A pediatric case of rhabdomyolysis with acute renal failure due to co-infection with Epstein-Barr virus and Human herpesvirus 6

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Rhabdomyolysis is a syndrome characterized by muscle breakdown and necrosis resulting in leakage of the intracellular muscle constituents into the circulation and extracellular fluid. It ranges from an asymptomatic illness with elevation in creatine phosphokinase (CK) levels to a life-threatening condition characterized by electrolyte imbalances, acute kidney injury (AKI) and disseminated intravascular coagulation [1].

One of the most common etiologies of rhabdomyolysis in the pediatric population is viral [2, 3]. We report a rare childhood case of rhabdomyolysis associated with a dual viral infection. Epstein-Barr virus (EBV) was identified serologically and Human herpesvirus 6 (HHV6) was individualized with quantification of DNA by real-time polymerase chain reaction (DNA PCR).

Informed consent of the patient's parents was obtained.

A 22-month-old child was admitted to the Pediatrics Department (University of Chieti) for incoercible vomiting (about 10 episodes in the past 12 h) and inappetence. She had a history of malaise, sore throat and irritability for about 2 days. There was no family history of renal, musculoskeletal or metabolic diseases. She did not take drugs in the previous 2 weeks before the admission. The child's mother reported a head injury by falling out of bed 24 h before. For this reason an urgent brain computed tomography scan was performed, showing no abnormalities. Physical examination was normal: blood pressure 108/67 mm Hg, pulse rate 115 beats/min and temperature 36°C. Chest and cardiac auscultation were normal, while the abdomen was widely painful. There were no evident signs of myopathy. Some small axillary and inguinal lymph nodes were palpated. Liver and spleen were not enlarged. Blood work revealed lactate dehydrogenase 2988 U/l (N: 313–618 U/l), creatine phosphokinase 2443 U/l (N: 30–135 U/l), aspartate aminotransferase 898 U/l (N: 14–36 U/l), alanine aminotransferase 2135 U/l (N: 19–52 U/l) and myoglobin 1510.0 ng/ml (N: 9.0–82.5 U/l), consistent with skeletal muscle necrosis. No measurement of myoglobin in urine was performed. White blood cells count was $10.25 \times 10^3/\mu l$ (N: $4–10 \times 10^3/\mu l$) with 51% neutrophils, 39.5% lymphocytes and 8.3% monocytes. Following the admission the child had impaired renal function: serum creatinine level was 2.60 mg/dl (N: 0.52–1.04), urea 87 mg/dl (N: 7–17), sodium 131 mmol/l (N: 133–145), potassium 5.6 mmol/l (N: 3.60–5.50), calci-

um 2.30 mmol/l (N: 2.10–2.55) and magnesium 2.5 mg/dl (N: 1.6–2.3). At the admission urine dipstick revealed glucose 1+, protein 2+ and blood 3+, and urine analysis showed protein-uria (50 mg/dl). The inflammatory markers were also elevated (C-protein reactive of 6.01 mg/dl (N: 0.00–0.50) and erythrocyte sedimentation rate of 16 mm/h (N: 1–15)). Venous blood gas analysis showed pH 7.35, pCO_2 23.5 mm Hg, pO_2 34.7 mm Hg, bicarbonate 11.9 mmol/l. The meta-bolic evaluation (acylcarnitines and organic acids) was normal. Other biochemical and hematolog-ical laboratory values were in the normal range. A chest radiograph and electrocardiogram were normal. Blood and urine cultures were negative. Serology for *Influenzavirus* types A and B, hepatitis A, B and C viruses, *Adenovirus*, *Mycoplasma pneu-moniae*, *Chlamydia* spp., parainfluenza viruses types 1, 2 and 3, *Toxoplasma gondii*, *Rubella virus*, *Herpesvirus* 1 and 2, *Cytomegalovirus* and respira-tory syncytial virus was all negative. In contrast, EBV immunoglobulin M (IgM) and IgG were elevat-ed (76.1 U/ml and 26 U/ml, respectively (N: 0–20.0 U/ml)), suggesting a recent infection. Furthermore, DNA PCR showed positivity for HHV6, document-

ing the coexistence of another viral infection. The clinical conditions were stable, except for some episodes of vomiting and diarrhea. However, the child appeared plaintive and she refused to walk. Blood tests at 22 h from admission documented worsening of creatinine values (3.60 mg/dl), an in-crease of potassium blood levels (6.3 mmol/l) and a peak of creatine phosphokinase (6.723 U/l). The clinical and laboratory findings were suggestive of rhabdomyolysis with AKI. Despite immediate and vigorous hydration with saline solution and urine alkalization with sodium bicarbonate, the patient developed non-oliguric acute renal failure requiring the transfer to the Pediatric Nephrology Department for further treatment options. Kayex-alate (sodium polystyrene sulfonate) and oral cal-cium gluconate were administered for hyperka-lemia. Heart rate, pulse oximetry, blood pressure and diuresis remained stable. For this reason, he-modialysis was not necessary. During hospitaliza-tion the patient presented a rapid decline in the serum CK level (Figure 1), gradual disappearance of fatigability and muscle weakness with a com-plete recovery of renal function 10 days after the onset of therapy. Noticeably, the serum CK and
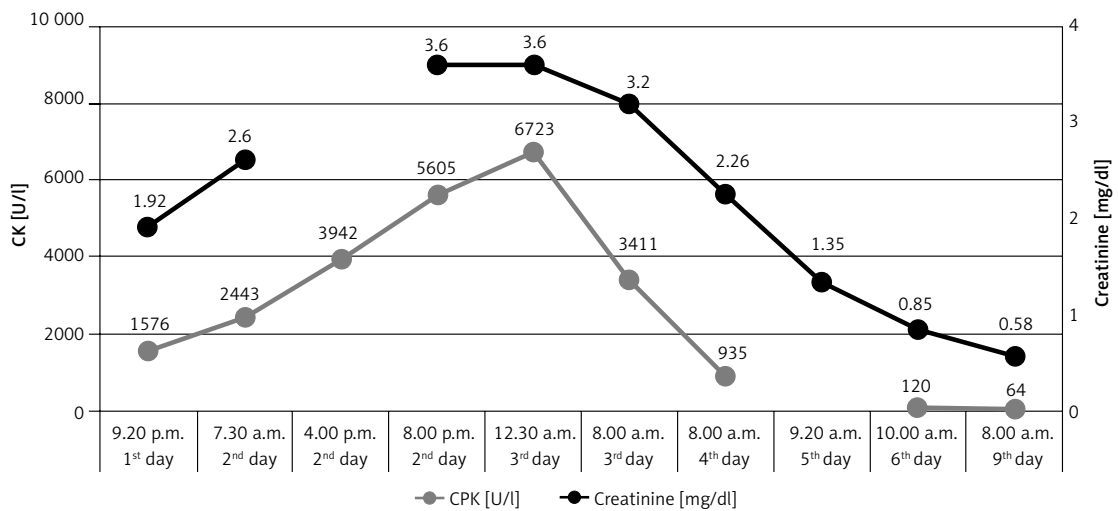

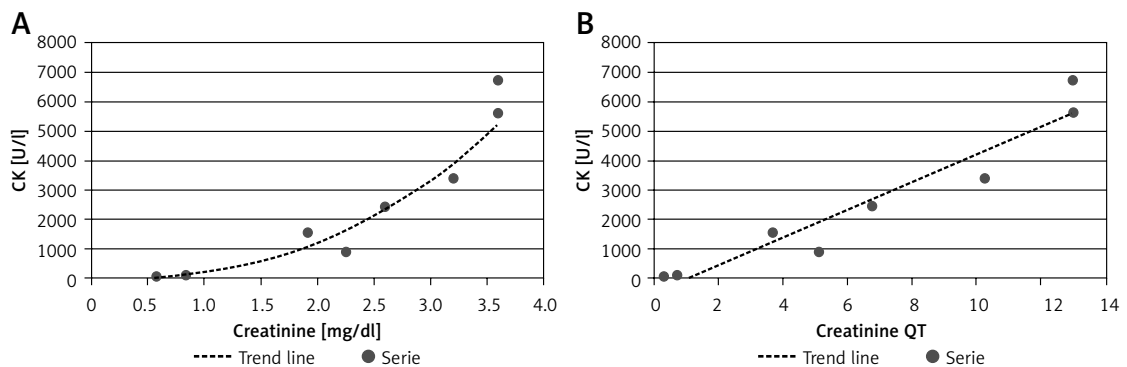**Figure 1.** Time variation of serum creatine phosphokinase (CK) and creatinine levels

Figure 2. A – Relationship between serum creatine phosphokinase (CK) and creatinine levels (Pearson's correla-tion, $r = 0.90$, $p = 0.002$), **B** – quadratic transformation of creatinine values ($r = 0.96$, $p < 0.001$)

creatinine levels demonstrated the same trend (Figure 1). In addition, we found a direct correlation between CK and creatinine levels (Figure 2 A, Pearson's correlation, $r = 0.90$, $p = 0.002$). This correlation was significantly increased after quadratic transformation of creatinine values (Figure 2 B, $r = 0.96$, $p < 0.001$).

In this case the presence of prodromal and gastrointestinal symptoms and increased inflammatory markers in a first episode of rhabdomyolysis suggest viral infectious etiology, confirmed by the increased EBV IgM and the presence of HHV6 DNA by PCR (bioMérieux ARGENE, kit ref. 69-100B CMV, HHV6,7,8 R-gene, target gene U57). Whether any relation exists between HHV6 and EBV infections and the contribution of EBV to the pathogenesis of the attack of rhabdomyolysis remain unclear. In the literature in children rhabdomyolysis has been reported to be associated with EBV in a few cases [4, 5] and with HHV6 infection in a single case [6].

In conclusion, to our knowledge this is the second pediatric case in which the cause of rhabdomyolysis is a co-infection. In our patient a direct effect of EBV on muscle has not been assessed. We might hypothesize that EBV, infecting usually in childhood or early adolescence [7], altered the patient's immune system, allowing the HHV6 infection. In this way HHV6 might have invaded directly into muscle tissue and caused the rhabdomyolysis. The same mechanism may have played a part in the dual infection with EBV and echovirus 6 in the case reported by Poels *et al.* [8]. These infections might have interacted synergistically.

In addition, we would like to emphasize that increased CK levels could be predictive of renal damage. In clinical practice this finding is of great interest for the management of the patient with rhabdomyolysis.

Conflict of interest

The authors declare no conflict of interest.

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