Late-onset rhabdomyolysis in pneumococcal meningitis: a case report

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Late-onset rhabdomyolysis in pneumococcal meningitis: a case report

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Rhabdomyolysis (RM) is a syndrome characterised by muscle breakdown and necrosis, resulting in elevated serum concentration of creatine kinase (CK) and myoglobinuria [1]. RM ranges from an illness without symptoms to a life-threatening condition. The classic triad of symptoms includes weakness, tea-coloured urine and muscle pain. RM may involve specific groups of muscles or may be generalised [2]. The main complication of RM is acute renal failure (ARF), which develops in 10–50% of RM cases with a mortality of approximately 20% [1, 2].

The major causes of RM are related to muscular trauma, toxin abuse, drugs, muscle enzyme deficiencies, electrolyte abnormalities, metabolic disorders and seizures. Infections are generally considered to account for less than 5% of the cases, with just one study reporting an infectious aetiology in 31% of their RM cases [1, 3]. *Legionella*, *Streptococcus* and *Salmonella* species are the most common bacteria which may have a causative role in precipitating RM. Other infectious agents that have been associated with RM are: influenza virus, HIV, enterovirus and malaria [2–4]. In infection-associated RM, ARF and mortality reach 57% and 38% respectively [4].

No data is available on *Streptococcus pneumoniae*-associated RM before 1982. Between 1982 and 2003 a total of 20 cases of RM associated with *S. pneumoniae* infection were described in the literature [5–8]. In most cases major underlying conditions were identified: alcohol abuse and smoking were the most frequent conditions, while splenectomy was present in three cases [6, 9, 10]. Although *S. pneumoniae* has been associated with RM, its appearance generally occurs at the onset of the illness, and to our knowledge, there are no reports of delayed RM occurring during a severe pneumococcal infection.

We report a case of a 62-year-old female Italian patient splenectomised 30 years earlier because of severe thrombocytopenia. She had not been immunised against *S. pneumoniae*, *Haemophilus influenzae* or *Neisseria meningitidis*. No other known underlying conditions for RM were present. The patient had had fever and myalgia for 4 days, and eventually, mental confusion and vomiting the day she was admitted to our hospital. At the emergency unit she experienced a generalised tonic-clonic seizure that immediately resolved with a single 10-mg dose of diazepam IV bolus. Physical examination revealed clinical signs of meningitis and her initial Glasgow Coma Score was 11. Temperature was 38°C, systolic blood pressure was 120 mmHg, pulse rate was 65 and respiratory rate was 15. Lumbar puncture performed on admission showed a slightly cloudy cerebrospinal fluid, lightly xanthochromic after centrifugation, with 28/mm^3 leukocytes, protein >300 mg/dl, glucose 10 mg/dl. Gram stain showed gram-positive diplococci, and culture yielded a penicillin-susceptible *S. pneumoniae*. Arterial blood gas determination showed a pH of 7.51, pCO_2 of 38.1 mmHg, pO_2 of 69.3 mmHg and lactic acid 1.5 mmol/l. Laboratory results disclosed the following significant data: peripheral white cell count 27 160 (22980 neutrophils), haematocrit 36.5%, platelets 131 000, AST 37 U/l, ALT 40 U/l, ALP 159 U/l, CK 53 U/l, LDH 294 U/l, myoglobin 58 ng/ml (normal

- RM is a possible severe complication during systemic infectious diseases
- *Streptococcus pneumoniae* may be a precipitating bacteria
- RM may appear as an early or late complication
- Monitor patients with severe *Streptococcus pneumoniae* infections for the symptoms of RM and check CK levels several times during the course of their illness

Fig. 1 Key points

values: 0–75 ng/ml), creatinine 1.8 mg/l, serum sodium 146 mEq/l, potassium 3.1 mEq/l, calcium 11.6 mg/dl, ESR 99 mm/h, C-reactive protein 42 mg/dl and fibrinogen 1001 mg/dl. Urine test results were normal and no red cells were present at the microscopic exam. Urinary antigen was positive for *S. pneumoniae* while blood cultures were negative. The patient received a treatment regimen which included antibiotic therapy with ceftriaxone (2 g infusion IV bid for 3 weeks), dexamethasone (8 mg bolus IV tid, for 4 days) and infusions of normal saline solutions and lactated Ringer's solutions. Another lumbar puncture was performed as fever, reduced level of consciousness and mental confusion were still present after 5 days of therapy. The test results were as follows: white blood cells (WBC) count 150/mm^3, protein 119 mg/dl, glucose 910 mg/dl; stain and culture were negative. Ten days after the admission, the patient became afebrile and recovered from the mental disturbances. During this first period of hospitalisation CK levels remained in the normal range (20–160 U/l) and the peripheral WBC count dropped to 18 000/mm^3. A potassium depletion was observed (lowest value reached 2.9 mEq/l) and it was corrected to the normal range with infusions of potassium chloride solution (a total of 240 mEq was given). Two days later the patient reported muscular weakness and myalgias involving upper and lower limb muscles. New laboratory studies revealed AST 42 U/l, ALT 45 U/l, CK 710 U/l, LDH 459 U/l and myoglobin 1614 ng/ml (CK-MB, troponin I and electrocardiography were normal). The patient's calcium and magnesium levels remained within the normal range. Serum sodium and potassium levels were 152 mEq/l and 2.8 mEq/l, respectively, despite continuous infusion of electrolyte solution and potassium replacement therapy. In the following three days, CK and myoglobin levels peaked at 8863 U/l and 6257 ng/ml, respectively, without elevation of the cardiac enzymes. Arterial blood gas determination showed a pH of 7.59, pCO_2 of 31.8 mmHg, pO_2 of 65 mmHg and lactic acid 2.3 mmol/l. A physical exam showed upper and lower limb weakness with depressed tendon reflexes. Electromyography was performed showing a middle entity sensory and motor polyneuropathy at the lower limbs, which was compatible with critical illness polyneuropathy. The patient's renal function was preserved thanks to aggressive fluid replacement therapy with normal saline (2500 ml), 1.4% isotonic sodium bicarbonate (500 ml/qd) and 5% glucose solutions (2000 ml/qd) plus 80 mEq potassium chloride/qd associated with loop diuretics (furosemide 20 mg IV bolus tid). After four days, CK and myoglobin levels decreased to the normal range. The patient was discharged within a week in a stable condition and with normal blood values.

RM is a potentially life-threatening condition, due to its complications, which include ARF, cardiac arrhythmias, disseminated intravascular coagulation, electrolyte imbalance and shock. RM associated with pneumococcal infection seems to be a clinical indicator of increased morbidity and mortality [11]. The extent of complications and survival during the acute stage of RM are dependent on early diagnosis and insuring therapy is both adequate and timely. Forced diuresis may protect the kidney function from acidosis and tubular damage. The prognosis for muscular atrophy and ARF following the acute stage of RM is excellent [2, 12, 13]. The role of *S. pneumoniae* infection as a precipitating factor of RM is rare and probably under-reported because patients with pneumococcal infections are seldom hospitalised. Furthermore, RM is often asymptomatic. The pathogenesis of skeletal muscle injury resulting from pneumococcal infection is not completely clear [10, 14].

The reported case is characterised by a late onset of RM (12 days after admission to our hospital) linked to a severe pneumococcal infection in a patient who had undergone splenectomy, an underlying condition which predisposes to RM. In previously reported *S. pneumoniae*-associated RM, the onset of muscular damage was already present at the time of admission to the hospital or it was detected within the first days of hospitalisation. The peculiarity of this case is the late onset of the RM. Therefore, we cannot consider the direct muscle invasion by *S. pneumoniae* as the primary cause of the damage. Other possible mechanisms may have played an important role in the occurrence of this case of RM, such as toxin production or metabolic effects in reducing the glycolytic enzyme activity [15, 16]. However, we must take into consideration other possible factors that generally contribute to the genesis of RM. First, we can reasonably exclude drug toxicity, because no drugs other than those described were used and none of these drugs are linked to RM. Hypotension or hyperthermia can be excluded as well, because signs and symptoms of RM occurred when the patient was haemodynamically stable and had been afebrile for 11 days. Acidosis was never detected despite several arterial blood gas analyses. Probably the length of immobilisation and, perhaps of greater relevance, the persistence of electrolyte abnormalities, although promptly corrected, were significant co-factors in determining the muscle damage. However, these findings are very common in the majority of critically ill patients, even in the absence of RM. We would like to point out that a Medline search on RM and *Pseudomonas aeruginosa* or *Acinetobacter* gave no results, even though these gram-negative bacteria are associated with sepsis and are frequently found in critically ill patients.

Another important point to remember is the need to administer the pneumococcal vaccine to patients at high risk for a potentially lethal *S. pneumoniae* infection like our splenectomised patient.

In conclusion, we cannot consider the *S. pneumoniae* infection as the sole and unique cause of the RM case here reported. Its occurrence leads us to emphasise the importance of monitoring the CK levels in patients with pneumococcal infections even when the critical phase of the infection has resolved. Following the CK level would allow prompt detection and treatment of RM.

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Intracerebral haemorrhage and recombinant factor VIIa: not so good news!

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The review of Marietta et al. [1] and the accompanying commentary of Edlow [2] emphasised well the favourable results, obtained in the frame of a phase 2 trial, of recombinant activated factor VII (rFVIIa) in the treatment of intracerebral haemorrhage [3]. The original study of Mayer et al. [3], to which they refer, was indeed a significant breakthrough in the management of a dramatic clinical condition with a paucity of effective therapeutic weapons. However, even in the original study, an excess of thrombotic complications emerged as a significant problem [3]. In the rFVIIa-treated group 7% of patients had myocardial infarction or ischaemic stroke, compared with a rate of 2% in those receiving placebo. The situation concerning thrombotic complications is likely to be even more gloomy than it appears from the published report [3], because during the trial an important exclusion criterion was modified. Originally, excluded patients were only those who had thromboembolic events within 30 days before starting the study, but subsequently exclusion was extended to all patients with any history of thromboembolism [3]. It can be easily understood how this midway change of exclusion cri-