated at 421,000 IU/l (confirmed by dilution). Urine myoglobin was greater than 1,250 ng/ml (normal less than 55 ng/ml).

She was admitted and given fluid resuscitation with normal saline, then continued on intravenous hydration. Urine output was 0.5 ml/kg per hour on the 1st day of admission. Acetazolamide was given in an attempt to alkalinize the urine. However, the patient developed acute chest pain and tingling of the extremities, and the medication was discontinued. Cardiac examination was unremarkable and electrocardiogram revealed a mildly prolonged QT interval consistent with hypocalcemia. By the 2nd hospital day, urine output increased to 1.4 ml/kg per hour and remained adequate throughout the remaining hospitalization. With hydration, the phosphorus decreased to 8.4 mg/dl. She was given bicarbonate-containing intravenous fluids and intravenous calcium gluconate.

A renal ultrasound showed enlarged echogenic kidneys. Additional diagnostic tests included antineutrophil cytoplasmic antibody, streptozyme, and throat culture, all of which were negative. Complement (C3)

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was normal. An antinuclear antibody titer was positive at 1:320 in a speckled pattern, but DNA binding was negative. A rapid respiratory viral antigen panel was negative, but the culture was subsequently positive for influenza A.

The patient's creatinine rose to a maximum of 11.8 mg/dl on the 4th hospital day. Her abdominal pain and emesis slowly improved. Mild hypertension with a maximum blood pressure of 147/72 mmHg was noted and resolved without treatment. By the 9th hospital day, the creatinine dropped to 4.7 mg/dl. Creatine kinase also dropped significantly to 18,539 IU/l. She was discharged home on the 10th hospital day. One week later, her serum creatinine was 1.7 mg/dl. It normalized to 0.8 mg/dl within 4 weeks.

Discussion

Rhabdomyolysis has been reported in association with a variety of infections, including coxsackie virus, infectious hepatitis, leptospirosis, rocky mountain spotted fever, and influenza [8]. Patients with influenza-associated rhabdomyolysis typically present with dark-colored urine and tender, painful muscles. The degree of muscle involvement and pain may be significantly greater than the usual myalgias seen commonly with influenza infection. However, not all patients with rhabdomyolysis exhibit clinical evidence of myositis [1]. Our patient had only mild tenderness of the large muscle groups of the extremities. In patients with rhabdomyolysis who go on to develop acute renal failure, characteristic laboratory findings include hyperkalemia, hyperphosphatemia, and a rapidly rising creatinine, all of which may be out of proportion to the degree of renal insufficiency [8]. Urinalysis typically reveals large occult blood by dipstick without microscopic evidence of hematuria. Hypocalcemia due to calcium phosphate and calcium carbonate deposition in injured muscle may be seen. It is sometimes followed paradoxically by hypercalcemia in the recovery phase as deposited calcium is mobilized [8]. Serum creatine kinase is invariably markedly elevated. Abnormal urine myoglobin levels are also usually demonstrated, although elevations may not be seen if samples are taken later in the course of the illness [5, 9].

The mechanism of renal injury in myoglobinuria remains unclear. Hypotheses include vasoconstriction due to inhibition of endothelial relaxing factor, oxygen free radical formation, decreased oxygen availability in the tissues due to myoglobin binding, and tubular obstruction with myoglobin casts [10]. Direct nephrotoxicity of myoglobin has also been proposed as a mechanism. However, animal experiments involving infusions of myoglobin do not consistently induce renal injury [10, 11]. Animal studies and clinical observations have also highlighted the importance of predisposing factors such as volume depletion (dehydration or blood loss) and acidosis [10, 11]. In the above case, the patient was significantly dehydrated from poor enteral intake compounded by vomiting. Hyperuricemia has also been suggested as a contributor to renal injury [8, 10, 11]. Other agents, such as non-steroidal anti-inflammatory medications, may also play a role in initiating or perpetuating injury [12, 13]. This patient took several doses of ibuprofen during the early phase of her illness.

A number of treatments have been utilized in patients with traumatic and non-traumatic rhabdomyolysis and renal failure. Prospective studies in humans are few. However, animal models, in particular glycerol-induced rhabdomyolysis in the mouse, have provided some insights. Zager [11] demonstrated that tubular deposition of myoglobin is highly pH dependent. This study gave credence to the clinical observation that patients with rhabdomyolysis benefit from efforts to alkalinize the urine. Systemic alkalinization, however, may induce hypocalcemic tetany. Urinary alkalinization can also be problematic in patients who have an elevated calcium phosphorus product and may be at risk for metastatic calcifications or calcium phosphate deposition in the tubules. Acetazolamide may provide an alternative method for alkalinization. In this patient, for unclear reasons, it was poorly tolerated.

In further studies, Zager et al. [14] examined the role of mannitol in the treatment of myoglobinuric renal failure. The protective effect seen was due primarily to its diuretic properties, rather than a direct beneficial action. They also found that mannitol transiently decreased tubule cell ATP levels. Given the risk of hyperosmolarity in patients with oliguria, the routine administration of mannitol is probably not advisable. Alternative diuretics, such as furosemide, should be considered. Dialysis (peritoneal or hemodialysis) may be required in more severe cases [3, 4, 8].

The outcome for myoglobinuric acute renal failure is generally good. Most patients (as reported primarily in the adult literature) regain full kidney function. However, the long-term effects have not been well studied and outcomes in children are not known. In general, extensive evaluation (including renal biopsy) may not be warranted in the acute phase, if myoglobinuria is strongly suspected or confirmed. Patients with a history of recurrent hematuria associated with viral illness may require further evaluation for carnitine palmityl transferase deficiency. This disorder may present as a spectrum from mild, clinically insignificant disease in adults, to severe, occasionally fatal rhabdomyolysis in children [7].

It appears that adults are more susceptible than children to myoglobinuric renal failure with influenza infection. This is particularly interesting since the peak incidence of myositis is in school-aged children [2]. It is possible that myoglobinuria is more common in children than appreciated but only becomes clinically evident in a small number of patients. Adults may become more acutely ill with influenza infection, and thus may be more at risk for dehydration and starvation ketosis. Non-steroidal anti-inflammatory medication use is probably more common in adults than children, but this practice may be changing.

Although significant myoglobinuria with progression to acute renal failure appears to be uncommon in children, our patient underscores the need to include this possibility in the differential diagnosis of any child who presents with acute renal failure and viral symptomatology.

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The magnitude of metabolic acidosis is dependent on differences in bicarbonate assays

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Metabolic acidosis has been recently recognized as an important comorbid event in the high mortality rates seen in patients with end-stage renal disease. The recognition of hypobicarbonatemia is dependent on a reliable assay for total carbon dioxide (TCO_2). It is common practice for dialysis facilities to send blood samples for testing to remote laboratories, which may assay bicarbonate differently than the local hospital. We noted that serum bicarbonate concentrations from blood samples sent to our reference laboratory were significantly lower (4 mEq/L) compared with blood samples sent to our local laboratory. Blood samples were assayed for TCO_2 using an enzymatic technique (in the reference laboratory) and direct measurement using an electrode (in the local laboratory). The blood test results for TCO_2 sent to the reference laboratory (18.7 ± 0.8 mEq/L) were significantly lower than samples assayed in our local laboratory (22.2 ± 0.7 mEq/L). In conclusion, recognition of the differences in assays used in the laboratory for routine bicarbonate measurements is important in defining the magnitude of metabolic acidosis and in helping to dictate appropriate therapy.

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Identification and localization of polycystin, the *PKD1* gene product

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Polycystin, the product of autosomal dominant polycystic kidney disease (ADPKD) 1 gene is the cardinal member of a novel class of proteins. As a first step towards elucidating the function of polycystin and the pathogenesis of ADPKD, three types of information were collected in the current study: the subcellular localization of polycystin, the spatial and temporal distribution of the protein within normal tissues and the effects of ADPKD mutations on the pattern of expression in affected tissues. Antisera directed against a synthetic peptide and two recombinant proteins of different domains of polycystin revealed the presence of an ~400-kD protein (polycystin) in the membrane fractions of normal fetal, adult, and ADPKD kidneys. Immunohistological studies localized polycystin to renal tubular epithelia, hepatic bile ductules, and pancreatic ducts, all sites of cystic changes in ADPKD, as well as in tissues such as skin that are not known to be affected in ADPKD. By electron microscopy, polycystin was predominantly associated with plasma membranes. Polycystin was significantly less abundant in adult than in fetal epithelia. In contrast, polycystin was overexpressed in most, but not all, cysts in ADPKD kidneys.