Central Nervous System Effects of Puffer Fish (Tetrodotoxin) Poisoning

HAO-YEH CHEN¹, CHI-WEN JUAN²,³, TA-LUN KAO⁴, CHEN-YUAN LIU¹

Tetrodotoxin (TTX) is a neurotoxin which is found in freshwater and marine species including puffer fish, blue-ringed octopus, Indo-pacific goby, gastropod mollusks, ocean sunfish, triggerfish and boxfish. The majority of reported cases have occurred in southeastern Asia, particularly Japan, where puffer fish is considered a delicacy. Although improved legislation governing marketing and preparation of the fish has reduced the incidence of puffer fish poisoning in Japan, it remains the most common cause of fatal food poisoning, as there are still some unlicensed cooks and untrained workers involved in preparing the fish. Symptoms of poisoning include paralysis, respiratory failure, blurred vision, vertigo, numbness, paresthesia, nausea and ataxia, which involve the cardiovascular, respiratory, peripheral and central nervous systems. We report a 59-year-old male taxi driver, who presented to our emergency department with dyspnea, generalized weakness and numbness due to tetrodotoxin poisoning. We recorded changes in the patient’s electroencephalogram (EEG) during and after the illness. To our knowledge, this is the first report in humans demonstrating only minor cortical dysfunction on an EEG during severe tetrodotoxin poisoning in a patient in a deep coma with fixed, dilated pupils.

Key words: tetrodotoxin, puffer fish, electroencephalogram (EEG)

Introduction

Puffer fish poisoning is probably the most common fish poisoning along the coasts of Asia¹. This fish is variously known as the blowfish, toadfish, balloonfish, Patkafish and Fugu, and belongs to the order Tetraodontiformes¹,². In spite of the toxic nature of the puffer fish and its recognized ill effects, it is a delicacy in Japan and is prepared by licensed puffer fish cooks²,³. Despite careful preparation, there are about 50 deaths annually in Japan from puffer fish poisoning³,⁴. Deaths have also been reported in Singapore, Hong Kong and Australia¹,²,⁵,⁶. In Taiwan, more than 100 cases were reported from 1988 to 2008, and the mortality rate was around ten percent. Poisoning has occurred in Taipei, Taoyuan, Miaoli, Hsinchu, Taichung, Changhua, Tainan, Kaohsiung, Pingtung, Ilan, Hualien and Taitung, with the highest frequency in central Taiwan and the Kaohsiung-Pingtung area. The poison’s sources include puffer fish, sea snails (commonly known as bitter snails), naticidae, olividae, tiger shrimp, fish and fragrant fish fillets, and poisoning occurs between winter and spring, most frequently in May and June⁷. The puffer fish poison is tetrodotoxin. Ingestion of the flesh, viscera or skin of toxic tetraodontiform fishes causes poisoning. As there is a distinct relationship
between gonadal activity and toxicity, the fish are most dangerous to eat immediately prior to and during their reproductive season. The highest concentration of the toxins is found in the viscera (gonads, especially the ovaries; liver; intestine) and skin. The body musculature is usually free of poison\(^1\). Since there is no specific treatment, people should be made aware of the potential risk of eating puffer fish, the warning symptoms and signs of puffer fish poisoning, and when to seek medical help.

**Case Report**

A 59-year-old, male taxi driver presented to our emergency department with dyspnea, generalized weakness and numbness after eating some porridge cooked with Takifugu niphobles for lunch. On arrival, he was tachypneic (respiratory rate 40/min), and hypertensive (blood pressure 165/90 mmHg) but his consciousness was clear and he was able to give a coherent history. He had mild hoarseness initially, then became aphonic and went into sudden respiratory distress with lip cyanosis. He was immediately intubated while awake, but respiratory effort ceased several minutes later and mechanical ventilation commenced. About one hour later, he was in a deep coma with a Glasgow coma scale score of 3, and fixed, dilated pupils, flaccid extremities, sinus bradycardia and severe hypotension. Chest radiography showed nothing abnormal, and electocardiography (EKG) revealed only bradycardia. Therefore, he was admitted to our intensive care unit. Over the next two days, he had a fluctuating blood pressure, hypothermia and polyuria. His fluid balance was negative 3550 ml in the first 24 hours. Biochemistry data showed sodium was 162 mmol/L, potassium 3.4 mmol/l and urine specific gravity 1.020. Arterial blood gas analysis showed combined metabolic acidosis and respiratory alkalosis. Diabetes insipidus was suspected. Thirty-six hours after admission, the patient regained consciousness and some upper limb motor function, but still had no spontaneous breathing effort. In addition, he had a brief period of vision loss without light perception, and EEG revealed minor diffuse cortical dysfunction which was likely metabolic in origin (Fig. 1). Later that

[Fig. 1] (Minor diffuse cortical dysfunction on electroencephalogram)
day, his vision recovered spontaneously and his ventilation effort also recovered. He was extubated the next day. On day 10, he was discharged without any neurological disability, and a follow-up EEG showed no evidence of focal cortical dysfunction.

We sent a blood sample to National Taiwan Ocean University, where tetrodotoxin measured by bioassay was 300 mouse units per gram (MU/g), which means 1 gm sample could kill the numbers of 20 gm-weighted male mouse in 30 minutes.

**Discussion**

Puffer fish poisoning is the best known among all types of fish poisoning and had been recognized from ancient times. A rapid ascending paralysis is the most common paralysis complication\(^{(8)}\). Patients with severe poisoning may fall into a coma and death may occur within four to six hours of ingestion\(^{(3,4)}\). Typically, death is due to respiratory muscle paralysis. The clinical effects of TTX poisoning have been graded by the severity of neurological and cardiovascular involvement (Table 1)\(^{(9)}\).

Most patients exhibit typical neurological features, including perioral numbness/paresthesia, distal limb numbness/paresthesia and ataxia. Gastrointestinal features are also typical, with nausea and occasional vomiting, but no diarrhea. Cardiovascular effects occur only in the most severe cases\(^{(10)}\).

The liver, gonads and skin of puffer fish contain tetrodotoxin, a powerful neurotoxin that can cause death in approximately 50% to 60% of persons who ingest it\(^{(5)}\). Tetrodotoxin is heat-stable, water-soluble and a non-protein quinazoline derivative\(^{(6)}\). It is a specific and reversible inhibitor of sodium conductance along the entire length of the neuronal axon with blocking at fast depolarizing phase one in skeletal muscles\(^{(11)}\). Thus, all of the observed toxicity is secondary to blockade of the action potential\(^{(6)}\). Tetrodotoxin acts on the central and peripheral nervous systems (i.e. autonomic, motor, sensory nerves). Tetrodotoxin also stimulates the chemoreceptor trigger zone in the medulla oblongata and depresses the respiratory and vasomotor centers in that area. In one report, peripheral nerve conduction studies revealed clear abnormalities. Nerves in affected patients were of high threshold, and exhibited slow conduction and reduced-amplitude compound potentials, indicating that some axons were unable to conduct at all\(^{(10)}\). This affect was greater in sensory than motor axons, correlating well with the greater prominence of sensory symptoms (dysesthesia and numbness) relative to motor symptoms (weakness) in affected patients\(^{(10)}\). Here we present a case of grade 4 TTX poisoning with features of reversible focal cortical dysfunction, observed clinically by a transient coma followed by temporary diabetes insipidus and then a brief period vision loss. We recorded the patient’s EEG changes during and after the illness course. To

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms and signs</th>
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<td>Grade 1</td>
<td>Perioral numbness and paraesthesia, with or without gastrointestinal symptoms (mainly nausea).</td>
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<tr>
<td>Grade 2</td>
<td>Numbness of tongue, face and other areas (distal); early motor paralysis and incoordination; slurred speech; normal reflexes.</td>
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<tr>
<td>Grade 3</td>
<td>Generalized flaccid paralysis, respiratory failure (dyspnea), aphony and fixed/dilated pupils; patient still conscious.</td>
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<tr>
<td>Grade 4</td>
<td>Severe respiratory failure and hypoxia; hypotension, bradycardia and cardiac dysrhythmias; unconsciousness may occur</td>
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our knowledge, this is the first report in humans demonstrating only minor cortical dysfunction on EEG during severe tetrodotoxin poisoning in a patient in a deep coma with fixed, dilated pupils.

Puffer fish is available in many Asian countries, including Taiwan, and it is said to be very delicious. Its cooking process requires a special technique which is not known to most people. Puffer fish poisoning has no specific treatment\(^{12}\) however, early recognition of the condition and supportive care in a modern intensive care unit should ensure a safe outcome\(^{10}\). The diagnosis of tetrodotoxin intoxication is made according to the medical history and toxidrome. In Taiwan, tetrodotoxins are measured in mouse units per gram. One mouse unit is the amount of tetrodotoxin which can kill a 20 gm male mouse in 30 minutes\(^{13}\). This method can help confirm the diagnosis of tetrodotoxin intoxication if the history is ambiguous. People should be made aware of the potential risk of eating puffer fish. During its preparation, the liver, gonads, intestines and skin should be removed, because they contain the highest levels of TTX. Moreover, attention should be paid to warning symptoms and signs. Emergent medical support is needed if poisoning occurs. In addition, health personnel should be trained and prepared to deal with these medical emergencies.

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河豚毒素對中樞神經的影響：個案報告

陳浩業1  阮祺文2,3  高大倫4  劉正元1

河豚毒素是一種神經毒素，它存在於一些淡水和海水生物當中，包括河豚魚、豹紋章魚、印度洋鯊虎、鰟鱇的軟體動物、翻車魚、鰻魚和硬鰭魚。大多數的案例發生於東南亞，尤其是日本，因為河豚在當地被視為一道佳餚。儘管日本政府已立法改善河豚魚的販賣與處理來降低中毒的機會，河豚中毒依然是日本食物中毒的最大死因，因為當地人仍有多無照廚師和未受過訓練的人來處理河豚魚。河豚毒素的中毒症狀包括肢體癱瘓，呼吸衰竭，視力模糊，眩暈，感覺麻木，感覺異常，噁心和步態不穩，這些症狀包含心臓血管，呼吸，周邊神經和中樞神經等系統。本文章報告一位59歲計程車司機，吃完河豚後產生氣促，全身麻木及無力來急診就醫的病人。我們記錄病患病中及病後的腦波，顯示大腦皮質因河豚毒素僅產生輕度大腦皮質功能異常的現象，即使病患陷入昏迷併瞳孔放大。就現今的文獻，這個病人可能是第一個用腦波記錄河豚中毒的案例。

關鍵詞：河豚毒，河豚，腦波

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