Netherlands
The Journal of Medicine

CASE REPORT

Severe rhabdomyolysis and acute renal failure following recent Coxsackie B virus infection

F. Fodili, E.F.H. van Bommel*

Department of Internal Medicine, Albert Schweitzer Hospital, PO Box 444, 3300 AK Dordrecht, the Netherlands, e-mail: e.f.h.vanbommel@asz.nl, * corresponding author

ABSTRACT

Viral infections have been associated with a wide spectrum of muscle disorders, ranging from acute nonspecific myalgia to myositis. However, severe rhabdomyolysis, with or without accompanying acute renal failure (ARF), has been described only rarely. We report the fourth case in the literature of recent Coxsackie B virus infection complicated by severe rhabdomyolysis and ARF, necessitating temporary haemodialysis in a previously healthy young man. Although most Coxsackie B virus infections are asymptomatic, one should be aware of this potentially life-threatening complication of this virus. As illustrated with the present case, serological testing may reveal the diagnosis in a case of rhabdomyolysis after a viral illness.

INTRODUCTION

Coxsackieviruses (group A and B) are RNA viruses and, together with polioviruses and enteric cytopathogenic human orphan (ECHO)viruses, are classified as *Enteroviruses*. They are a genus of the picornaviridae and are widespread throughout the world.[1] Although asymptomatic infection is common, there are at least six serotypes of Coxsackie B viruses which in neonates and young children predominantly affect the central nervous system and muscles causing potentially severe complications such as aseptic meningitis, encephalitis, myositis and myocarditis.[2,3] In older children and adults, Coxsackie B virus infections tend to be less severe.[1,2] However, Coxsackievirus-induced rhabdomyolysis has been described in rare cases.[4]

We report the fourth case in the literature of recent Coxsackie B virus infection complicated by severe rhabdomyolysis and acute renal failure in a previously healthy young man.

CASE REPORT

A previously healthy 32-year-old man was admitted to our hospital because of severe muscular pain, especially of the upper legs, and discoloured coca cola-like urine. He had a five-day history of malaise, sore throat, fever up to 40°C and headache. There was no family history of renal or musculoskeletal disease nor had he experienced any trauma, drug abuse or vigorous exercise. On physical examination we found a moderately ill patient with a blood pressure of 130/90 mmHg, pulse rate of 90 beats/min and a temperature of 37.5°C. Examination of lungs, heart and abdomen were normal but he had markedly swollen and tender calves and upper legs. There were no signs of myopathy.

Relevant laboratory values included a creatine phosphokinase level of 250,000 U/l (normal [N] 50-120), aspartate aminotransferase 1310 U/l (N. 0-30), alanine aminotransferase 320 U/l (N. 1-30) and lactate dehydrogenase 14,160 U/l (N. 100-320 U/l), consistent with skeletal muscle necrosis. The white blood cell count was 15.5 x 10^9/l (N. 4-10) with 13.2 x 10^9 granulocytes in the differential count and a platelet count of 419 x 10^9/l (N.150-400). Serum creatinine on admission amounted to 273 µmol/l (N. 75-110), urea 15.4 mmol/l (N. 2.5-7.5), sodium 138 mmol/l (N. 138-142), potassium 4.9 mmol/l (N. 3.5-5), calcium 2.38 mmol/l (N. 2.2-2.6) and phosphorus

2.08 mmol/l (N. 0.9-1.5). Arterial blood gas analysis showed a pH of 7.55, pCO_2 28.9 mmHg, bicarbonate 25.1 mmol/l, pO_2 95 mmHg and oxygen saturation of 97%. Fractional sodium excretion amounted to 0.7%.
Urinanalysis revealed mild haematuria (2-5 per field), leucocyturia (0-2 per field) but no casts, and mild proteinuria (0.8 g/l). Other biochemical and haematological laboratory values were normal or in the normal range. No measurements of myoglobin in serum or urine were performed. Additional testing for ANA, ENA, dsDNA, complement factor C3 and C4 levels and ANCA were negative or within the normal range. A chest radiograph and electrocardiogram were normal. Blood and urine cultures were negative. Serology *for Influenzavirus* types A and B, hepatitis B and C virus, Hantaanvirus, *Adenovirus, Mycoplasma pneumoniae, Chlamydia* spp, *Parainfluenzavirus* types 1, 2 and 3, *Toxoplasma gondii, Coxiella burnetii* and respiratory syncytial (Rs) virus was all negative. However, a fourfold rise in Coxsackie B2 antibody titre over a 14-day period was demonstrated (1:128 to 1:512), suggesting recent infection. The initial antibody titre was determined from a sample taken on the second day of hospitalisation (i.e., seven days after first onset of symptoms).
Despite immediate and vigorous hydration with normal saline and urine alkalisation with sodium bicarbonate to maintain a urine pH >7, the patient developed nonoliguric acute renal failure requiring temporary alternate-day haemodialysis three days after admission, which continued for two weeks (*figure 1*). Recovery was otherwise uneventful with a rapid decline in the serum creatine kinase (CK) level (*figure 1*), gradual disappearance of calf swelling and muscle pain, and almost complete recovery of renal function (creatinine on discharge from the hospital 150 µmol/l). At the time of his latest follow-up 18 months later, he had no further symptoms and the creatinine (108 µmol/l) remained stable.

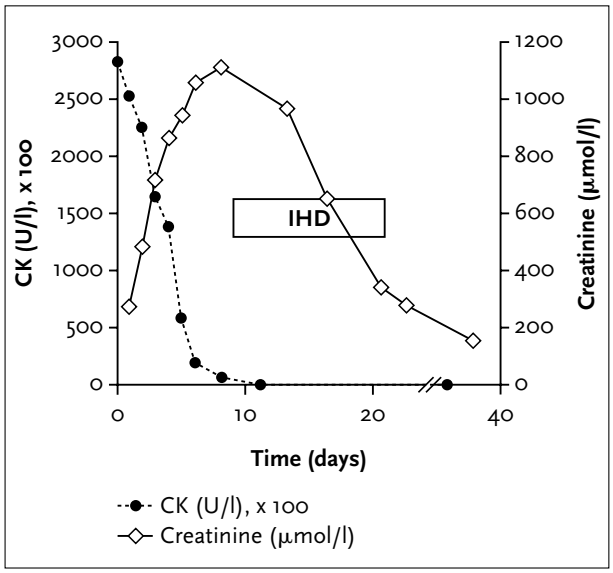


Figure 1
Time course of serum creatine phosphokinase (CK) and creatinine levels
Intermittent haemodialysis (IHD) was performed using a polysulphone hollow-fibre filter membrane (molecular cut-off point 20.0 kDa) with a blood flow rate of 200 ml/min and dialysate flow rate of 500 ml/min. Contrary to small molecules (e.g. creatinine, urea), large(r) molecules (>1.0 kDa) cannot be readily eliminated with diffusive techniques such as IHD.

DISCUSSION

We present a rare case of Coxsackie B virus-induced rhabdomyolysis, complicated by ARF. No symptoms of recurrent rhabdomyolysis were present, suggesting that an inherited disorder of muscle metabolism was highly improbable. In addition, other precipitating factors (e.g., alcohol, trauma, strenuous exercise or – less frequently – hypothyroidism, metabolic myopathies or drugs) were either absent or could be excluded in our patient.[5,6]
However, the onset of the disease as an upper respiratory tract infection with fever, headache and myalgia suggested a viral infection, which could be confirmed by a fourfold rise in Coxsackie B2 antibody titre over a 14-day period. Indeed, it is generally accepted that there should be a fourfold rise in antibody titre over a period of four to six weeks to make a definitive diagnosis of acute Coxsackievirus infection.[4]
Although considered rare, it is known that viral infections (notably *Influenzaviruses*) may induce a wide spectrum of muscle disorders, ranging from acute nonspecific myalgia to myositis.[6] To date, 11 cases of Coxsackievirus-induced rhabdomyolysis have been described in the literature, with a wide range of involved serotypes (A9, A16, B2-B6).[4-12] Their ages ranged from 9 to 57 (mean 30) years; male/female ratio was 0.6. Serum CK levels varied from 8500 to 685,000 U/l.[4-12] Although the precise mechanism of virus-induced rhabdomyolysis has still not been defined, it is assumed that initial acute tissue damage may be caused by the lytic effects of the virus on the muscle cell with subsequent release of myoglobin.[1,5,12] In experimental models, Coxsackie A9 and B5 injected into mouse resulted in muscle necrosis, suggesting that these viruses may indeed produce direct muscle damage.[4,5,12] The tropism of Coxsackieviruses for (striated) muscle is also illustrated by the isolation of this virus from the myocardium in patients with acute myocarditis.[1,2,5]
In three of the 11 reported cases, the course of disease was complicated by ARF necessitating intermittent haemodialysis for two to three weeks; all of them subsequently showing a complete recovery of renal function.[8,10] Our patient also

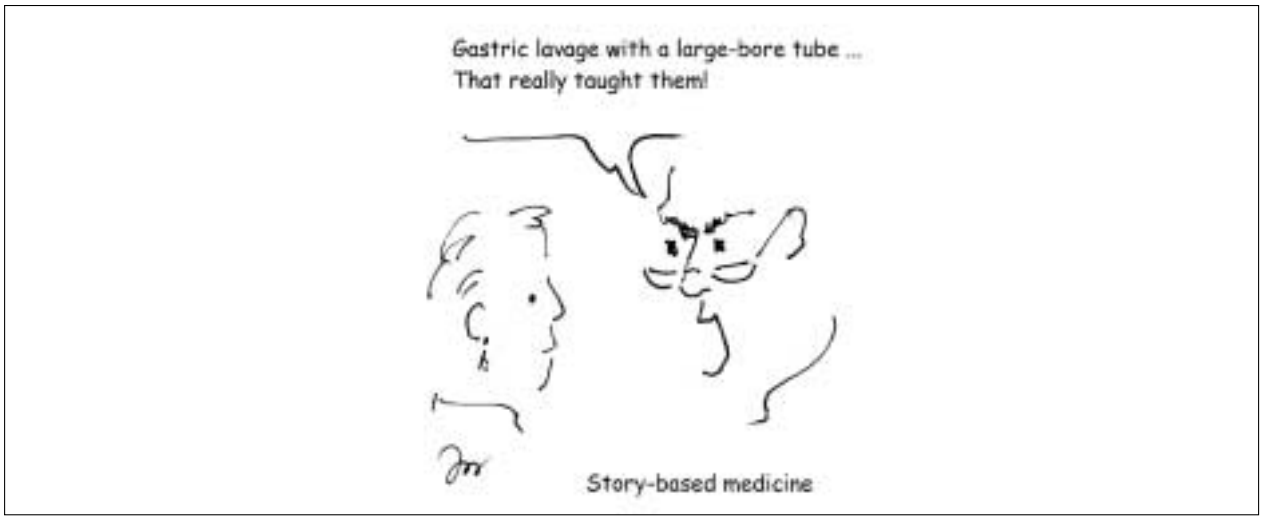
developed (nonoliguric) ARF despite vigorous hydration and urine alkalisation so that temporary intermittent haemodialysis was necessary for two weeks but subsequent recovery of renal function was also complete. ARF development caused by myoglobin may occur as a result of tubular obstruction by myoglobin, direct toxicity by haeme pigment, cortical ischaemia and decreased glomerular permeability resulting from fibrin strand deposition.[8,10] Dehydration, hypovolaemia and aciduria will accelerate this process. Of note, however, is that ARF has also been shown to occur as a result of an immune-complex mediated acute glomerulonephritis associated with recent Coxsackievirus B4 infection.[13]

It is suggested that, contrary to intermittent haemodialysis, use of convective dialysis techniques with large-pore membranes (i.e. haemofiltration) to remove myoglobin (MW 17.5 kDa) from the circulation may ameliorate or prevent impending ARF.[14] However, although substantial convective clearance of myoglobin can be found with haemofiltration (K_c 14-22 ml/min), myoglobin kinetics is such that endogeneous clearance is far superior to any form of therapeutic manipulation, even in the absence of renal function.[15]

In conclusion, a rare case of Coxsackie B virus-induced rhabdomyolysis and ARF in a previously healthy young man is described. Although most infections are asymptomatic, one should be aware of this potentially life-threatening complication of this virus. As illustrated with the present case, serological testing may reveal the diagnosis in a case of rhabdomyolysis after a viral illness.

REFERENCES

1. Morens DM, Pallansch MA, Moore M. Polioviruses and other enteroviruses. In: Belshe RB (ed). Textbook of Human Pathology. 2nd ed. St Louis: Mosby-Year Book, 1991:431-48.
2. Gray JA. Some long-term sequelae of Coxsackie B virus infection. J Royal Coll Gen Pract 1984;34:3-6.
3. Lau G. Acute fulminant, fatal Coxsackie B virus infection: a report of two cases. Ann Acad Med Singapore. 1994;23:917-20.
4. Berlin BS, Simon NM, Bovner RN. Myoglobinuria precipitated by viral infection. JAMA 1974;227:1414-5.
5. Marinella MA. Exertional rhabdomyolysis after recent Coxsackie B virus infection. Southern Med J 1998;91:1057-9.
6. Tanaka T, Tatsuyoshi T, Takagi D, Takeyama N, Kitazawa Y. Acute renal failure due to rhabdomyolysis associated with Echovirus 9 infection: a case report and review of literature. Jpn J Med 1989;28:237-42.
7. Porter CB, Hinthorn DR, Couchonnal G, et al. Simultaneous streptococcus and picornavirus infection. JAMA 1981;245:1545.
8. Dunnet J, Payton J, Robertson C. Acute renal failure and Coxsackie viral infection. Clin Nephrol 1981;16:262-3.
9. Fukuyama Y, Tsunesaburo A, Yokota J. Acute fulminant myoglobinuric polymyositis with picornavirus-like crystals. J Neurol Neurosurg Psychiatry 1977;40:775-81.
10. Beressi A, Sunheimer R, Huish S, Finck C, Pincus M. Acute severe rhabdomyolysis in an human immunodeficiency virus- seropositive patient associated with rising anti-Coxsackie B viral titers. Ann Clin Lab Sci 1994;24:278-81.
11. Konrad R, Goodman D. Tumor necrosis factor and Coxsackie B4 rhabdomyolysis. Ann Intern Med 1993;119:861.
12. Bowles NE, Sewry CA, Dubowitz V, Archard LC. Dermatomyositis, polymyositis and Coxsackie B virus infection. Lancet 1987;1:1004-7.
13. Bayatpour M, Zbitreur A, Dempster G, Miller KP. Role of Coxsackie virus B4 in pathogenesis of acute glomerulonephritis. Can Med Ass J 1973;109:873.
14. Amyot SL, Leblanc M, Thibeault Y, Geadah D, Cardinal J. Myoglobin clearance and removal during continuous venoveno hemofiltration. Intensive Care Med 1999;25:1169-72.
15. Wakabayashi Y, Kikuno T, Ohwada T, Kikawada R. Rapid fall in blood myoglobin in massive rhabdomyolysis and acute renal failure. Intensive Care Med 1994;20:109-12.



Fodili, et al. Severe rhabdomyolysis and acute renal failure following recent Coxsackie B virus infection.