Medical Staff Conference

Refer to: Rhabdomyolysis—Medical Staff Conference, University of California, San Francisco. West J Med 125:298-304, Oct 1976

Rhabdomyolysis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *Today we are going to present the case of a patient in whom rhabdomyolysis developed for which we have no clear-cut explanation. In our ignorance we assume that it was secondary to "a virus infection." Dr. Haughom will summarize the case presentation.*

Case Summary

DR. HAUGHOM:† This was the first admission to the University of California Medical Center for a 45-year-old mother of seven children. The patient had been transferred from Modesto for evaluation of severe swelling and tenderness of the legs and arms following an influenza-like syndrome. Approximately two weeks before admission, the patient reported that an influenza-like illness had developed in her children, associated with cough, symptoms of upper respiratory infection and weakness. They subsequently recovered, but then the patient herself noted the onset of similar symptoms one week before admission. She noted symptoms at that time of feeling weak, coughing with production of a small amount of white to brown sputum, a runny nose, sore throat, occasional temperature to 104°F and intermittent chills. Five days before admission she further noted the onset of low back pain and bilateral leg pains. Leg pain increased and her legs began to swell, for which she consulted her private physician.

An initial diagnosis of influenza-like syndrome was made and pain medications were prescribed. These failed to relieve the pain, and the swelling continued until she was unable to walk or stand on her legs. The patient was admitted to a local hospital where her legs were noted to be swollen and tender to a pronounced degree; her arms were somewhat less swollen. Significant laboratory data at that time showed a leukocyte count of 17,000 per cu mm with 80 percent neutrophils, a value for creatine phosphokinase (CPK) of 5,653 IU per liter and normal findings on analysis of urine. Treatment with glucocorticoid hormones was begun. The following day the urine was found to be dark red in color, but no red blood cells were seen in the sediment. The patient was then transferred to the University of California Medical Center so that further evaluation and treatment could be carried out.

In response to questions, the patient said that there had been no significant previous illness, and that she had noted no headaches, stiff neck, photophobia, difficulty in vision, shortness of breath, nausea, vomiting, diarrhea, dysuria, hematuria or arthralgia. There was no recent history of animal or insect bites, recent travel or medicine ingestion. She also said that there had been no recent chemical or toxin exposure. The remainder of the medi-

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ABBREVIATIONS USED IN TEXT
BUN = blood urea nitrogen
CPK = creatine phosphokinase
CPK-2 = CPK isozyme-2
CPK-3 = CPK isozyme-3
PAH = para-aminohippurate
SGOT = serum glutamic-oxaloacetic transaminase
TEM = tetraethylammonium

cal history and review of systems was noncontributory.

On physical examination, the patient was noted to be somewhat heavyset and in moderate distress because of pain in the legs. Blood pressure was 140/90 mm of mercury, pulse 110 beats and regular, temperature 98°F (36.7°C) rectally and respiratory rate was 20 per minute and regular. The skin was dry and cool to the touch, no rash was present and no adenopathy was detected. The neck was supple and there was no jugular venous distention noted. Examination of the chest showed a few dry bibasilar rales but the chest was otherwise clear. Findings on cardiovascular examination were remarkable only for grade II/VI systolic ejection murmur. The abdomen was soft, bowel sounds were normal and there were no masses, tenderness or hepatosplenomegaly. Results of rectal examination were within normal limits. A stool specimen was guaiac negative. Musculoskeletal examination showed no costovertebral angle tenderness and there was no sacral edema. The legs were notably swollen bilaterally; the skin was tense and very tender but no erythema was found. The feet were cool bilaterally from the ankles down with poor peripheral pulses. Both arms were also swollen and tender but less so than the legs. Neurological examination was within normal limits.

Laboratory data on admission included a hematocrit reading of 40.7 percent and leukocyte count of 27,500 per cu mm with 76 percent polymorphonuclear cells. A specimen of urine was seen to be burgundy in color; on analysis, pH was 6, there were no red cells in the sediment, and the specimen was strongly positive for myoglobin. Findings on x-ray films of the chest showed no abnormalities. On an electrocardiogram diffuse precordial T-wave inversion was seen. Studies of electrolytes gave the folowing values: serum sodium, 121; potassium, 5.2; chloride, 90, and carbon dioxide (CO_2), 22 mEq per liter; serum calcium was 7.1 mg per 100 ml on admission. CPK was greater than 14,000 IU per liter, with 48 percent CPK isozyme-3 (CPK-3) and 52 percent CPK isozyme-2 (CPK-2); aldolase was 210 milliunits (mU) per ml (normal: 2 to 9), and serum glutamic-oxaloacetic transaminase (SGOT) was 560 IU per liter (normal: 5 to 40).

It was felt at the time of admission that the patient was suffering from an acute viral myositis with associated rhabdomyolysis and myoglobinuria. An intravenous line was placed and hydration carried out vigorously with normal saline and sodium bicarbonate solution to alkalinize the urine. High doses of glucocorticosteroids were also administered, but with rapid clinical improvement these were quickly tapered to zero during the next week. The muscle tenderness persisted and very slowly resolved under physical therapy during the next three to four weeks. Because of impairment of peripheral pulses in the lower extremities, consultation with a vascular surgeon was obtained. A joint decision was made to follow the patient closely rather than to carry out any surgical procedure designed to relieve vascular obstruction. With subsidence of the inflammation, circulation to the extremities was improved. Serial measurements of CPK remained notably elevated, and isoenzyme fractionation determined that a large fraction was CPK-2, suggesting cardiac origin. However, this was thought to reflect the high release of muscle CPK rather than indicating any myocardial disease. Findings on electromyography studies were consistent with widespread loss of muscle fiber function. At no time in the course of the patient's illness did any neurological impairment develop, and tests of renal function gave normal findings throughout the stay in hospital.

On the third hospital day, a shaking chill with fever developed, and an infiltrate was seen on x-ray films of the chest. Sputum Gram stain findings were suggestive of pneumococcal infection; this was confirmed on subsequent sputum culture. Therapy was begun with penicillin and chest physical therapy, and there was rapid response to this treatment. A second problem occurring was the development of a slowly falling hematocrit reading which reached 24 percent before starting to increase. The anemia was normochromic and normocytic without evidence of hemolysis or a bleeding abnormality. A low serum iron value was thought to be secondary to loss of iron in the form of myoglobin in the urine. Anemia was at-

tributed to the acute viral syndrome, and it fully resolved during her stay in hospital. The patient was discharged, three weeks after admission to the University of California Medical Center, with normal renal function and without evidence of leg pain, tenderness or swelling. However, it was still possible to detect muscle weakness in the lower extremities.

DR. HUMPHREYS:* Clinically significant rhabdomyolysis presents with a characteristic pattern of clinical signs and symptoms and laboratory findings, many of which were present in this patient during her illness. In this discussion, I plan to point out some of these characteristic findings and to discuss them with respect to both pathogenesis and treatment.

I would like to focus attention initially on some characteristics of myoglobin itself. Myoglobin is a heme-containing compound with a molecular weight of 17,400. It consists of a ferrohemate complex attached to a globin residue which structurally is somewhat different than the globin chains found in the hemoglobin molecule. It is present chiefly in skeletal muscle and in that tissue is present at concentrations of 2.5 grams per 100 grams dry weight of muscle. Its function in muscle tissue is not yet completely characterized, but it is thought to act as an oxygen storing and oxygen transferring compound. Of importance to the present consideration, it has been found that incubation of myoglobin at pH 5.4 results in dissociation of the molecule into its ferrohemate and globin moieties.[1] The ferrohemate complex has a molecular weight of 670 and may be able to penetrate cell membranes readily.

The differential diagnosis of pigmenturia involves chiefly the differentiation of three major entities.[2] In porphyria, the urine is positive for porphobilinogen as measured by the Watson-Schwartz test, and is negative by benzidine. In addition, the serum is clear. In both hemoglobinuria and myoglobinuria results of a Watson-Schwartz test are negative; findings are positive on benzidine test or occult blood test in the urine. Occasionally, the serum of patients with hemoglobinuria will appear pink in color, whereas serum from myoglobinuric patients will be clear. However, in many cases these criteria are not sufficient to discriminate hemoglobinuria from myoglobinuria, and so more specific measures must be used. Absorption spectrometry is a highly reliable means of discriminating between hemoglobin and myoglobin; however, breakdown of heme pigments in the urine renders this test virtually useless. A commonly employed test is that of differential filtration, taking advantage of the fact that hemoglobin has a molecular weight approximately four times that of myoglobin. Once again, this test is less than perfect, since some hemoglobin breakdown products can pass through the types of filters used for this test. Differential solubility of these pigments in ammonium sulfate has also been employed, but this test also is not specific.

Recent emphasis has been on the utilization of more specific methods such as gel electrophoresis and immunodiffusion techniques for the recognition of the myoglobin molecule. In addition, column chromatography has been employed. Whenever the diagnosis of myoglobinuria is entertained, one of these latter specific tests should be used in an effort to determine that myoglobin is the pigment present in the urine.

The clinical settings and some causes of rhabdomyolysis are listed in Table 1.[3] These can be classified broadly into the factors which alter the normal relationships between energy production and consumption in muscle, and into factors

TABLE 1.—*Causes of Rhabdomyolysis**

Increased Energy Consumption
Exercise stress, heat stroke
Malignant hyperthermia, fever
Convulsions, delirium tremens, tetanus
Amphetamines
Decreased Energy Production—Genetic
Impaired carbohydrate metabolism: phosphorylase deficiency, diabetic acidosis, hyperosmolar coma
Impaired lipid metabolism: carnitine deficiency
Decreased Energy Production—Acquired
Potassium depletion
Ethanol
Myxedema
Hypothermia
Hypophosphatemia
Muscle Ischemia With Decreased O_2 Delivery: K Depletion, Crush Syndrome, Arterial Embolism, Etc.
Primary Muscle Injury
Polymositis, dermatomyositis
Trauma, crush
Burns
Infections: Gas Gangrene, Tetanus, Leptospirosis, Viral Influenza, Coxsackie Infection, Shigellosis
Miscellaneous
Venoms: Snake bite, hornet, brown spider
Drugs: Heroin, barbiturates, propoxyphene, methadone, amphetamines, licorice, carbenoxolone
Ethylene glycol

*Adapted from Knochel.[3]

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which produce rhabdomyolysis through direct muscle injury. States such as exercise stress, heat stroke, malignant hyperthermia, convulsions, tetanus and amphetamine ingestion all can be associated with rhabdomyolysis presumably because the increased energy consumption associated with prolonged muscle activity outstrips the ability of the muscle to increase its energy production. On the other hand, certain genetic or acquired deficiencies in muscle energy production can also be associated with rhabdomyolysis. Included among these are muscle phosphorylase deficiency, diabetic acidosis and acquired deficiencies such as potassium depletion and hypophosphatemia. Finally, muscle ischemia with associated decrease in oxygen delivery may also result in rhabdomyolysis and can be seen in crush syndromes, arterial embolism and potassium depletion. Primary muscle injury such as polymyositis, trauma and crush injuries and burns may produce rhabdomyolysis. Infections associated with rhabdomyolysis include gas gangrene, leptospirosis and, of relevance in the case presented this morning, viral influenza. Presumably, rhabdomyolysis results from these infections through a direct damage to muscle cells. Finally, there is abroad miscellaneous category of events associated with rhabdomyolysis; the exact mechanisms by which these agents produce rhabdomyolysis are not known. In the case of many of the drugs mentioned, it is likely that rhabdomyolysis occurs as a result of prolonged coma and associated muscle ischemia.

Clinically, the systems involved in rhabdomyolysis result in a triad consisting of myopathy, neuropathy and nephropathy. Significant rhabdomyolysis will be associated with readily detectable muscle tenderness, weakness and pain. Indeed, the edema and soft tissue reaction associated with the muscle damage may be so severe as to produce compression of adjacent arteries and nerves; the weakened foot pulses present in the case reported today are an example of this. In many such patients, fasciotomy will be required in order to relieve vascular compression. It is perhaps obvious that this superimposition of additional muscle ischemia may exacerbate the clinical presentation. Neuropathy in the setting of rhabdomyolysis may occur through two mechanisms. One is by the compression of nerves passing through a restricted muscle compartment which has become swollen, edematous and tense. The other is from direct compression of nerves from prolonged coma associated, for example, with drug overdoses. Any of the peripheral nerves may become involved, but peroneal and sciatic nerve involvement is common, and abnormalities of the brachial plexus have been reported.[4] The combination of muscle and nerve involvement in an extremity may help to account for the great length of time which is generally required for normal function to be restored in such patients.

TABLE 2.—*Pathogenesis of Acute Renal Failure in Patients with Rhabdomyolysis*

1. Tubular Obstruction
2. Toxicity of Heme Pigments
3. Renal Ischemia
4. Decreased Glomerular Permeability

I would like now to turn my attention to a discussion of the third member of the clinical triad of rhabdomyolysis, namely the development of acute renal failure. This is a common and serious complication, and indeed one might legitimately question what features about the illness in the patient discussed today prevented the occurrence of acute renal failure. Four major theories have been advanced to explain the development of acute renal failure in this setting, although the exact pathogenesis has not been clearly shown. The four postulated mechanisms are listed in Table 2.

Tubular obstruction was one of the earliest mechanisms invoked to explain oliguric acute renal failure caused by myoglobinuria. This was because the presence of pigmented casts in the urine, and of casts in renal tubules observed in renal biopsy specimens, led to the speculation that excretion of myoglobin in some way caused the precipitation of proteinaceous material in the tubule and secondary obstruction.

A second proposed mechanism invoked myoglobin itself as a toxic agent for the renal tubules. Support for this mechanism was obtained from the studies of Braun and his associates.[5] They were able to show that muscle damage in rats resulting from glycerol injections produced acute renal failure which was characterized by impairment of organic acid (para-aminohippurate) and organic base (tetraethylammonium) transport. These findings were correlated with *in vitro* studies of para-aminohippurate (PAH) and tetraethylammonium (TEM) uptake by renal cortical slices. The presence of myoglobin in the incubation medium significantly decreased PAH uptake by the cortical slices, and hemoglobin and methemoglobin, in addition to myoglobin, all decreased

TABLE 3.—*Features of Myoglobinuric Acute Renal Failure*

Clinical Situation: Crush injury, burns, status epilepticus, heat stroke, drug ovedrose and others
Laboratory Findings
Urine Hematest positive, sediment without red blood cells
Urine positive for myoglobin
Hyperkalemia
Blood urea nitrogen: creatinine ratio <10:1
Hyperphosphatemia out of proportion to the degree of renal insufficiency
Hyperuricemia
Hypocalcemia early, hypercalcemia late in course
Abnormal muscle enzymes

hippurate uptake if the slices were studied after ten minutes of hypoxia or with ammonium chloride in the incubation medium. All three heme compounds reduced PAH uptake when incubated at the medium pH of 5.4, and these findings could be reproduced when only ferrohemate was added to the medium. These authors concluded that the heme pigments themselves were toxic to renal tubular function and that it was possible that the ferrohemate portion of the heme molecule was responsible for this toxicity.

A third mechanism proposed to account for oliguric acute renal failure in the presence of myoglobinuria has been that of renal ischemia. In glycerol-induced experimental myoglobinuric acute renal failure, renal cortical blood flow is decreased.[6] It is known that under certain circumstances, glomerular filtration is critically dependent on the rate of plasma flow through the glomerulus,[7] and increasing glomerular plasma flow has increased glomerular filtration rate in a model of ischemic acute renal failure in rats.[8] The factors responsible for the production of this renal ischemia are not known with certainty but may involve actions of the renin-angiotensin system and possibly the sympathetic nervous system.

The fourth suggested mechanism is more controversial. In a clinical study, Clarkson and his colleagues were able to show the presence of fibrin strands in electron micrographs taken from kidney biopsy specimens of patients with myoglobinuric acute renal failure.[9] These investigators postulated that fibrin deposition in some way led to the decreased glomerular filtration rate and the acute renal failure in this setting. Additional support for this suggestion was obtained from the experimental studies of Wardle and Wright.[10] They produced myoglobinuric acute renal failure in rabbits following intramuscular glycerol injection and found evidence for enhanced clotting activity in the glomeruli of these animals. Therefore, it is possible that intraglomerular fibrin deposition could impair glomerular permeability and thereby contribute to the pathogenesis of oliguria in this condition.

Turning now to a consideration of the clinical manifestations of myoglobinuric acute renal failure, the major features are listed in Table 3. From what has been said before, it is obvious that the clinical setting in which the renal failure occurs should be one of the first tip-offs to the possibility of myoglobinuria as the cause. Another indication comes from examination of the urine. In the presence of myoglobinuria, the urine test for occult blood will be positive but usually the sediment will be free of red blood cells. The presence of myoglobinuria can then be confirmed by measuring urine myoglobin using one of the specific tests described earlier.

The clinical course of acute renal failure in this setting is usually marked by several characteristic features. Hyperkalemia develops early and may often be the first indication to commence dialytic support for these patients. Presumably, muscle damage leads to release of large amounts of intracellular potassium into the circulation to account for the rapid rise in serum potassium. The blood urea nitrogen (BUN)-to-creatinine ratio, normally greater than 10, may be less than 10 in these patients; this is thought to be due to the release of muscle creatine or creatinine into the circulation, raising the serum creatinine concentration out of proportion to the elevated BUN level.[11] Also related to the muscle damage is the development of hyperphosphatemia out of proportion to the degree of the renal insufficiency. An associated finding is the presence of severe hyperuricemia probably due to the catabolism of muscle purines. Uric acid excretion in such patients before the development of oliguria may be notably elevated.[3]

Another common finding is the presence of hypocalcemia early in this phase of the illness. Studies have suggested that this results from release of intracellular phosphorus into the circulation, elevation of the calcium-phosphorus product and subsequent deposition of calcium salts into osseous and extraosseous tissues, including the damaged muscle. It is frequently observed that the reverse of this phenomenon can also occur—namely, that previously deposited calcium salts

are released into the circulation as muscle healing takes place—and hypercalcemia may result. This temporally often corresponds to the improvement in renal failure and the onset of the diuretic phase. The hypercalcemia observed in this setting does not cause difficulties, and usually no specific treatment other than careful observation will be required. Finally, the profound muscle disease always results in pronounced elevation of muscle enzymes, with rises in CPK being particularly striking as in the case presented today. Elevations of CPK-2 fraction, normally associated with myocardial damage, may occur even in the absence of myocardial disease.[12]

Figure 1 attempts to integrate certain aspects of the pathogenesis of acute renal failure resulting from rhabdomyolysis. It is clear that there are many possible routes which can lead to the development of renal insufficiency, and it is also possible that different routes may play different roles from patient to patient or at separate times in the same patient.

The natural history of acute renal failure in this setting is also characteristic. Initially pronounced catabolism is present, and frequent, sometimes daily, dialytic support is often required. The chief indications for dialysis are the notable hypercatabolism and the early development of significant degrees of hyperkalemia. We have seen patients in our hospital who have been virtually anuric for three to four days; this was initially thought to indicate a poor prognosis, but we now regard it as just another manifestation of the renal insult. Once the condition of a patient is stabilized with acute hemodialysis, the management becomes simpler and the ultimate outcome is good. In our hospital such patients require fewer uses of hemodialysis as a group, and the overall mortality is low.[13] It should be stressed that hemodialysis is the mode of dialysis to be employed in such patients, as a number of investigators have documented that peritoneal dialysis may be insufficient to accommodate the rapid rate of catabolism.[14]

We should perhaps at this point address a question that was raised earlier in the discussion: Why does not acute renal failure develop in some patients, typified by the case today, who have severe myoglobinuria and rhabdomyolysis? It is our experience that most patients with rhabdomyolysis and myoglobinuria in whom acute renal failure develops are also compromised in some other fashion that influences renal function. Often in such patients there has been volume depletion or a loss of plasma volume into areas of tissue damage with subsequent reduction in renal perfusion. Experimentally, volume expansion appears to minimize or prevent the acute renal failure following myoglobin release,[15] and the *in vitro* studies of Braun and his associates[5] suggest that hypoxia may potentiate the toxic effects of heme pigments in renal cortical slices. It is possible that in patients such as the woman in the case presented today acute renal failure does not develop despite significant degrees of myoglobinuria because renal perfusion is maintained, and volume depletion is not a component of the clinical presentation. On the other hand, there is a strong suggestion in the literature that acute renal failure certainly can develop from myoglobin release in patients in whom there appears to be sufficient hydration.[11] The final answer to this question remains elusive.

Related to this problem is the issue of prophylaxis and early treatment of acute renal failure in this setting. As mentioned above, volume expansion appears to be effective in minimizing experimental acute renal failure, and volume expansion with agents such as mannitol have been advocated to prevent or reverse acute renal failure in

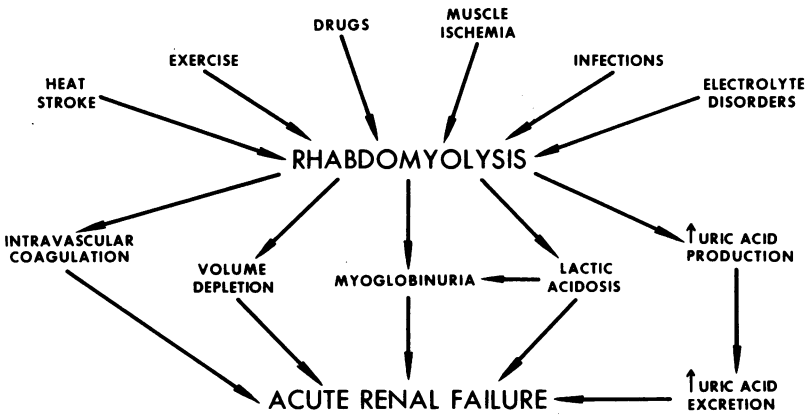

Figure 1.—Possible mechanisms by which rhabdomyolysis, resulting from a variety of causes, may produce acute renal failure.

humans. The data that have been offered to show the efficacy of this approach are controversial, and at this time there is no proven circumstance in which mannitol or furosemide administration to patients has resulted in a prompt improvement in established acute renal failure.[16]

Nevertheless, it is the policy in our hospital to do two things in patients presenting with the presumptive diagnosis of myoglobinuric acute renal failure. The first is to make sure that whatever volume depletion may be present is treated optimally with adequate fluid replacement. Once this is accomplished, we advocate the infusion of a solution of mannitol and sodium bicarbonate made by adding 2 ampules (25 grams) of mannitol and 2 ampules (100 mEq) of sodium bicarbonate to 800 ml of 5 percent dextrose in water. This reconstituted liter of solution represents roughly isosmotic fluid which will deliver 100 mEq of sodium bicarbonate per liter to the patient. Alkalinization of the urine with bicarbonate administration should enhance the rate of excretion of myoglobin and minimize its nephrotoxicity. Mannitol, in addition to producing further volume expansion, may also improve renal hemodynamics. We infuse this solution at a rate of 250 ml per hour for four hours. If at the end of that time there is an increase in urine flow rate, we continue the infusion at a rate equal to or slightly in excess of the rate of urine flow. If there is no increase in urine flow, we then consider that there is established acute renal failure in the patient and institute measures for conservative medical management. Under no circumstances do we recommend the administration of furosemide.[16]

In summary, it should be clear that rhabdomyolysis can result from a variety of different causes and clinical circumstances. The clinical presentation includes damage to muscle, to peripheral nerve and to kidney, where myoglobin or one of its breakdown products appears to be the nephrotoxin responsible for the renal damage. With appropriate medical management, however, the ultimate prognosis of acute renal failure from myoglobinuria is good.

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