Puffer fish poisoning: a potentially life-threatening condition

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Puffer fish poisoning has been documented rarely in Australia. It results from ingesting tetrodoxtoxin found in the liver, ovaries, intestines and skin of the fish. Over a recent 16-month period, 11 cases of puffer fish poisoning were reported to the NSW Poisons Information Centre. Symptoms of poisoning may include paralysis, respiratory failure, numbness, paraesthesia, nausea and ataxia. Health professionals should be aware of the condition so as to institute early and appropriate management.
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TETRODOTOXIN (TTX) is present in high concentrations in the liver, ovaries, intestines and skin of puffer fish (Box 1).[1] Although TTX poisoning caused by ingestion of the fish is common in some parts of the world, it occurs only sporadically in Australia, with only 16 published cases reported over the past 200 years.[2-7] (This figure does not include the 11 cases described here.) One of the earliest descriptions of puffer fish poisoning in this region can be found in Captain James Cook's journal from his second voyage in 1774 (see Time Capsule, *page 653*).[3]

The majority of reported cases have occurred in south-eastern Asia,[1,8-10] particularly Japan, where puffer fish is considered a delicacy.[1,11] 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.[1,11] Before 1950, all reported cases in Australia were fatal,[5] and in Japan up to 100 deaths a year were reported.[11]

We describe 11 patients with puffer fish poisoning, four of whom underwent comprehensive neurophysiological testing.

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Clinical findings

For the period 1 January 2001 to 13 April 2002, records of 149 453 calls to the NSW Poisons Information Centre were searched for instances of puffer fish poisoning. The Centre covers New South Wales and Tasmania 24 hours a day and the rest of Australia overnight. Of 195 calls coded as food or fish poisoning, there were five calls regarding puffer fish. Two were minor cases involving people who had been squirted with fluid from puffer fish. The three remaining calls were from hospitals: a total of 11 affected people (described here) were involved.

Patient 1

A 33-year-old woman presented to a semi-rural hospital with nausea and vomiting, perioral paraesthesia, dysarthria, ataxia and hyperventilation after ingesting seven puffer fish several hours earlier (see Box 1). Her vital signs were stable and the FEV_1 (forced expiratory volume in one second) was 2.2 litres (normal range, 3.3–4.0 L). However, an hour after presentation she became more dysarthric and developed limb paresis with hyporeflexia. In view of progressive leth-

1: The common toadfish (*Tetractenos hamiltoni*)

The fish pictured here is approximately 10 cm in length. Photo courtesy of Erik Schlogl.

2: Description of 11 patients presenting with puffer fish poisoning

Patient	Sex, age	Onset (minutes)	Gastrointestinal features	Neurological features	Duration of symptoms	Severity grade*
1	F, 33	NR	Nausea, vomiting	Perioral paraesthesia, dysarthria, ataxia, limb weakness, hyporeflexia and ophthalmoplegia. Decreased FEV_1, with respiratory failure.	5 days	3
2	M, 40	60	Nil	Perioral and extremity paraesthesia, dizziness.	18 hours	2
3	F, 5	NA	Nil	Nil.	NA	NA
4	F, 12	NR	Nil	Perioral and extremity paraesthesia.	<6 hours	2
5†	M, 33	30	Nausea, vomiting	Perioral and lingual numbness, dysaesthesia of extremities, dizziness and gait ataxia.	5 days	2
6†	F, 47	NR	Nausea, vomiting	Perioral and extremity paraesthesia, dizziness and gait ataxia.	5 days	2
7	M, 39	60	Vomiting	Perioral and lingual numbness, dysaesthesia of extremities, dizziness and gait ataxia. Mildly reduced power in upper and lower limbs.	5 days	2
8†	M, 41	60	Nil	Perioral numbness, dysaesthesia of extremities, dizziness and gait ataxia. Decreased sensation in hands and feet ("glove-and-stocking" distribution).	5 days	2
9	F, 35	60	Vomiting; simultaneous incomplete miscarriage	Perioral and lingual numbness, dysaesthesia of extremities, slight dizziness and gait ataxia. Normal power and sensation. Respiratory distress.	5 days	2
10†	M, 47	30	Nausea	Perioral and lingual numbness, dysaesthesia of extremities, dizziness and gait ataxia. Mildly reduced power in upper and lower limbs.	5 days	2
11	M, 50	90	Nausea	Perioral numbness, dizziness and gait ataxia. Normal power and sensation.	5 days	2

NA = not applicable. NR = not recorded. *Clinical grading system for tetrodotoxin poisoning based on symptoms and signs present (after Fukuda and Tani[12]):
Grade 1: perioral numbness and paraesthesia, with or without gastrointestinal symptoms (mainly nausea).
Grade 2: numbness of tongue, face and other areas (distal); early motor paralysis and incoordination; slurred speech; normal reflexes.
Grade 3: generalised flaccid paralysis, respiratory failure (dyspnoea), aphonia and fixed/dilated pupils; patient still conscious.
Grade 4: severe respiratory failure and hypoxia; hypotension, bradycardia and cardiac dysrhythmias; unconsciousness may occur.
†Neurophysiological testing was done on these patients (see Box 3).

argy, dyspnoea and a fall in FEV_1 to 1.5 L, she was intubated and ventilated, then transferred to the intensive care unit of a metropolitan teaching hospital.

On arrival, the patient was haemodynamically stable but her pupils were dilated and non-reactive to light. Investigations, including a lumbar puncture and cranial computed tomography scan, were normal. With a presumptive diagnosis of tetrodotoxin poisoning, the patient was managed with supportive care. Over the next two days, her condition improved, deep tendon and pupillary reflexes returned, and she was extubated on Day 2. The other symptoms gradually resolved, and she was discharged on Day 5 after full neurological recovery.

Patient 2

A 40-year-old man presented to a metropolitan teaching hospital (see Box 2). He stated that he had eaten 10 small toadfish eight hours earlier, together with drinking a significant quantity of alcohol. Following ingestion of the toadfish he had collapsed a number of times and felt tingling of his hands and feet and around his mouth. With each collapse, he experienced generalised weakness, but did not lose consciousness. He had no relevant past medical history. On examination he was afebrile, with a pulse rate of 110 beats/minute, blood pressure of 140/80 mmHg, respiratory rate of 16 breaths/minute and oxygen saturation of 96%. A neurological examination was entirely normal. After uneventful overnight observation, he was discharged.

Patients 3–11

Seven adults and two children ate a soup made from about 30 puffer fish, gutted with heads intact and boiled in fresh water. The cook referred to the fish as puffer fish, and one of us (J U) identified one of the fish as a puffer fish. All nine patients had been previously well, not taking medication, and with no known allergies. The patients' clinical features are shown in Box 2.

One child was completely asymptomatic, and the other had mild symptoms of perioral numbness and dysaesthesia of the extremities for five hours. Both were discharged from the emergency department.

Most of the seven adults presented to hospital with nausea, perioral and lingual numbness, dysaesthesia of the extremities, dizziness and gait ataxia. Several patients had vomiting and one was experiencing respiratory distress. Neurological examination revealed marked ataxia in all seven patients and limb weakness in two patients (more marked in the upper than lower limbs). One patient had decreased sensation in the hands and feet. Most symptoms resolved over 48 hours, but slight weakness and ataxia of the lower limbs remained. These resolved completely over the

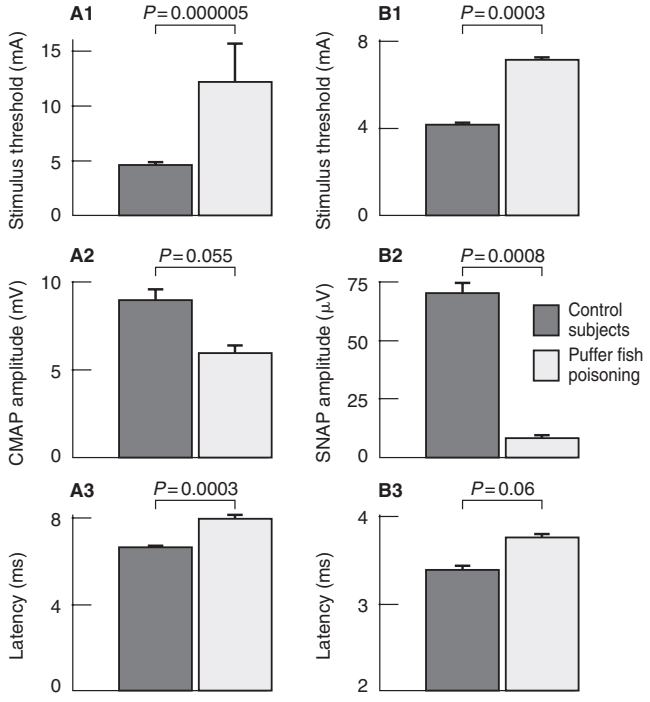
3: Neurophysiological investigation of patients with puffer fish poisoning

Neurophysiological investigation* was performed in four adult patients (numbered 5, 6, 8 and 10 in Box 2) within 24 hours of puffer fish ingestion. None of the patients studied had a history of medical conditions known to affect nerve function, and none were taking any regular prescribed medication.

Results of motor (Figures A1–A3) and sensory (Figures B1–B3) nerve conduction studies of the median nerve in patients with puffer fish poisoning and control subjects are compared. (Results are expressed as mean ± standard error of the mean and compared using an unpaired two-tailed *t*-test.)

Stimulus–response curves showed that the stimulus current (threshold) required to generate compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs) was significantly higher in patients with puffer fish poisoning than control subjects, suggesting an overall reduction in axonal membrane excitability (Figures A1, B1).[13] Compound potentials were smaller in amplitude (Figures A2, B2) and of longer latency (Figures A3, B3) in affected patients compared with controls. These parameters are dependent on Na^+ channel function and suggest reduction both in the number of conducting axons and in the conduction velocity of those axons still available for impulse transmission.

Overall, these findings indicate a reduction in Na^+ conductance in the nerves of affected patients, consistent with direct blockade of axonal Na^+ channels by tetrodotoxin.



**Method:* Motor and sensory nerve conduction studies of the median nerve were performed using surface electrodes. Results were compared with established normative data using previously described standard techniques.[14,15] The median nerve was stimulated at the wrist, with the evoked orthodromic compound muscle action potential (CMAP) recorded from thenar muscles and antidromic sensory nerve action potential (SNAP) recorded using ring electrodes around the index finger. Latency was measured to peak response. Skin temperature was recorded at the site of stimulation in each patient throughout the study, and individual measurements were compensated for temperature using the relationship found in normal subjects.[16,17]

4: Puffer fish poisoning

Tetrodotoxin (TTX) is present in high concentrations in the liver of puffer fish, with progressively decreasing amounts in the ovaries, intestines and skin.[1] TTX poisoning can occur from ingestion of a wide range of bony fish from families in the order Tetraodontiformes, most importantly the family Tetraodontidae (puffer fish).[11] While none of our cases were confirmed by expert identification of the fish, the description by the patients suggested puffer fish (sometimes called "toadfish" in Australia), and the clinical features were consistent with TTX poisoning.

Although ciguatera is also caused by ingestion of fish, the clinical effects differ, and tropical reef fish are mainly implicated.[18] The fish ingested by patients 2–11 were from the Georges River, in southern Sydney. While 35 species from the family Tetraodontidae occur in New South Wales, the species in the cases described here were most likely *Tetractenos hamiltoni* (common toadfish), *T. glaber* (smooth toadfish), or *Torquigener pleurogramma* (weeping or banded toadfish), all of which are common and have been recorded in the Georges River and Botany Bay (Doug Hoese and Mark McGrouther, Fish Section, Australian Museum, personal communication).

The common toadfish is a sandy to whitish colour, with small brown spots over most of the back and upper sides. The lower sides often have brown bars and blotches (Box 1). It occurs from southern New South Wales to northern Queensland in shallow coastal waters and estuaries. The smooth toadfish looks similar to the common toadfish, but has larger spots and distinct body spines. With other species of puffer fish found in tropical waters, the potential for TTX poisoning exists in many coastal regions of Australia.

The in-vitro effects of TTX are well characterised. It is a selective blocker of voltage-sensitive sodium channels and prevents conduction in motor and sensory nerves by blocking sodium channels at the nodes of Ranvier.[11,19] Less is known about the in-vivo effects in humans. Nerve conduction studies have been limited,[20,21] and demonstrate effects on muscle and sensory action potential amplitudes.[20]

following week. Neurophysiological investigation was undertaken in four of the adult patients (see Box 3) within 24 hours of ingestion.

Discussion

Although puffer fish poisoning is rare in Australia, our report highlights the seriousness of TTX poisoning and its potential to be life-threatening.[11] However, early recognition of the condition and supportive care in a modern intensive care unit should ensure a safe outcome.

The clinical effects of TTX poisoning have been graded by the severity of neurological and cardiovascular involvement (Box 2).[11] In this series, one patient had Grade 3 poisoning, and most others Grade 2 poisoning. Most of the patients exhibited typical neurological features, including perioral numbness and/or paraesthesia, distal limb numbness/paraesthesia and ataxia — symptoms similar to those seen in previous case series.[1-10] Gastrointestinal features were also typical, with nausea, occasional vomiting, but no diarrhoea. Cardiovascular effects (not present in this series) occur only in the most severe (Grade 4) cases.

The onset of symptoms in TTX poisoning is usually rapid, but is dependent on the severity of poisoning. In the moderately severe cases in this series, symptoms had all

occurred within 90 minutes. In reported fatal cases and severe poisoning, symptoms have almost always developed within 1–2 hours.[10] The majority of moderate to severe cases in this series resolved within five days, consistent with previous reports,[3,6] although this also depends on the severity. In minor cases the duration of symptoms may only be a few hours.

The relatively mild symptoms experienced by patients 3–11 probably reflect the relatively low dose of TTX ingested. TTX is present in high concentrations in the viscera of puffer fish, particularly the liver and intestines (Box 4). These organs were removed before cooking the fish soup, and the amount of TTX was subsequently diluted by adding fresh water to the soup and possibly by subsequent boiling. With higher levels of TTX, paralysis and respiratory failure are inevitable, although consciousness is not lost except in extreme cases (Box 2). Of interest, such a process has been implicated in the phenomenon of "zombification" in Haiti.[22,23]

Nerve conduction studies revealed clear abnormalities. Nerves in the patients tested were of high threshold, and exhibited slow conduction and reduced-amplitude compound potentials, indicating that some axons were unable to conduct at all. This effect was greater in sensory than motor axons, correlating well with the greater prominence of sensory symptoms (dysaesthesiae and numbness) relative to motor symptoms (weakness) in these patients. Voltage-dependent Na^+ channels underlie action potential generation and are the chief determinants of membrane excitability in human nerves.[24,25] Tetrodotoxin blocks Na^+ channels at very low concentrations, affecting action potential generation and impulse conduction.

It is important that health professionals are aware of TTX poisoning because of the potential for severe and life-threatening effects. All but the mildest cases (Grade 1) should be admitted to hospital for observation until the peak of the clinical effects has passed. After 24 hours it is extremely unlikely that life-threatening effects will occur in patients who have not already developed severe effects. Early diagnosis by recognition of the combination of clinical effects in people ingesting puffer fish is essential to management.

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Competing interests

None identified.

References

1. Tsunenari S, UchimuraY, Kanda M. Puffer poisoning in Japan — a case report. *J Forensic Sci* 1980; 25: 240-245.
2. Ellis RM, Jelinek GA. Never eat an ugly fish: three cases of tetrodotoxin poisoning from Western Australia. *Emerg Med* 1997; 9: 136-142.
3. Torda TA, Sinclair E, Ulyatt DB. Puffer fish (tetrodotoxin) poisoning: clinical record and suggested management. *Med J Aust* 1973; 1: 599-602.
4. Field J. Puffer fish poisoning. *J Accid Emerg Med* 1998; 15: 334-336.
5. Duncan C. A case of toadfish poisoning. *Med J Aust* 1951; 2: 673-675.
6. Tibballs J. Severe tetrodotoxic fish poisoning. *Anaesth Intensive Care* 1988; 16: 215-217.
7. Cleland JB. Injuries and diseases in Australia attributable to animals (except insects). *Med J Aust* 1924; 2: 339-345.
8. Kanchanapongkul J. Puffer fish poisoning: clinical features and management experience in 25 cases. *J Med Assoc Thai* 2001; 84: 385-389.
9. Yang CC, Liao SC, Deng JF. Tetrodotoxin poisoning in Taiwan: an analysis of poison center data. *Vet Hum Toxicol* 1996; 38: 282-286.
10. Kan SK, Chan MK, David P. Nine fatal cases of puffer fish poisoning in Sabah, Malaysia. *Med J Malaysia* 1987; 42: 199-200.
11. Meier J, White J, editors. Handbook of clinical toxicology of animal venoms and poisons. Boca Raton, Florida: CRC Press, 1995: 75-83.
12. Fukuda A, Tani A. Records of puffer poisonings. Report 3. *Nippon Igaku Oyobi Kenko Hoken* 1941; (3528): 7-13.
13. Kiernan MC, Bostock H. Effects of membrane polarization and ischaemia on the excitability properties of human motor axons. *Brain* 2000; 123(Pt 12): 2542-2551.
14. Kiernan MC, Burke D, Andersen KV, Bostock H. Multiple measures of axonal excitability: a new approach in clinical testing. *Muscle Nerve* 2000; 23: 399-409.
15. Kiernan MC, Lin CS, Andersen KV, et al. Clinical evaluation of excitability measures in sensory nerve. *Muscle Nerve* 2001; 24: 883-892.
16. Kiernan MC, Cikurel K, Bostock H. Effects of temperature on the excitability properties of human motor axons. *Brain* 2001; 124: 816-825.
17. Burke D, Mogyoros I, Vagg R, Kiernan MC. Temperature dependence of excitability indices of human cutaneous afferents. *Muscle Nerve* 1999; 22: 51-60.
18. Pearn J. Neurology of ciguatera. *J Neurol Neurosurg Psychiatry* 2001; 70: 4-8.
19. Kao CY. Tetrodotoxin, saxitoxin and their significance in the study of excitation phenomena. *Pharmacol Rev* 1966; 18: 997-1049.
20. Oda K, Araki K, Totoki T, Shibasaki H. Nerve conduction study of human tetrodotoxication. *Neurology* 1989; 39: 743-745.
21. Yamazaki M, Shibuya N. Motor nerve conduction velocity is useful for patients with tetrodotoxin. *Anesth Analg* 1995; 80: 857.
22. Anderson WH. Tetrodotoxin and the zombi phenomenon. *J Ethnopharmacol* 1988; 23: 121-126.
23. Littlewood R, Douyon C. Clinical findings in three cases of zombification. *Lancet* 1997; 350: 1094-1096.
24. Burke D, Kiernan MC, Bostock H. Excitability of human axons. *Clin Neurophysiol* 2001; 112: 1575-1585.
25. Schwarz JR, Reid G, Bostock H. Action potentials and membrane currents in the human node of Ranvier. *Pflugers Arch* 1995; 430: 283-292.

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time capsule

Poisonous tales

T A Torda et al (*Medical Journal of Australia* 1973; 1: 599-602) quote a vivid description of puffer fish poisoning from Captain Cook's journal of his second voyage. On 7 September 1774, an unfamiliar fish was obtained from natives of newly discovered New Caledonia. Before it was cooked, Mr Forster, the ship's naturalist, examined the specimen:

"…luckily for us the operation of drawing and describing the fish took so much time that it was too late so that only the liver and roe was dressed of which Mr. Forster and myself did but taste. About three to four o'clock in the morning, we were seized with most extraordinary weakness in all our limbs attended with numbness of sensation like to that caused by exposing one's hands and feet to a fire after having been pinched much by frost. I had almost lost the sense of feeling nor could I distinguish between light and heavy objects, a quart pot full of water and a feather was the same in my hand. We each took a vomit and after that a sweat which gave great relief. In the morning one of the pigs which had eaten the entrails was found dead."

A J Metcalfe, of Thursday Island (*Medical Journal of Australia* 1923; 2: 571), describes two deaths from eating "toad fish":

"Two Malays out of bravado ate a 'puff-toad' at mid-day and felt no ill-effects. At 5.30 p.m. they ate the liver, which is said to have been a large one. This had been left on the ashes of the fire from the mid-day meal and was only partly cooked. Within a few minutes both complained of being ill. This was followed in five minutes by loss of sensation and paralysis of the fingers, hands and arms. Paralysis quickly spread to the tongue and throat and they were unable to speak. It next attacked the lower limbs and gradually spread upwards. The first man died in half an hour; to the next man an emetic was given and he vomited, but died in three hours."