Massive Indoor Cycling-Induced Rhabdomyolysis in a Patient with Hereditary Neuropathy with Liability to Pressure Palsy

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PATIENT DESCRIPTION

A 21 year old female was hospitalized in December 2011 because of pain and profound weakness in her thighs rendering her unable to walk, and tea-colored urine. The muscular symptoms had begun 5 days prior to her admission, starting immediately after she had participated, for the first time in her life, in an indoor-cycling class (“spinning”) lasting 45 minutes. The color of her urine changed and prompted her to immediately seek medical care. The patient has hereditary neuropathy with liability to pressure palsy, an autosomal dominant neuropathy, which was diagnosed at the age of 12 following prolonged weakness in her fingers. However, she is generally healthy, recently completed her mandatory army service, and is physically active but had never attended an indoor cycling class before. Her mother and two siblings also carry this genetic abnormality and reported that no other family member with HNPP had ever been hospitalized due to elevated CK levels or any other rhabdomyolysis-related symptoms.

On admission, physical examination revealed an alert and well-oriented young woman who moved with difficulty and needed assistance when walking. Her pulse was 104 beats/minute. Bilateral tenderness was observed on palpation of both quadriceps. Muscle strength in the lower extremities was profoundly decreased. Severe pain and stiffness were observed when she stretched both legs. She did not suffer from any other medical condition and had no history of recent exposure to medications, vaccines, alcohol drinking, or any signs and symptoms of a viral infection. Laboratory results showed a CK level of 132,170 U/L (range < 10–145 U/L) and increased transaminase levels (alanine transaminase 280 U/L (< 3–31 U/L), aspartate transaminase 1256 U/L (< 3–32 U/L) [Table], serum sodium 140.5 mmol/L (136–148 mmol/L), potassium 3.78 mmol/L (3.6–5.3 mmol/L), calcium 8.6 mg/dl (8.6–10.2 mg/dl), phosphorus 3.6 mg/dl (2.7–4.5 mg/dl), lactate dehydrogenase 6995 U/L (240–480 U/L). Urine pH was 5.0, dipstick measurement was positive for blood, but no red blood cells were found on microscopic examination, and the test for myoglobin was positive. Blood levels of urea, creatinine and other

<table>
<thead>
<tr>
<th>CK and transaminase levels</th>
<th>CK (U/L)</th>
<th>AST (U/L)</th>
<th>ALT (U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DAY 1</strong> (admission)</td>
<td>132,170</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>DAY 2</strong></td>
<td>126,740</td>
<td>1636</td>
<td>382</td>
</tr>
<tr>
<td><strong>DAY 3</strong></td>
<td>91,680</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>DAY 4</strong></td>
<td>28,938</td>
<td>892</td>
<td>NA</td>
</tr>
<tr>
<td><strong>DAY 5</strong></td>
<td>7890.0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>DAY 6</strong> (Discharge)</td>
<td>3781.0</td>
<td>225</td>
<td>238</td>
</tr>
</tbody>
</table>

CK = creatine kinase, AST= aspartate transaminase, ALT= alanine transaminase, NA = data not available

HNPP = hereditary neuropathy with liability to pressure palsy

CK = creatine kinase
routine tests were normal. Severe rhabdomyolysis was diagnosed. In order to avoid hypernatremia, intravenous fluid resuscitation with NaCl 0.45% was initiated, together with sodium bicarbonate (0.5 g/L) for alkalization of the urine. Fluid resuscitation was then continued with NaCl 0.9%. During the first 24 hours of treatment the urine color returned to normal.

The differential diagnosis for muscle weakness includes primary muscle diseases (congenital dystrophies, inflammatory, or metabolic) or secondary muscle diseases (following infections, connective tissue diseases, endocrine dysfunction, paraneoplastic, or drug-induced), neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton), or upper or lower motor neuron problems (such as Guillain-Barré syndrome, or toxins, metabolic disorders, nutrition, infection, immune related and hereditary). Our patient described an etiology and medical history that seemed appropriate for rhabdomyolysis with extraordinarily high levels of serum CK.

After 4 days, IV hydration was replaced with oral hydration of 3 L/day. The patient was released on the sixth day of hospitalization. Weakness of the lower extremities was still profound, but she was now able to walk.

**COMMENT**

Rhabdomyolysis is a condition of muscle necrosis and release of intracellular muscle constituents into the circulation, associated with symptoms ranging from an asymptomatic elevation of CK levels to severe muscular pain, weakness and even paralysis accompanied by electrolyte abnormalities, myoglobinuria and renal failure [1]. The clinical diagnosis is based on complaints of muscle pain or weakness in the presence of elevated serum CK. Although there are no clear definitions regarding CK levels in rhabdomyolysis, clinical practice guidelines for rhabdomyolysis define a serum CK level ≥ 5 times the upper limit of normal (approximately 750 U/L). A minimal laboratory workup in rhabdomyolysis includes serum levels of CK, calcium, electrolyte renal functions, in conjunction with detection of myoglobin in urine and an electrocardiogram. Some cases of rhabdomyolysis include the development of compartment syndrome, for which magnetic resonance imaging has recently emerged as a diagnostic modality [1].

Causes for rhabdomyolysis include traumatic muscle injury, increased voluntary or involuntary muscle activity, exogenous toxins, alcohol and illicit drugs, drugs (such as statins), viral infections, hereditary myopathies, and hereditary inflammatory muscle diseases. Exercise-induced rhabdomyolysis is typically seen in high endurance athletes involved in marathons, triathlons and super marathons, but was also occasionally reported in low and high intensity workouts. In the past, it was suggested that muscle fiber-type proportions can be an underlying contributing cause of exercise-induced rhabdomyolysis. When reviewing the literature, we found that most CK levels in rhabdomyolysis were below 100,000 U/L. Indoor cycling (“spinning”), as in our patient, has been infrequently reported as a cause of exercise-induced rhabdomyolysis, and CK elevation above 100,000 U/L was recently described only in male athletes after vigorous training [2].

The standard of care for rhabdomyolysis is directed at the prevention of renal failure, hyperkalemia, metabolic acidosis, and hypovolemia [1]. Myoglobin is a compound released from damaged muscle cells to the circulation, where it binds to haptoglobin. During rhabdomyolysis, excessive levels of myoglobin remain unbound and are therefore rapidly excreted in the urine, often resulting in the production of red/brown urine. As in our patient, myoglobinuria presented as tea-colored urine with a dipstick positive for blood, while no erythrocytes were seen on microscopy. Myoglobin was shown in several models to be nephrotoxic by various underlying mechanisms [3]. These mechanisms include: a) contribution to renal vasoconstriction (mainly in hypovolemic patients), b) interaction with Tamm-Horsfall proteins and formation of intraluminal casts, and c) direct toxicity via lipid peroxidation and tubular injury. These mechanisms were also shown to be potentiated by acidic pH of tubular fluid [3].

The mainstay of therapy is directed toward appropriate urine output, achieved by aggressive intravascular volume expansion with normal saline in order to correct hypovolemia, promote vigorous diuresis and dilute the released toxic products. Additionally, alkalization of the urine to a pH < 6.0 was shown to prevent the development of acute renal failure, but the use of bicarbonate and mannitol is still under debate [1].

HNPP (“tomaculous neuropathy”) is an autosomal dominant disease clinically characterized by a recurrent episodic neuropathy localized to areas frequently affected by compression or trauma [4]. The neuropathy is followed by a spontaneous slow recovery. In most patients, symptoms first appear in the second decade. The commonly affected nerves are those located in trauma-afflicted sites and include the axillary, median, radial, ulnar and peroneal nerves, and/or the brachial plexus. Genetically, most patients with HNPP exhibit a large 1.5 Mb deletion in chromosome 17p11.2-12 that results in reduced expression of the peripheral myelin protein 22 (PMP22) gene [4], making nerves more susceptible to minor trauma or compression.

DNA analysis by FISH (fluorescence in situ hybridization) is available for confirmation of the HNPP diagnosis. A unique histological feature seen in sural nerve biopsies is a focal sausage-like thickening of myelin sheaths (tomacula) [4]. Electrophysiological studies show a distinctive sensorimotor neuropathy pattern that can help to establish the diagnosis. This pattern is characterized by a diffuse slowed sensory nerve
conduction velocity and a prolongation of distal motor latencies (the interval between the stimulus and the onset of the compound muscle action potential), while the motor conduction velocity is barely reduced. This indicates a disproportionate distal-conduction slowing typical to this disorder [4]. Nerve conduction velocity abnormalities are not restricted to the nerves, which are affected by palsy, but are found in a generalized pattern and even in muscles of asymptomatic gene carriers [4].

Whether our patient’s HNPP played a role in her severe rhabdomyolysis may only be speculated. In 2001, Brncic et al. [5] described a case of Salmonella infection-related rhabdomyolysis in a patient with Charcot-Marie-Tooth disease [5]. CK levels were 64,000 U/L. CMT disease results in denervation and trophic and metabolic changes in nerves and muscles. Brncic and team [5] suggested that CMT might be a predisposing factor to rhabdomyolysis and therefore might be of major significance in the development of this complication. Interestingly, duplication or deletion of the same chromosomal region, which contains the gene for PMP22, leads to the development of CMT type 1A or HNPP, respectively [4]. Although CMT and HNPP are related to a defect in the same protein, both disorders are different and there is no evidence for increased risk for rhabdomyolysis in either pathology. However, the exact role of PMP22 is still unknown, and it may be hypothesized that alterations in its expression could predispose to higher vulnerability toward intra- and extracellular electrolyte perturbations and calcium load in both CMT-1A and HNPP patients, resulting in rhabdomyolysis and elevated CK levels. The association between the two pathologies described in this patient might seem weak; nevertheless, we believe that such a link does exist and should be further examined in animal models and clinical assessments.

Patients with HNPP are advised to avoid using excessive force, repetitive movements, and extreme or static joint positions. We also suggest that patients with HNPP consult a sports medicine specialist and routinely measure blood CK following increases in exercise intensity in order to detect abnormal signs that could precede rhabdomyolysis.

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**References**


**Capsule**

**Cross-neutralization of influenza A viruses mediated by a single antibody loop**

Immune recognition of protein antigens relies on the combined interaction of multiple antibody loops, which provide a fairly large footprint and constrain the size and shape of protein surfaces that can be targeted. Single protein loops can mediate extremely high affinity binding, but it is unclear whether such a mechanism is available to antibodies. Ekiert et al. report the isolation and characterization of an antibody called C05, which neutralizes strains from multiple subtypes of influenza A virus, including H1, H2 and H3. X-ray and electron microscopy structures show that C05 recognizes conserved elements of the receptor-binding site on the hemagglutinin surface glycoprotein. Recognition of the hemagglutinin receptor-binding site is dominated by a single heavy chain complementarity-determining region 3 loop, with minor contacts from heavy chain complementarity-determining region 1, and is sufficient to achieve nanomolar binding with a minimal footprint. Thus, binding predominantly with a single loop can allow antibodies to target small, conserved functional sites on otherwise hypervariable antigens.

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Eitan Israeli

**Hollywood is a place where they’ll pay you a thousand dollars for a kiss and fifty cents for your soul**

Marilyn Monroe (1926-1962), American actress, singer and cultural icon. In 1999 she was ranked the sixth-greatest female star of all time by the American Film Institute.