Haff Disease after Eating Buffalo Fish: Report of a Severe Case in Northern California and Review of the Literature

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Introduction: Toxic contamination of fish may compromise food safety. Haff disease is a rare syndrome characterized by rhabdomyolysis following consumption of cooked, freshwater fish. Case Report: A healthy 42 year old female presented three hours after eating fried buffalo fish (Ictiobus cyprinellis). Her symptoms began while eating the fish, described as diffuse muscle aches followed by generalized muscle fatigue, most pronounced in her proximal lower extremities. Vital signs were normal. Her physical exam was notable for diffuse muscle tenderness and difficulty standing. Baseline complete blood count and chemistries were normal, but serum creatine phosphokinase (CPK) was 12,777 U/L. Alanine aminotransferase and aspartate aminotransferase were 268 U/L and 1431 U/L respectively. She was treated with aggressive hydration, sodium bicarbonate, and oral N-acetylcysteine. The serum CPK peaked at 76,364 U/L, twenty hours post-exposure. Her creatinine remained normal. Over the next 5 days the CPK slowly resolved. Discussion: Haff disease is a rare syndrome characterized by rhabdomyolysis following consumption of certain cooked, freshwater fish. Although the exact toxin has yet to be identified, this disorder is felt to be caused by a heat-stable toxin contaminating certain fish. Our case was unique due to the immediate onset of symptoms and the extremely high serum CPK levels. Conclusion: Haff disease may result in the rapid onset of severe rhabdomyolysis. Aggressive treatment with fluids and bicarbonate prevented renal damage in this case. Because cases may occur outside of endemic areas, fish consumption should be included in the history for any case of rhabdomyolysis of unknown etiology. Suspected cases of Haff disease should be reported to local public health authorities and samples collected for analysis. Keywords: Haff disease; Rhabdomyolysis; Fish poisoning; Ictiobus cyprinellis

INTRODUCTION
The health benefits of dietary fish are well known. However, toxic contamination of fish may compromise food safety. Previously reported outbreaks of fish-related poisoning have been caused by scorpoid, ciguatera, tetrodotoxin poisoning, palytoxin poisoning, mercury contamination, paralytic shellfish poisoning, and amnestic shellfish poisoning (1). We report a case of Haff disease that occurred in a healthy, conscious female who consumed buffalo fish in California. Haff disease is a rare syndrome, first reported in the Baltic Region in 1924, which is characterized by rhabdomyolysis following consumption of certain cooked, freshwater fish (2-5). Haff disease is felt to be caused by an as-yet- unidentified toxin. This toxin is possibly similar to the potent marine poison palytoxin as both poisonings may cause severe muscle pains and rhabdomyolysis after seafood consumption (2,4,6).

CASE REPORT
A healthy 42 year old female presented to the emergency department three hours after eating fried buffalo fish (Ictiobus cyprinellis) (Figure 1). This was her first time eating this fish. She purchased the fish from a health food grocery in Berkeley, CA. Her symptoms began while eating the fish, described as diffuse muscle aches followed within minutes by generalized muscle fatigue, most pronounced in her proximal lower extremities. She stated that her muscles felt “rubbery” and found it difficult to walk. She also described fingertips and peri-oral paresthesias. She denied gastrointestinal symptoms, fever, abdominal pain, flushing, or hot/cold reversal. She was taking no medications. She denied smoking, consuming alcohol, or drug abuse.

At presentation, vital signs were at normal range except a mild hypothermia and hypertension (Table 1). Her physical exam was notable for diffuse muscle tenderness and difficulty standing due to weakness. Her deep tendon reflexes were normal. Baseline complete blood count and chemistries were normal, but serum creatine phosphokinase (CPK) was highly increased (Table 1). Hepatic transaminase tests were increased while total bilirubin and alkaline phosphatase were normal. The INR was normal at 0.9. She was treated with aggressive fluid hydration consisting of 3 liters normal saline (sodium chloride 0.9% solution) in the first 3 hours after her diagnosis. She was then placed on half normal saline infusion (sodium chloride 0.45% solution) at 150
**Table 1.** Clinical and laboratory findings at presentation

<table>
<thead>
<tr>
<th>Examination</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>146</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>92</td>
</tr>
<tr>
<td>Pulse rate (beats/min)</td>
<td>87</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>18</td>
</tr>
<tr>
<td>Body Temperature* (Centigrade)</td>
<td>36.4</td>
</tr>
<tr>
<td>Oxygen saturation (Percent)</td>
<td>100</td>
</tr>
<tr>
<td>CK (U/L)</td>
<td>12,777</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>1431</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>268</td>
</tr>
<tr>
<td>Total Bilirubin (U/L)</td>
<td>0.5</td>
</tr>
<tr>
<td>ALP (mg/dL)</td>
<td>67</td>
</tr>
<tr>
<td>INR (IU)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

* Oral measurement

CPK; Creatinine Phosphokinase
AST; Aspartate Aminotransferase
ALT; Alanine Aminotransferase
ALP; Alkaline Phosphatase
INR; International Normalized Ratio

mL/hr. Concurrently, bicarbonate infusion was initiated (150 mEq sodium bicarbonate in 1 liter of D5W) at 100 mL/hr. Oral N-acetylcysteine (NAC) was also started during the first hospital day (140 mg/kg then 70 mg/kg every 4 hours). The serum CPK peaked at 76,364 U/L approximately 20 hours after fish exposure (Figure 2). Fluid hydration was continued through the hospital stay. Sodium bicarbonate infusion and NAC were discontinued on the third hospital day. The patient’s serum creatinine remained normal throughout her hospitalization. Over the next 5 days, the CPK slowly resolved and she was discharged. The aspartate aminotransferase (AST) peaked at 1481 U/L and also resolved in tandem with the serum CPK levels. The patient’s clinical symptoms also improved, though she still complained of generalized muscle weakness at the time of hospital discharge. Hepatitis serologies were found to be negative.

Samples of the contaminated buffalo fish were collected by the California State Department of Public Health and tested without a toxin identified. A sample was also sent to the U.S. Food and Drug Administration laboratory at Dauphin Island, AL for further analysis. At this time, the sample is being held for future testing in association with other suspected Haff disease samples.

At 6 weeks follow-up, she still complained of some
diffuse muscle weakness, but CPK and hepatic transaminase levels remained normal. In addition to her muscle weakness, she complained of cognitive difficulties which included difficulty reading more than a few pages or holding her train of thought. All follow-up labs, including thyroid testing, were normal.

Over the following months, the patient described progressive improvement in her muscle weakness, but persistence of her cognitive impairment. At 8 months following the exposure, she underwent formal neurologic and neuropsychiatric testing which was found to be normal. At 10 months following exposure, she was able to walk and ride a bike without problems, but felt unable to return to her work as a waitress because of cognitive difficulties.

**DISCUSSION**

We described a healthy female who developed severe Haff disease after ingesting buffalo fish. Our patient was a health food enthusiast who had never purchased or consumed buffalo fish previously. Her case was unique due to the immediate onset of her symptoms and the extremely high serum CPK levels reached. With aggressive treatment, she never developed renal manifestations despite her severe rhabdomyolysis.

Following her rhabdomyolysis, our patient reported of diffuse muscle weakness that resolved slowly over the course of months. She also complained of cognitive difficulties that were more persistent. While muscle weakness is not surprising following her severe rhabdomyolysis, persistent cognitive deficits have not previously been reported after cases of Haff disease (2-8). The reason for these complaints is unclear. Because the exact toxin and mechanism of action has not been identified for Haff disease, a definitive explanation is not possible. This patient also experienced a very rapid onset of her symptoms and higher CPK levels than previously reported cases. It is possible that she was exposed to a particularly high toxin dose.

The observed elevations of AST and alanine aminotransferase (ALT) were typical of lab abnormalities related to rhabdomyolysis (9). We did not believe that these findings were likely due to any direct hepatotoxic effect. The patient’s liver function tests (including INR and bilirubin) were normal during admission and the transaminase elevations resolved in tandem with the patient’s rhabdomyolysis.

Haff disease describes a syndrome of rhabdomyolysis following consumption of certain cooked, freshwater fish (2,4,7). This syndrome was first reported in 1924, in persons near the Königsberg Haff (‘haff’ means lagoon in German) on the Baltic coast (2). The original cases exhibited muscle pains, rigidity, and dark urine. Subsequent outbreaks in the Baltic regions have affected thousands of patients (2,4). Although deaths have been reported, most patients recover without any consequence. Most outbreaks have occurred in Europe (2,4). Outbreaks have rarely been reported in the United States (2-4,7,8). There have been 23 cases reported in the US prior to our case. Twelve of these were related to the consumption of Buffalo fish (Ictiobus cyprinellis) (2-4,8). Cases associated with crayfish (unspecified species) and salmon (unspecified species) have also occurred (4,7). A recent outbreak of Haff disease due to crayfish (unspecified species) was also reported in China (5). These are the first known cases of Haff disease in Asia (5). Previously reported cases have involved cooked fish. There is no characteristic odor or taste of the fish causing Haff disease (2,4).

Haff disease is felt to be caused by a yet unidentified, heat-stable toxin (2-4). In one previous investigation, researchers were able to induce Haff disease in cats and white mice by feeding them carp from a pond (5). In these cases bacteriologic studies were negative. They felt that the toxin was a thermostable, fat-soluble compound in blue-green algae eaten by small fish (5). The associated toxin may be similar to the potent marine toxin, palytoxin (2,4,6).

Palytoxin is a very potent toxin that has been found in certain marine fish (10,11). The symptoms of palytoxin poisoning are similar to Haff disease as both result in significant rhabdomyolysis. Palytoxin has been identified in certain zoanthid “soft” coral species of the genus Palythoa and is felt to become concentrated in fish as it passes up the marine food chain (10,11). Palytoxin poisoning has been reported from mackerel (Decapterus macrosoma), triggerfish (Melichthys vidua), crab (Demania reynaudii), blue humphead parrotfish (Ypsiscarus ovifrons) and grouper (Epinephelus sp.). It has not been reported from freshwater fish (2,4). The most commonly reported complication of palytoxin poisoning is rhabdomyolysis (11). Other characteristic manifestations include bitter/metallic taste in the mouth, weakness, excessive sweating, abdominal cramps, nausea, diarrhea, parasthesia, bradycardia, dark urine, renal failure, cyanosis, and respiratory distress (4,10,11). Fatalities from palytoxin have been reported (11).

The treatment for Haff disease is primarily supportive. There is no antidote. Early, aggressive hydration is the most important aspect of therapy for rhabdomyolysis (3,4,12). Urinary alkalinization with sodium bicarbonate infusion should also be considered (4,12). Hemodialysis must be considered in cases with oliguria or anuria (4,12). It is also imperative that any suspected cases of Haff disease are reported to local health authorities so that other contaminated fish may be recovered and exposed persons warned of possible health risks (2). Since, most previous cases of Haff disease have occurred in the context of outbreaks (2-4,7), rapid activation of public health systems may prevent further cases from developing. Recovered fish samples should also undergo testing for potential known toxins or to identify the responsible toxin which is still unknown.

**CONCLUSION**

Haff disease may result in the rapid onset of severe rhabdomyolysis. Aggressive treatment with fluids and bicarbonate appeared to prevent renal damage in this case.

Because cases may occur outside of endemic areas, fish consumption should be included in the history for any case of rhabdomyolysis of unknown etiology. Suspected cases of
Haff disease should be reported to local public health authorities and samples collected for analysis.

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REFERENCES