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Case Report Open Access

A Case of Severe Puffer Fish Poisoning: Serum Tetrodotoxin Concentration Measurements for 4 Days after Ingestion

Yasumasa Iwasaki[1], Akira Namera[2], Hiroshi Giga[1], Yoshiko Kida[1], Kohei Ota[1], Kazunobu Une[1], Tadatsugu Otani[1], Shinichiro Ohshimo[1], Nobuyuki Hirohashi[1], Koichi Tanigawa[1]

[1]*Department of Emergency and Critical Care Medicine, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan*

[2]*Department of Forensic Medicine, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan*

***Corresponding author:** Yasumasa Iwasaki, Department of Emergency and Critical Care Medicine, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan, Tel: 81-90-8242-4859; E-mail: yiwasaki@hiroshima-u.ac.jp

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Introduction

Puffer fish poisoning is common in Asian countries with coastline areas. In addition to Japan, there have been reports of such cases in Singapore [1], Taiwan [2], Bangladesh [3], and Hong Kong [4]. In Japan, deaths due to puffer fish poisoning exceeded 100 cases annually throughout the 1950s. Since then, a license is required to prepare puffer fish dishes throughout Japan, and the annual number of deaths has subsequently dropped to 0–3 cases over the past 10 years [5]. Tetrodotoxin (TTX), the causative agent of puffer fish poisoning, is a potent toxin that specifically binds to voltage-gated sodium channels. A previous report has stated that TTX is detectable for approximately 4 days after ingestion in poisoning cases using 24-hours urine collection, while TTX only remains in the serum component for a short period (less than 24 hours) [6]. No report has demonstrated a relationship between symptoms and blood TTX concentrations from 24 hours after ingestion. Here we report a case of severe puffer fish poisoning in which the patient developed prolonged respiratory muscle paralysis and temporary complete blindness. We were able to measure blood and urine TTX concentrations for 4 days after ingestion.

Case Report

The patient was a 70-year-old man and his medical history included a surgical procedure for esophageal cancer at 8 months before poisoning. On the day of poisoning, the patient caught two puffer fish at a nearby beach in the morning and brought them to his home, where he thoroughly kneaded the flesh and livers of the fish in water and then soaked them in water for 8 hours. After that, he ate some flesh raw and the other after briefly boiling. In addition, he boiled the liver for 20 minutes before eating it. Approximately 10 minutes after eating the fish, he began to experience tongue and peri-oral paresthesia. Because he then started to exhibit symptoms of inarticulation, he suspected puffer fish poisoning by himself and visited the emergency room (ER) of our hospital approximately 1 hour after ingestion by his own car with his family.

On ER admission, paresthesia of extremities, weakness of both lower limbs, difficulty in respiration, and dyspnea were revealed. He could not stand up or speak. The patient was also in a state of agitation. His spontaneous respiration was 25 breaths/min, SpO2 was 96% (room air), chest movement was poor, heart rate was 71 beats/min with normal sinus rhythm, blood pressure was 172/82 mmHg with no cold extremities, and Glasgow coma scale score was 12 (E4, V2, M6). Table 1 shows laboratory data on arrival. Blood gas analysis indicated respiratory alkalosis and biochemical examinations indicated very slightly elevated lactic acid levels. After the patient was admitted to the intensive care unit, he was intravenously administered buprenorphine (0.2 mg) and midazolam (5 mg) and underwent intratracheal intubation. Volume controlled mechanical ventilation was started.

Blood gas analysis (face mask O2 5 L)		**Biochemistry**		
pH	7.617	T.Bil	0.7 mg/dl	
PaCO2	24.3 mmHg	AST	35 U/L	
PaO2	182 mmHg	ALT	32 U/L	
BE	4.8 mEq/L	LDH	218 U/L	
HCO3–	25.1 mEq/L	CK	123 U/L	
		BUN	22.3 mg/dl	
CBC		Cr	0.7 mg/dl	
WBC	7730/mm3	Na+	141 mEq/L	
RBC	4.21 × 104/mm3	K+	3.2 mEq/L	
Ht	38.1%	Cl-	99 mEq/L	
Hb	12.9 g/dl	CRP	0.83 mg/dl	
Plt	20.0 × 104 /mm3	BS	149 mg/dl	
		Lac	2.6 mmol/L	
Coagulation test				
PT-INR	1.03			
APTT	26.5 sec			
FDP	<2.5 μg/ml			
D-dimer	<0.5 μg/ml			

Table 1: Laboratory data on arrival. BE: Base Excess; CBC: Complete Blood Cell Count; WBC: White Blood Cells; RBC: Red Blood Cells; Ht: Hematocrit; Hb: Hemoglobin; Plt: Platelet; PT-INR: Prothrombin Time-International Normalized Ratio; APTT: Activated Partial Thromboplastine Time; T. bil.: Total Bilirubin; AST: Aspartate Transaminase; ALT: Alanine Transaminase; CK: Creatinine Kinase; BUN: Blood Urea Nitrogen; Cr: Creatine Kinase; CRP: C-Reactive Protein; BS: Blood Sugar; Lac: Lactic Acid.

We could not perform gastric lavage with activated charcoal administration because the patient had undergone small-diameter gastric tube reconstructive surgery after subtotal esophagectomy and gastric tube insertion was impossible. Although no muscle relaxants were used, spontaneous respiration quickly disappeared after intratracheal intubation. The left and right pupil were mydriasis and the diameters were both 6 mm, and both light reflexes were absent. Mydriasis and the absence of light reflex persisted for approximately 60 hours after arrival. The absence of spontaneous breathing continued until approximately 50 hours after arrival at our hospital. Hypotension (systolic blood pressure < 80mmHg) requiring noradrenaline was exhibited for approximately 24 hours after arrival. A chest X-ray and head computed tomography scan image revealed no abnormal findings. Twelve-lead electrocardiography also revealed no problems. The patient's clinical course over a 72-hour period after arrival is shown in Fig. 1. Serum TTX concentrations at 23,41, and 63 hours after arrival were 89, 17, and 7.7 ng/mL, respectively, and at 87 h after arrival, only a trace amount remained (Figure 1). Urine TTX concentrations at 23,41,63, and 87 hours after arrival were 723,443,60, and 6.8 ng/mL, respectively (Figure 2). Until 60 hours after intratracheal intubation, the pupil diameter of both the eyes dilated to 6 mm and then decreased to 4 mm over the following 12 hours, while light reflexes were absent for 72 hours after tracheal intubation. Enough spontaneous breathing returned at 62 hours after arrival, and the patient was lucid and also responsive to instructions to squeeze or release his hand. Finally, mechanical ventilation was discontinued and the tracheal tube was removed. After extubation, the patient complained that he could only see blackness even with his eyes open. For approximately 10 h after extubation, the patient was in a state of complete blindness. His eyesight gradually returned from approximately 72 hours after arrival and had normalized by 84 hours after arrival. After undergoing a course of rehabilitation, the patient was discharged on post-hospitalization day 7 with no sequelae.

Discussion

Puffer fish poisoning is caused by the consumption of TTX and it is famous for lethal poisoning agent. The toxicities of puffer fish varies with season, locality even for the same species in the same region [7]. The sites of the fish with the highest concentration of TTX are the liver and ovaries, followed by the intestine and skin [3, 8]. TTX is quickly absorbed by the intestinal tract, moves to the blood, and is excreted in urine. There is a high concentration of TTX-sensitive voltage-gated sodium channels (TTX-s Na channels) in the Ranvier nodes found in peripheral nerve axons. TTX blocks Na+ conductance by binding extracellularly at receptor site 1 of Na+ channels. Therefore, Na+ influx is prevented, action potentials do not occur, and nerve excitability is suppressed [9]. However, the fish themselves do not exhibit TTX toxicity because there is no TTX-binding site in the Na+ channels of puffer fish.

The first symptoms are perioral paresthesia or numbness, nausea, and vomiting. Subsequently, tongue numbness, limb muscle weakness, facial muscle weakness, inarticulation, dizziness, and rapid breathing. With increasing severity, other symptoms such as systemic flaccid paralysis, aphonia, respiratory insufficiency, mydriasis, hypotension, and bradycardia may also occur [10]. The progression of TTX poisoning is classified as follows [10]:

Grade 1 Paresthesia around the mouth, with mild gastrointestinal symptoms.

Grade2 Paresthesia spreading to the trunk and extremities, with early motor paralysis and lack of coordination.

Grade 3 Widespread paralysis, hypotension, and aphonia.

Grade 4 Impaired conscious state, respiratory paralysis, severe hypotension, and cardiac arrhythmia.

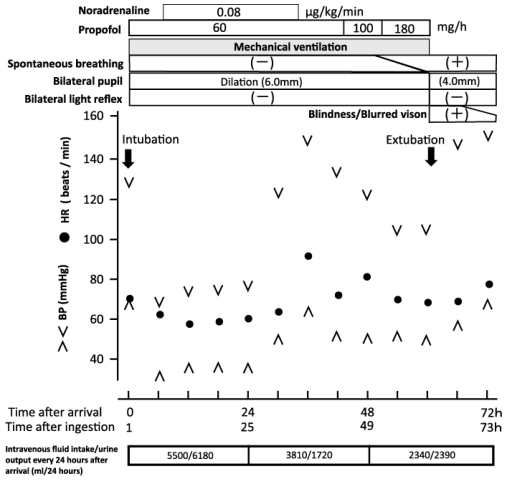

Figure 1: Clinical course over a 72-hour period after arrival BP: Blood pressure, HR: Heart rate. Hypotension (systolic blood pressure <80 mmHg) requiring noradrenaline was exhibited for approximately 24 hours after arrival.

The onset of symptoms in TTX poisoning is usually rapid, but is dependent on the severity of poisoning [11]. Our case also exhibited tongue and peri-oral paresthesia approximately 10 minutes after ingestion and grade 4 symptoms approximately 90 minutes after ingestion.

For approximately 24 hours after arrival, our case exhibited hypotension (systolic blood pressure < 80 mmHg) requiring noradrenaline. In TTX poisoning, hypotension is caused by the stimulation of the chemoreceptor trigger zone in the medulla oblongata and depression of the respiratory and vasomotor centers in that area [12-14]. In contrast to the disturbance of central nervous system, vasodilation due to peripheral sympathetic nervous suppression by TTX has also been suggested [15].

Our case exhibited mydriasis, absence of light reflex, and complete blindness. Blindness and blurred vision are common symptoms of puffer fish poisoning, as reported by Chowdhury et al. [16] in 12 of 53 such cases. It has been reported that TTX has no effect on consciousness [17]. In addition, our patient was lucid while experiencing impaired vision after extubation; thus, it appears unlikely that these symptoms were a direct TTX action on the central nervous system. Our patient complained that he was unable to "see anything except darkness" after extubation, which was similar to the symptoms in a case reported by Oishi [18]. Therefore, the same as the report by Oishi [18], we also speculate that optic nerve disruptions or the interception of the activity of inner retina spike neurons by TTX may cause temporary complete blindness, mydriasis and abcence of light reflex in cases of puffer fish poisoning.

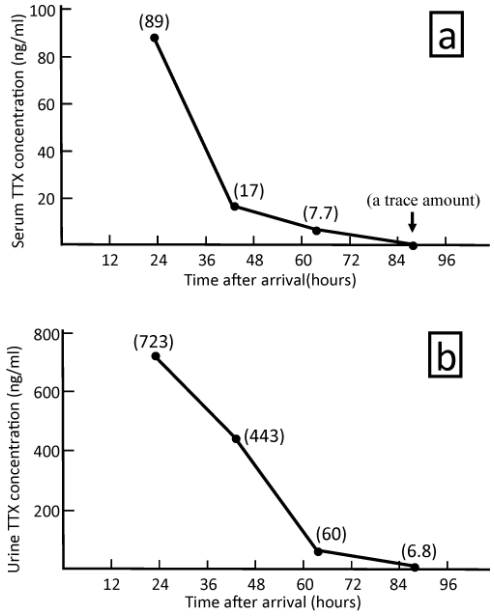

Figure 2: TTX concentrations in serum [a] and in urine [b] for 96 hours.

Our patient arrived at the ER approximately 1 hour after the ingestion of puffer fish. Serum TTX concentrations at 23,41, and 63 hours after arrival were 89,17, and 7.7 ng/mL, respectively, although only a trace amount remained at 87 hours after arrival. The patient had normal kidney function, and changes in TTX concentrations from 23 to 41 hours after arrival suggested that the serum half-life of TTX is approximately 12 hours. With regard to the relationship between symptoms and serum TTX concentration, as hypotensive state continued for approximately 24 hours after arrival and the TTX concentration was 89 ng/mL at 23 hours after arrival, the risk of hypotension due to TTX appears to increase when the TTX concentration is approximately 90 ng/mL or greater. Although a post-mortem study reported a serum TTX concentration of 353ng/g [19], the serum TTX concentration of 89 ng/mL observed in our patient at 23 hours after arrival appears to be the highest concentration at which the patient was discharged with no future sequelae. Respiratory arrest due to muscle paralysis has been reported at concentrations of >9 ng/mL [20], which is a lethal concentration if mechanical ventilation is not performed immediately. In our patient, spontaneous breathing was absent until approximately 48 hours after arrival. Because the TTX concentration was 17ng/mL at 41 hours after arrival, it appears that symptoms of respiratory muscle paralysis, as described in a report by Islam et al. [20], appear at concentrations of approximately >10 ng/mL. Mydriasis and the absence of light reflex continued until approximately 60 hours after arrival, and the patient was in a state of complete blindness for some time after that. Because the TTX blood concentration was 7.7 ng/mL at 63 hours after arrival, it was presumed that mydriasis and blurred vision are exhibited at a TTX concentration of approximately 7.7 ng/mL. After the consumption of puffer fish, TTX is quickly absorbed from the digestive tract and moves to the blood. Because TTX concentration increases very quickly, it appears that both respiratory muscle paralysis and blurred vision happens almost at the same time.

It has been reported that TTX only remains in the serum for <24 hours [6]. In contrast, the serum TTX concentration in our patient was 7.7 ng/mL at 63 hours after arrival (64 h post-ingestion). This is the first report of TTX detection in serum more than 2.5 days after ingestion, which could explain why symptoms of puffer fish poisoning, including respiratory muscle paralysis, absence of light reflex, and blindness/blurred vision, continued for such a long time. There seems to be two reasons for the high TTX concentrations in serum. One of the reasons is that the patient ate much liver of the puffer fish which contains TTX. The other is that the gastric lavage for TTX removal could not be performed because of the operation for esophageal cancer, which may have increased the volume of TTX absorbed. Therefore, the serum TTX concentration could be greater compared with the case which was performed a gastric lavage.

A urine TTX concentration of 6.8ng/mL was detected at 87 hours after arrival, even if the serum TTX was at a trace amount. Similarly, a previous study of four cases with serum TTX concentrations of <5 ng/mL at 24 hours after ingestion had urine TTX concentrations of 125–258ng/mL [6]. Even in cases of mild poisoning, TTX is likely detectable in urine; thus, the detection of TTX in urine appears to be a suitable method to confirm a diagnosis of TTX poisoning.

Experimentally, monoclonal antibodies have been successfully used to treat TTX poisoning in mice [21]. However, at present, there are no effective antidotes to treat TTX poisoning in humans. The administration of anticholinesterase drugs soon after presentation and during recovery appears to be effective in accelerating the return of muscle power and the improvement appears to be maintained [8]. However, a recent report concluded that both qualitatively and quantitatively, the current literature is insufficient to provide an evidence base for or against the use of neostigmine (anticholinesterase drugs) in adults with TTX-associated respiratory failure [22]. Accordingly, at present, it is thought that appropriate prehospital and ER ventilator support is mandatory for those patients exhibiting respiratory failure [23]. Our patient arrived at the ER within 1 h of ingesting puffer fish and mechanical ventilation was quickly initiated; thus, the patient was ultimately discharged with no sequelae, despite symptoms being prolonged. Thus, the most important aspect during the treatment of TTX poisoning is emergent respiratory care before respiratory arrest and, in severe cases, managing circulation to respond to hypotension.

Conclusions

Here we reported a case of severe puffer fish poisoning with prolonged respiratory muscle paralysis, hypotension and temporary complete blindness for which we were able to measure blood and urine TTX concentrations for 4 days after ingestion. Serum TTX concentrations at 23,41, and 63 hours after arrival were 89,17, and 7.7ng/mL, respectively, with only a trace amount at 87 hours. Urine TTX concentrations at 23,41,63 and 87 hours after arrival were 723,443,60, and 6.8 ng/mL, respectively. At 62 h after arrival, spontaneous respiration was sufficient to discontinue mechanical ventilation and remove the tracheal tube. The patient was in a state of complete blindness for approximately 10 hours after extubation; however, his eyesight gradually returned subsequently. On post-hospitalization day 7, the patient was discharged with no sequelae.

References

1. Yong YS, Quek LS, Lim EK, Ngo A1 (2013) A case report of puffer fish poisoning in singapore. Case Rep Med 2013: 206971.
2. Yang CC, Liao SC, Deng JF (1996) Tetrodotoxin poisoning in Taiwan: an analysis of poison center data. Vet Hum Toxicol 38: 282-286.
3. Ahasan HA, Mamun AA, Karim SR, Bakar MA, Gazi EA, et al. (2004) Paralytic complications of puffer fish (tetrodotoxin) poisoning. Singapore Med J 45: 73-74.
4. Wan CK, Tsui SH, Tong HK(2007) A case series of puffer fish poisoning. Hong Kong J Emerg Med 14:215-20.
5. Bureau of Social Welfare and Public Health, Tokyo Metropolis. Accessed Dec 10, 2014.
6. O'Leary MA, Schneider JJ, Isbister GK (2004) Use of high performance liquid chromatography to measure tetrodotoxin in serum and urine of poisoned patients. Toxicon 44: 549-553.
7. Yu CF, Yu PH-F (2002) Are puffer fish more toxic in their spawning season? Marine Biol 140: 1053-1057.
8. Chew SK, Goh CH, Wang KW, Mah PK, Tan BY (1983) Puffer fish (tetrodotoxin) poisoning: clinical report and role of anti-cholinesterase drugs in therapy. Singapore Med J 24: 168-171.
9. Kiernan MC, Isbister GK, Lin CS, Burke D, Bostock H (2005) Acute tetrodotoxin-induced neurotoxicity after ingestion of puffer fish. Ann Neurol 57: 339-348.
10. Halstead BW (1967) Class osteichthyes, tetrodotoxic fishes: Poisonous and venomous marine animals of the world.Washington, D.C.: United states government printing office.
11. Isbister GK, Son J, Wang F, Maclean CJ, Lin CS, et al. (2002) Puffer fish poisoning: a potentially life-threatening condition. Med J Aust 177: 650-653.
12. Koizumi K, Levine DG, Brooks CM (1967) Effect of tetrodotoxin (puffer fish toxin) on the central nervous system. Neurology 17: 395-404.
13. Flachsenberger WA (1986) Respiratory failure and lethal hypotension due to blue-ringed octopus and tetrodotoxin envenomation observed and counteracted in animal models. J Toxicol Clin Toxicol 24: 485-502.
14. Benzer TI (2013) Tetrodotoxin Toxity.
15. Mizobata Y, Yokota J, Ishida T, Tohira H (2000) Puffer fish poisoning accompanying marked changes in hemodynamics. JJAAM 11: 214-218.
16. Chowdhury FR, Nazmul Ahasan HA, Mamunur Rashid AK, Al Mamun A, Khaliduzzaman SM (2007) Tetrodotoxin poisoning: a clinical analysis, role of neostigmine and short-term outcome of 53 cases. Singapore Med J 48: 830-833.
17. Cong NH, Tuan le TQ (2006) Electrodiagnosis in puffer fish poisoning--a case report. Electromyogr Clin Neurophysiol 46: 291-294.
18. Oishi Y, Watanabe Y, Mikane T, Kobayashi H, Iwasaki E, et al (2012) A case of puffer fish poisoning complicated with temporary blindness. J Jpn Soc Intensive Care Med 19: 429-430.
19. Suenaga K, Kotoku S (1980) Detection of tetrodotoxin in autopsy material by gas chromatography. Arch Toxicol 44: 291-297.
20. Islam QT, Razzak MA, Islam MA, Bari MI, Basher A, et al. (2011) Puffer fish poisoning in Bangladesh: clinical and toxicological results from large outbreaks in 2008. Trans R Soc Trop Med Hyg 105: 74-80.
21. Rivera VR, Poli MA, Bignami GS (1995) Prophylaxis and treatment with a monoclonal antibody of tetrodotoxin poisoning in mice. Toxicon 33: 1231-1237.
22. Liu SH, Tseng CY, Lin CC (2015) Is neostigmine effective in severe pufferfish-associated tetrodotoxin poisoning? Clin Toxicol (Phila) 53: 13-21.
23. How CK, Chern CH, Huang YC, Wang LM, Lee CH (2003) Tetrodotoxin poisoning. Am J Emerg Med 21: 51-54.