Influenza A (H1N1) induced-myopathy: an important extrapulmonary complication

Miopatia induzida pelo vírus influenza A (H1N1): uma complicação extrapulmonar importante

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Skeletal or voluntary muscles represent, in the aggregate, approximately 40 to 45% of the weight of our body. Regarding the prominence and visibility of muscle function, disorders of voluntary muscles would be immediately apparent. However, disorders of the muscular system, the myopathies, in some cases, may go undiagnosed for long periods. Even when myopathy is considered and a diagnosis is made, the assessment of its course and the clinical state of the affected individual may at times be difficult to delineate with precision, even when an inflammatory myopathy is considered[1].

The inflammatory myopathies constitute a heterogeneous and large group of disorders, and they are the most common form of acquired myopathies. Some are focal and confined to one muscle or group of muscles, while others are widespread and involve the limb and axial muscles in a multifocal fashion. The inflammatory myopathies may be further classified etiologically into those that occur due to a known infective organism (viral, bacterial, fungal, or parasitic) and the idiopathic inflammatory myopathies, whose etiology is uncertain, but in many of which there is strong evidence that the muscle damage is immunogically mediated[2].

Despite the existence of several types of virus inflammatory myopathy (virus myositis) in animals, the occurrence of this type of infective muscle inflammation in man has had an uncertain status.

Influenza A and B viruses can cause widespread outbreaks of human disease with devastating consequences. Influenza A viruses are classified based on the characteristics of two surface glycoproteins, hemagglutinin (H1 to H15), and neuraminidase (N1 to N9). All subtypes have been detected in viruses recovered from aquatic birds, which are the natural reservoir for influenza viruses. So far, only H1, H2, and H3 and N1 and N2 are associated with large-scale influenza outbreaks among humans. The WHO recently declared that the novel influenza H1N1 virus was responsible for the 2009 flu pandemic. As the virus continues to spread globally and affect more individuals, more complications of this virus infection are being recognized.

In 1896, Leichtenstern first described the association as 'muscular neuralgias' affecting the back, thighs, and calves of patients[3]. Influenza-associated myopathy has been a well-known phenomenon, mainly in pediatric patients, but it has been rarely reported in adults. Most cases are described during large influenza epidemics. Isolated cases and small clusters of influenza A (H1N1)-induced myocarditis, alone or in conjunction with pericarditis or rhabdomyolysis, have been reported. A severe necrotizing myopathy with myoglobinuria has rarely been reported in influenza[4-8].

Although, in a recent prospective cohort study of 152 patients in England, measurement of cardiac troponins I and T to detect myocardial injury was used, none of the 12% of patients with elevated creatine kinase levels had evidence of cardiac involvement, suggesting that rhabdomyolysis is more common than myocarditis[9].

The pathogenesis of this influenza A form of myopathy is uncertain. Direct invasion of the muscle by the virus has been postulated, and the susceptibility of human muscle to the virus was demonstrated in tissue culture[10]. However, convincing evidence of viral invasion in vivo remains to be presented. Skeletal-muscle biopsies generally do not reveal direct viral infection. In patients with severe myalgia in the calves and with high creatine kinase (CK), degenerative

changes of a non-specific type were found in biopsy preparations. Pathological signs range from non-specific degenerative changes and muscle cell vacuolization to patchy or extensive muscle necrosis. In rare patients, extensive muscle necrosis and infiltration of neutrophylic leukocytes, and plasma cells in the endomisium have been demonstrated[11].

In this issue, a paper is presented, demonstrating abnormalities findings in skeletal muscle of ten critical ill patients (within 20 to 57 of age) with influenza A (H1N1) virus infection, the highest series in the literature, containing important clinical considerations about interaction between virus and muscle[12].

The skeletal-muscle biopsy was performed due to the high CK levels found (3,744,4±5,544,14 U/L). Traditionally, muscle enzymes have been used as indicators of disease activity. Although elevated serum CK reflects muscle injury and is frequent on those with acute myositis, muscle necrosis was detected only in four patients. The main hallmarks of inflammatory myopathy, including inflammatory cells and perifascicular atrophy, or direct viral infection, were not demonstrated in this series. Pathological signs ranged from non-specific degenerative changes and alterations suggestive of metabolic dysfunction, which could be related to influenza A (H1N1) virus, toxic myopathy (oseltamivir), or poor clinical condition (critical illness).

Oseltamivir is the pro-drug of Ro64-0802 (GS4071), a potent and selective inhibitor of influenza A and B virus neuraminidases, it has been used to treat patients with influenza A infection. Antiviral drugs have been documented to shorten the course of the illness by only one or two days. One study on oseltamivir found that treatment may reduce some complications, but no studies have shown that treatment reduces fatal outcomes. Its administration did not significantly affect the distribution of convalescent serum antibody titres compared to placebo in any of the studies, suggesting that it does not impair the ability of the host to mount an immune response to the influenza virus. As previous trials in healthy subjects and in patients, the present studies showed oseltamivir to be well-tolerated. Mild-to-moderate, transient gastrointestinal adverse events were observed in some oseltamivir recipients. No muscle alterations have been described[13].

The term critical illness has been widely used to describe the condition of a patient with illness that is severe enough to be considered at risk of death or related to sepsis and multiple organ failure. Critical illness myopathy may be developed in patients treated in an intensive care unit (ICU), usually with respiratory support, for periods longer than ten days. The clinical picture is that of severe flaccid weakness of voluntary limb and neck muscles with paralysis of respiratory muscles (mainly the diaphragm), leading to difficulties in weaning patients off the respirator. The serum CK is usually elevated but not to extreme levels, and some patients have normal levels. Electromyography (EMG) findings are heterogeneous: a mix of myopathic potentials and neurogenic features can be found. Muscle biopsy may show either non-specific changes, such as atrophy of both fiber types, angulated fibers, and fiber size variation, or myofiber necrosis and apoptotic changes, but the unique feature found in up to 80% of critical illness myopathy patients is selective loss of thick (myosin) filaments with preservation of Z-bands on electron microscopy[14]. This process has been related to excessive breakdown of muscle proteins, i.e., it represents a catabolic myopathy[15].

The study of Lorenzoni et al.[12] that shows the presence of very high CK and muscle findings not characteristic of critical illness myopathy reinforces the association between the skeletal muscle-biopsy alterations described and influenza A (H1N1) infection. The mechanisms of viral pathogenesis are most likely complex. In addition to direct viral replication in epithelial cells, pro-inflammatory cytokine release and abnormalities in the interferon system may contribute to the morbidity and mortality. Death has been attributable to multisystem disease, including tracheobronchitis, pneumonia, myopericarditis, acute renal failure, disseminated intravascular coagulation, hepatic centrilobular necrosis, and severe rhabdomyolysis with myoglobinuria[13].

Severe rhabdomyolysis could be one of the most important causes of death in such presented patients.

The spectrum of influenza-induced myopathy, the cellular mechanism of tissue injury, and the effect of involvement of other tissues on mortality among, otherwise healthy people, require further elucidation.

Considering one reported case of a child with fatal rhabdomyolysis associated with influenza B infection and muscle biopsy, which shows a clinically unsuspected carnitine palmitoyl transferase II deficiency, it is possible that unrecognized metabolic disorder may predispose patients to rhabdomyolysis in influenza A (H1N1) infection leading to poor prognosis[16].

In the face of the worldwide H1N1 pandemic, physicians must recognize both the pulmonary and extrapulmonary complications of this novel infection. The study of Lorenzoni et al.[12] demonstrates the importance of recognizing rhabdomyolysis as a complication of H1N1 infection, possibly related to metabolic condition, and its potential association with life-threatening and prognosis.

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