An unusual cause of acute rhabdomyolysis

Sir, Last February, a previously healthy 27-year-old male was admitted to our hospital with a 2-day history of afebrile abrupt onset malaise and myalgias involving arms, legs and trunk. Because of simultaneous cephalgias and rhinorrhoea, the primary care physician had suspected influenza and immediately prescribed oseltamivir, a neuraminidase inhibitor. The patient had massive tissue oedema and a rapidly progressive paresis of the proximal and distal muscles of all extremities. His heart rate was 132/minute, his blood pressure 130/90. The ESR was 12 in the first hour. His serum creatine kinase (CK) levels were 125 860 U/l (CK-MB1080 U/l), troponin T was negative, the pro-brain derived natriuretic peptide (proBNP) was 1492 µg/l (normal <125). His leucocyte count was 17 800 × 10⁹/l (79% neutrophils), serum CRP was 105 mg/l, creatinine 13 mg/l, ALT 764 U/l and urate 105 mg/l. There was hypocalcaemia (1.6 mmol/l) and hyperphosphataemia (79 mg/l). The patient voided dark brown urine (200 ml within the first 12 h). The urine peroxidase reaction was positive and in the absence of erythrocytes indicative of myoglobin.

The patient denied recent trauma, drug use and a family history of muscle disease. Chest X-ray, ECG and echocardiogram were normal. MRI and ⁹⁹ᵐTc pyrophosphate scintigraphy revealed a disseminated muscle oedema (Fig. 1A). A muscle biopsy performed at day 2 of admission from an involved region (M. vastus lateralis) showed a regular checkerboard distribution of type I and type II fibres, intact enzyme activities and normal PAS and oil red stains. Single fibre necrosis was observed very rarely, myophagocytosis and inflammatory infiltrations were completely absent. Electron microscopy showed activated satellite cells, an intact myofibrillar lattice and disrupted sarcoplasmic membranes (Fig. 1B).

Serum carnitine and acetyl carnitine, carnitine palmitoyl transferase and ANA were within normal limits [1]. Legionella pneumophila antigen was negative in the urine, as were serum antibodies for HIV, parainfluenza, adenovirus, influenza A, cytomegalo-, Epstein-Barr and herpes simplex viruses.

Blood drawn at admission yielded a positive ELISA result for influenza B virus IgG (22.9 U; cutoff at 9.0 U), a repeat serum after 15 days showed an almost 8-fold rise (174.0 U). RT-PCR for influenza B virus RNA from the muscle biopsy specimen was negative.

Twelve hours after admission, the patient was unable to lift arms and legs from the bed. The CK had doubled (265300 U/l). Despite instantaneous urine alkalization, volume substitution (91 within the first 24 h) and treatment with recombinant urate oxidase, there was renal failure requiring haemodialysis. Plasmapheresis was performed on three consecutive days. After 12 days, the myalgias diminished, muscle strength began to improve and the CK had declined (5700 U/l). At the same time

![Fig. 1. (A) Fat saturated MRI visualizing symmetric myositis of all the thigh and gluteal muscles. (B) Electron microscopy reveals early cytolysis (left) next to a normal muscle fibre (right), oedematous widening of sarcoplasmic compartments, pseudopapillary projections (P), membrane discontinuities (arrow) and extracellular organelles (star). Virus-like particles were not detected.](https://academic.oup.com/rheumatology/article-abstract/45/5/643/1788831)
troponin T (which was measured daily) became positive and proBNP had increased (11304 μg/l). Chest X-ray and repeat echocardiograms were normal, as were ECG curves with the exception of sinus tachycardia (110/min). After 4 weeks, the patient had no muscle tenderness, was able to walk, CK had normalized and haemodialysis was discontinued.

Although myalgias are common in influenza, myositis has only been described in a few adults. Almost all adult cases were caused by influenza A. Our case is unusual in its association with influenza B and its magnitude of CK elevation.

The lack of prevention by oseltamivir of this influenza B-associated complication and the late-onset myocardial involvement deserve consideration. Rhabdomyolysis was previously observed in a 51-year-old man who had received oseltamivir for influenza A infection and in whom muscle breakdown developed shortly after the flu symptoms had resolved [2]. This temporal course has raised the possibility of a drug-related aetiology [2].

Our case is the first to visualize widespread muscle involvement, the mechanism of which is unknown. Cytokines may contribute to skeletal muscle breakdown [3]. Viral antigen and myxovirus-like particles were detected in the muscle only rarely [4], although direct infection, replication and cytopathic effects have been demonstrated in mononucleate myoblasts and multinucleate myotubes [5]. The muscle of adult animals appears to be resistant to infection [4, 6], but denervation and muscle regeneration may promote susceptibility. In this context, it is interesting that our patient was a karate fighter in whom micro-injuries during training sessions may have initiated muscle regeneration.

Influenza myositis should be included in the differential diagnosis even in afebrile patients. Nasal swabs and repeat serology are the most reliable way of diagnosis.

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### Rheumatology

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<td>- Influenza may cause severe rhabdomyolysis despite near normal muscle light microscopy. Skeletal muscle involvement may precede myocarditis. Prevention of influenza complications by neuraminidase inhibitors is unreliable.</td>
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Sir, We were generally pleased with the editorial by Moseley and Gandevia [1] that accompanied our paper which described the novel findings of generating somaesthetic disturbances in healthy individuals [2]. However, their editorial contains a number of inaccuracies that need to be addressed as they could form the basis of important criticisms of our paper if not corrected.

Moseley and Gandevia state that our ‘subjects were related to patients’ who were currently undergoing therapeutic mirror visual feedback and that this may have biased our findings. This was simply not the case. Some subjects were recruited from the hospital and may have been related to patients with a musculoskeletal disease attending the hospital, but none were related to the patients with complex regional pain syndrome (CRPS) who received mirror visual feedback therapy.

The authors also state that ‘the time course of the sensations… was not described in detail’, and that without this it is difficult to confirm the relationship ‘between apparent incongruence and symptoms’. They also query why a longer time period was not selected as this may have established whether habituation to the task would reduce evoked symptoms. These aspects were clearly described in the Methods, Results and Discussion sections of our paper. There was a ‘timed 20-second’ experimental condition and immediate resolution of abnormal sensations once normal visual input was restored. Consequently, it is not unreasonable to assume a direct relationship between the experimental condition and symptom generation. A longer time period was considered but discounted as we were concerned that muscle fatigue would distort our findings, although we recognize that, if technically possible, this would be a useful extension to our work.

Our finding that nearly 40% of the study population perceived sensory anomalies during congruent mirror visual feedback is considered surprising by Moseley and Gandevia, given the fact that a similar protocol was used for analgesic benefit and functional return in those with chronic pain [3, 4]. This provides us with an opportunity to clarify our position. In patients with CRPS and phantom limb pain, we hypothesize that a pre-existing gross sensory–motor incongruence is responsible for the generation of some of their symptoms. The almost immediate pain relief in some, with corrective sensory feedback, would appear to confirm this hypothesis. Therefore, the smaller variations between movement and limb that appear to occur in some healthy individuals during congruent mirror feedback are unlikely to be perceived as problematic in those with a significant pre-existing sensorimotor conflict. Conversely, the incoming sensory input of a now healthy-looking limb corrects an already disturbed system rather than alerting a normal one.

We agree with Moseley and Gandevia that cortical reorganization alone can not be solely responsible for the generation of pain in all such cases. The example they provide of enlarged representation of digits in Braille readers clearly demonstrates this point [5]. The somatosensory cortical map, however, is only