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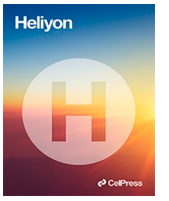

Case report

Going for a stroll on lurasidone: Considerations on an atypical case of acute compartment syndrome of both legs

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ABSTRACT

Non-traumatic acute bilateral compartment syndrome is a rare condition that may lead to limb ischemia. We describe a case of this syndrome occurring after a five-kilometer walk in a young woman receiving chronic treatment with lurasidone, leading to a bilateral foot-drop and rhabdomyolysis of the anterolateral compartment of both legs. Due to her late presentation in the emergency department, we opted for a conservative approach, closely monitoring her renal function. We noticed a subsequent clinical and biochemical improvement over the following days, with the patient returning to her daily routine in a matter of weeks, despite a persisting bilateral foot drop. Since atypical antipsychotics are known to be associated with rhabdomyolysis, while possibly exerting a toxic effect on mitochondria, we hypothesize that a mild aerobic physical exertion might have triggered the event, in the context of an iatrogenic muscle susceptibility to oxidative distress.

1. Introduction

Acute non-traumatic bilateral compartment syndrome of the legs is a rare condition that may lead to limb ischemia if left untreated, and early detection is key to ensure a successful treatment. This severe manifestation can be seen as a consequence of intense physical exertion (1) but is also associated with a miscellany of conditions that include immobilization, soft tissue infection, substance abuse, and antipsychotic medications (2). There are only a few reports of bilateral compartment syndrome associated with antipsychotic treatment, mainly in the context of the malignant neuroleptic syndrome [1–5]. Lurasidone is a high-affinity full antagonist at dopamine-D2 and serotonin 5HT-2A and 5HT-7 receptors with both antipsychotic and antidepressant properties [6]. It received European Medical Agency approval in 2014 and, currently, there are no reports of rhabdomyolysis or neuroleptic malignant syndrome associated with its use.

In the present report, we describe the case of an acute non-traumatic bilateral compartment syndrome of the legs associated with

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physical exertion in a patient receiving lurasidone.

2. Case report

A 34-year-old woman with a history of severe obesity and unipolar major depression with psychotic features in therapy with lurasidone (92.5mg/day) for four months, presented to our emergency department for a three-day history of bilateral foot drop and painful swelling of the legs. The evening prior to symptom onset the patient reported a 5 km flat walk, which was unusual for her otherwise sedentary routine, and unprecedented since the time she began antipsychotic therapy.

At the emergency examination, the patient presented bilateral peroneal nerve paralysis and hardened painful forelegs, which were visibly swollen and reddish in color. A mild fever (37.9 °C), along with elevation of inflammatory blood tests (CRP 280mg/dL, WBC 25,000/μL, neutrophils 20,000/μL) and signs of rhabdomyolysis (CPK 15,000U/L, GOT 409U/L, GPT 152U/L, LDH 1322U/L) were noted. Indirect signs of myositis and panniculitis were detected at an emergency echographic assessment of the lower limbs, while the main arteries and veins of both lower limbs were left patent. Electroneurography (ENG) of the lower limbs showed bilateral motor nerve block below the fibular head, while needle electromyography (EMG) showed no signs of spontaneous nor voluntary activity in peroneal innervated muscles (tibialis anterior, peroneus longus, extensor longus hallucis). At this time, the patient reported having shaven both legs the day of symptom onset, using an already used and poorly preserved blade, which raised suspicion for infective panniculitis, despite no clear evidence of skin cuts. Due to the many false hints pointing to a possible infectious genesis of the event, broad-spectrum antibiotic therapy was started, while an immediate surgical consultation provided no indications for a fasciectomy. Abundant intravenous hydration and bicarbonate infusions to prevent acute kidney injury were administered.

After her admission to the neurology department, anticoagulant prophylaxis, along with steroid therapy (dexamethasone 8 mg/day) was initiated. A subsequent magnetic resonance imaging (MRI) showed rounded morphology of both peroneal muscle compartments with outward convex bulging of the overlying crural fascia and muscle edema (Fig. 1A and C), along with an area of necrosis in both tibialis anterior muscles, consistent with a compartment syndrome of both forelegs (Fig. 1B and D).

Lurasidone was suspended, in relation to a similar report of rhabdomyolysis after a walk occurred in a patient with concomitant antipsychotic drug use [7]. During a two weeks long hospitalization, our patient's clinical conditions improved, with pain and leg swelling progressively subsiding, as did the inflammatory blood tests (at discharge RCP 1.5 mg/dL, CPK 1000 U/L). She began walking again seven days after symptom onset, despite an evident bilateral foot-drop. Complete Wallerian degeneration of the motor and sensory component of both peroneal nerves was documented at a follow-up ENG, performed 10 days from symptom onset. Neutrophils remained high thorough the stay (at discharge WBC 25,000/μL, neutrophils 17,000/μL), presumably being reactive to rhabdomyolysis. A three months follow-up MRI showed a bilateral volume reduction of the peroneal muscle compartments due to a reduction of the edema, while SE T1-weighted imaging following intravenous contrast administration revealed the presence of small

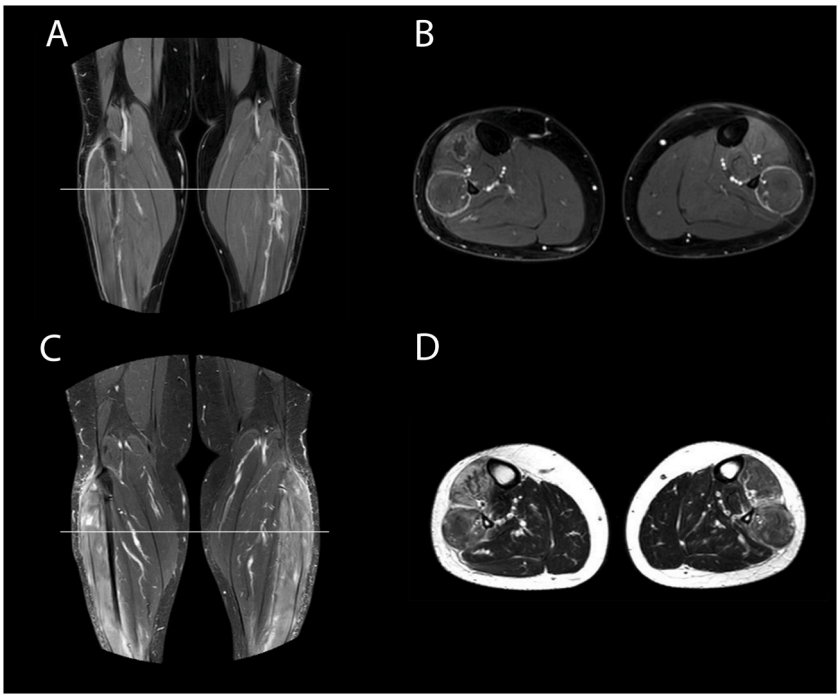

Fig. 1. Magnetic resonance imaging of leg muscles in our patient. A and B show coronal and axial T1-weighted sequences following intravenous contrast administration; C and D show coronal and axial STIR and T2-weighted sequences. The white continuous line in coronal images (A and C) marks the section plane from which axial images were drawn.

non-enhancing necrotic changes in both peroneal muscles. At this time, ENG-EMG showed initial signs of axonal regeneration in the peroneal innervated muscles of the left foreleg, while no voluntary activity was recordable from the right foreleg muscles, where we could only find profuse signs of active denervation. At this time, CPK levels were in the normal range. Five months after the event the patient fully resumed her daily routine, being able to carry on her activities of daily living, despite a persisting bilateral weakness of peroneal innervated muscles, more evident on her left side. At her latest follow-up, the patient reintroduced lurasidone therapy at a lower dosage, as advised by her treating psychiatrist, without any further problems.

3. Discussion

We believe this report offers some points of reflection regarding the etiopathogenesis of acute non-traumatic compartment syndrome, along with the role that antipsychotic treatment may play in this context.

In our patient, symptoms became manifest after a moderate-length walk. During a mainly aerobic exercise, the oxidative capacity of the anterior muscles of the leg is lower than that of the triceps surae muscles, in agreement with the notion that fiber-type phenotype varies among leg muscles [8], providing the anterior leg compartment with a relative vulnerability against prolonged eccentric exercise, which, under extraordinary circumstances, may lead to rhabdomyolysis and muscle swelling [9,10]. Inextensibility of the myofascial compartment under increased interstitial pressure can then act as the final determinant of further microvascular, muscular, and nervous injury. Acute exertional compartment syndrome has been mostly described in athletes after strenuous physical effort [9]. Most patients develop pain, swelling, and neurologic deficits without impaired limb perfusion. Since clinical suspicion is generally lower than in classical fracture-related acute compartment syndrome, this may lead to a substantial diagnostic delay [11]. Fever and leukocytosis are seldom reported in this clinical setting.

This association of fever, neutrophilia, and rhabdomyolysis somehow reminds of a neuroleptic malignant syndrome (NMS). In our case, we did not observe rigidity, mental state changes, nor dysautonomia, and the increase in body temperature was only modest. Although NMS typically develops during the first weeks of antipsychotic treatment, or after dose escalation, an idiosyncratic reaction may occur even after prolonged treatment with the same agent at the same dose for many years [12,13]. The pathogenesis of NMS is poorly defined. Central dopamine receptor blockade at the level of the hypothalamus, nigrostriatal system, and sympathetic neurons may account for hyperthermia, rigidity, and dysautonomia [14], while damage to muscle fibers through a direct toxic effect on mitochondria and calcium regulation is reported to have a role, as well [15]. Multiple lines of research have disclosed that antipsychotic drugs target mitochondrial function, possibly contributing to their efficacy [16] and adverse effects [17,18]. Notably, lurasidone has been proven to significantly increase hydrogen peroxide production in mitochondria at relatively low concentrations [17].

Our hypothesis is that a relatively mild physical exercise in a physically deconditioned patient might have been the triggering event for rhabdomyolysis, in the setting of a muscle system vulnerability represented by concomitant antipsychotic treatment with lurasidone (Adverse Drug Reaction Probability Scale = +2).

To our knowledge, only one other case of acute bilateral compartment syndrome of the legs after walking a moderate distance, in a patient undergoing chronic antipsychotic treatment with risperidone, has been previously reported. The similarities with our report are stunning, either in terms of anamnesis, or clinical and imaging findings [7]. No reports of this association with lurasidone have been described, yet.

Concerning treatment options, our patient developed severe myonecrosis and edema of the anterior compartment of the leg, leading to complete axonal damage of both peroneal nerves. Due to her late presentation in the emergency department and concomitant suspicion of infective panniculitis, fasciotomy was not considered, in favor of non-operative management, consisting of careful monitoring of her metabolic and renal response to the injury. Delayed surgical decompression can be harmful and non-counterbalanced by reasonable benefit, and the utility of a fasciotomy in late-discovered cases is still debated, considering the limited literature providing insight for treatment decisions, even less so for non-traumatic cases [19].

In conclusion, the present report raises some currently unanswered questions, specifically, regarding the potential myotoxicity of lurasidone, and the role that it may have in favoring an otherwise unlikely rhabdomyolysis event.

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no competing interests.

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