

SHORT COMMUNICATION

The first documented case of neurotoxicity in two patients following octopus flesh ingestion in the Mediterranean: a case study from the Maltese Islands (central Mediterranean)

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Abstract

Tetrodotoxin is a naturally occurring potent neurotoxin, widely distributed in marine animals, including a number of members of the Tetraodontidae fish family (e.g. *Lagocephalus sceleratus*, the silver-cheeked toadfish), a marine invasive species native of the Indo-Pacific region which is increasingly being reported from the Mediterranean. Various human fatalities have been documented globally as a result of intoxication through tetrodotoxin, but these have rarely been associated with the ingestion of octopus flesh. We hereby report the case of two patients from the Maltese Islands (central Mediterranean) who presented symptoms consistent with neurotoxicity, following the consumption of the well-cooked flesh of the common octopus. Both patients required supportive care, until complete recovery within a few days, with one of whom requiring intensive care. The reported cases of neuromuscular disturbances following the consumption of octopus flesh is highly suggestive of neurotoxicity due to tetrodotoxin poisoning, the first such cases documented for the Mediterranean waters, although alternative scenarios are also postulated in this study due to the lack of definite evidence for the TTX poisoning, including the release of histamine by psychrotrophic bacteria or the accumulation of HAB-related toxins. The postulated TTX intoxication mechanism involves predation by *Octopus vulgaris*, the common octopus or 'scuttle', on a toxic marine species harbouring tetrodotoxin.

Keywords: Neurotoxicity, tetrodotoxin, octopus, Mediterranean

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Human intoxication cases due to consumption of marine species resulting in hospitalisation are still relatively rare in the Mediterranean while it is common

in tropical marine regions (e.g. the Indo-Pacific). Non-indigenous species (NIS) originating in tropical marine areas are largely responsible for the cases reported from the Mediterranean, with fish species within the Tetraodontidae family being responsible for the majority of the cases.

We report two patients, a father and his daughter, who showed up independently and spontaneously at the Accident and Emergency department of Mater Dei Hospital in Msida, Malta, on the 23rd March 2018, exhibiting signs of somnolence within a couple of hours after consuming an octopus-containing meal. The octopus had been caught by the male patient, an experienced fisherman, one week prior to ingestion, having been frozen until thoroughly cooked in a stew. Within two hours of ingestion, the 64-year-old male patient known to suffer from ischaemic heart disease, felt unwell and highly lethargic. He also developed an unsteady gait and was increasingly confused. On arrival at the Accident and Emergency (A&E) Department, he exhibited a Glasgow Coma Scale of 13 (V4, E2, M5), and a blood pressure value of 110 mmHg systolic. The electrocardiogram (ECG) was consistent with sinus bradycardia (56 beats per minute, attributable to long-term administration of beta blockers). His arterial blood gases (ABG) on admission revealed no evidence of an acid-base disorder. Computed tomography (CT) imaging of the brain was normal. A routine toxicology screen was negative. Routine blood investigations conducted on the same patient, revealed that a complete blood cell count, renal and liver functions were within normal limits. Transfer to the intensive care unit was arranged in view of his altered consciousness, so as to ensure close monitoring and institute supportive care. Symptoms resolved spontaneously within 48 hours and he was discharged from hospital 72 hours following his admission.

His daughter, a 37-year old healthy lady, who also ingested the same meal, left home immediately after her meal, but within an hour, she complained of lethargy, somnolence and slurring of speech, and showed up at the A&E Department as well. She reported loss of proprioceptive sensation which had however, resolved prior to seeking medical assistance. Physical examination was otherwise normal apart from mild dysarthria. There was no rash. Investigations conducted on this patient included ECG, brain CT imaging, ABGs and routine blood tests, results for which were all unremarkable. She was admitted to a general medical ward for close observation. Her symptoms resolved without medications within 24 hours and she was discharged from hospital the following day.

Public health services were notified about these two cases since it was hypothesized that an unknown environmental toxin was responsible for the acute nature of the patients' similar symptomatology of neurotoxicity, which was of public interest given that it occurred shortly following the ingestion of an octopus species.

Human intoxication by marine species can occur through two broad mechanisms – either through the injection of venom (known as ‘envenomation’) or through the direct consumption of venom-laced flesh. Toxic species can poison predators passively through toxins they produce or which they assimilate within their bodies from their own prey. The most important venomous marine invertebrates belong to Gastropoda and Cephalopoda. The Gastropoda class includes molluscs able to inject venom in their prey and, occasionally, even in humans. The cephalopod species capable of causing direct envenomation of humans include squid, octopi, cuttlefish (Haddad and Moura 2007).

Octopi have a number of defense mechanisms, but little is known about their toxins. One such toxin found in their salivary glands is linked to their mandible or beak (Haddad and Moura 2007). Certain octopus species, such as the blue-ringed octopus (*Hapalochlaena lunulata* Quoy and Gaimard 1832, not known so far from the Mediterranean), inoculate maculotoxin from their saliva glands through their horny beak (Haddad and Moura 2007). Their bite, though a rare occurrence (Cavazzoni *et al.* 2008) is considered to be highly toxic to humans, causing pain at the site of the bite, followed by possible excessive bleeding, gastrointestinal symptoms, respiratory failure and even cardiac arrest (Fell 2017). Maculotoxin has been demonstrated to be identical to tetrodotoxin (Haddad and Moura 2007), which is also considered to be the major toxic component in the venom of the blue-ringed octopus (Chand 2009). The nomadic jellyfish (*Rhopilema nomadica*), a Lessepsian species native of the Indo-Pacific region, which was first recorded from the Mediterranean in the late 1970s, is yet another species commonly associated with human envenomation in the Basin through its nematocyst-loaded tentacles.

Besides envenomation through the injection of venom as a result of bites or stings, human intoxication is also possible through the direct consumption of marine species flesh laced with venom. Tetrodotoxin is a naturally occurring potent neurotoxin that has been responsible for human intoxications and fatalities (Gupta 2016), and is widely distributed in marine animals, including the fish species in Tetraodontidae (Wu *et al.* 2014; Noguchi *et al.* 2006). The occurrence of the toxic chemical within this species of octopus is normally attributable to the ingestion of contaminated puffer fish by the same species (Bane *et al.* 2014). In humans, tetrodotoxin blocks axonal sodium channels and provokes a muscular paralysis, potentially leading to a fatal respiratory arrest (Haddad and Moura 2007). Other octopus species are known to secrete cephalotoxin in their saliva (Haddad and Moura 2007). However, the presence of the blue ringed octopus has, to date, not been reported in the Mediterranean Sea whilst the octopus species known from the Mediterranean are considered to be non-toxic. The three most frequently encountered octopus species present in local waters are: the common octopus or scuttle *Octopus vulgaris* (Cuvier 1797), the white-spotted or long-armed octopus *Callistoctopus macropus* (Risso 1826) and the musky octopus *Eledone moschata* (Lamarck 1798). In a study by

Moustafa and Awaad (2016), extracts from the posterior salivary gland and the ink sac of *O. vulgaris* were administered orally to mice. This resulted in liver toxicity and haematological disorders in the tested mice (Moustafa and Awaad 2016). However, the same effect has not been extrapolated to humans. It seems that the fisherman in question, being an experienced one, is able to distinguish between the three different indigenous species of octopi such that he is confident that the individual he and his daughter consumed belonged to *O. vulgaris*, suggesting that they did not ingest a toxic species.

Toxicity in humans following ingestion of octopus meat has been rarely reported in literature. The two patients featured in this study complained independently of similar symptoms following ingestion of the same previously frozen, thoroughly-cooked octopus, with symptoms occurring with the same time frame following ingestion. However, the cephalopod was caught and preserved by an experienced fisherman who denied adopting different preservation practices from customary ones. In addition, there were no associated gastrointestinal symptoms in either of the patients, a scenario one would expect when food infected by pathogenic microorganisms is ingested. The symptoms that our patients suffered from are highly consistent with neurotoxicity. The patients' manifestations are most likely to have arisen from either the ingestion of toxin contained in the salivary gland or in the flesh of the consumed octopus. Both patients denied having ingested any components of the octopus head, thus eliminating the salivary glands as a possible source of toxin. The food was allegedly cooked thoroughly but neurotoxins from the salivary glands can remain active even under high temperatures (Haddad and Moura 2007).

For this reason, and given the non-toxic nature of the ingested species, one can hypothesize another scenario, that of predation by *O. vulgaris* on a toxic species harbouring tetrodotoxin such as the silver-cheeked toadfish *Lagocephalus sceleratus* (Gmelin 1789), which was already reported twice from Maltese coastal waters by Deidun *et al.* (2015) and Karachle *et al.* (2016) or any other related species such as *Lagocephalus suezensis* (Clark and Gohar 1753 (never recorded locally) or the blunthead puffer *Sphoeroides pachygaster* (Muller and Troschell, 1858) (quite frequent in our waters) although the latter two species are less toxic than *Lagocephalus* species. Figure 1 illustrates an individual of *L. sceleratus* recorded from Maltese waters in 2015 (Deidun *et al.* 2015). This event may have resulted in a case of secondary intoxication, also given the benthic/demersal nature of these fish species which renders them congenial for a surprise attack by a local octopus species.

Unfortunately, the exact biochemical nature of the toxins present in our patients could not be determined at the time of the events. However, the timing of the onset of symptoms in our patients closely follows that within other related international studies which studied the effect of tetrodotoxins ingested along with puffer fish flesh.



Figure 1. An individual of *Lagocephalus scleratus* recorded by one of the authors (AD) from Maltese waters in 2015, representing the first record of the species for the area. Since then, a total of four individuals of the species have been recorded from Maltese waters.

The onset of symptoms following ingestion of tetrodotoxin from puffer fish was observed within 30 minutes in 66%, within 31 to 60 minutes in 24%, within 61 to 90 minutes in 7% and within 91 to 120 minutes in 2% of cases studied during an outbreak reported in Bangladesh (Bane *et al.* 2014). Symptoms decreased gradually over 8 to 28 hours after ingestion and subsequently resolved completely. In another outbreak in Israel, reported between 2005 and 2008, the onset of symptoms was observed within 10 to 60 minutes following ingestion, while in Taiwan in 2001, the onset of symptoms was typically within 6 hours of ingestion, with an eventual complete resolution of symptoms (Bane *et al.* 2014). In the United States, tetrodotoxin poisoning was reportedly rare, but a report indicated several cases of people fishing for and consuming puffer fish exhibiting elevated levels of these toxins and suffering the associated ill-effects (Gupta 2016). Ideally, in our study, blood and urine samples should have been tested for tetrodotoxin content, since this class of toxins can be found in blood within less than 24 hours after its ingestion, but can be found in urine samples up to four days from the time of ingestion. Therefore, it is important to collect urine and blood samples from affected patients within 24 hours after ingestion so as to confirm a clinical diagnosis of the hypothesized cause of intoxication (Bane *et al.* 2014).

A related literature search identified a case report of a female patient who had very similar clinical manifestations following the ingestion of octopus flesh (Haddad and Moura 2007). The case describes an adult female patient who

developed malaise, paresthesia in perioral and extremity areas, intense muscular weakness neuromuscular symptoms and arterial hypotension within a few hours of ingesting partially-cooked octopus in a northeast Brazilian coastal city. This patient too did not exhibit gastrointestinal symptoms or fever. These symptoms resolved spontaneously within a few hours. The following day, the patient developed a rash which persisted for a total of five days and resolved spontaneously. Confirmatory investigations were also not performed in this case.

Wu *et al.* (2014) featured symptoms in two patients in Taipei, a 39-year-old and a 42-year-old man. One patient experienced for 15 minutes an acute numbness of the mouth, lips, fingers, and toes after eating one specimen of octopus, accompanied by dimmed vision, muscle weakness, fatigue, headache, dizziness, nausea and vomiting. Clinical examination revealed hyperesthesia of the upper limbs and a fluctuating heart rate. Other patients, who had ingested several specimens of octopus, developed severe respiratory symptoms which justified assistance through the deployment of mechanical ventilation and inotropes. The symptoms subsided completely within five days. Testing of the uneaten octopus and victims' urine samples in this case revealed tetrodotoxin poisoning. Symptoms and recovery timeframes were very similar to those reported for our patients. The type, severity and variety of symptoms depend on the amount of toxin ingested, age and health of the victim (Wu *et al.* 2014). The most elderly patient in our study in fact suffered from more severe symptoms than the younger patient, possible due to his underlying co-morbidities.

Given that the underlying cause of the intoxication in the two patients could not be definitely identified, mainly due to the lack of comprehensive blood and urine sample analyses, and given the fact that the symptoms presented are not only representative of neurotoxin intoxication and given that cephalopods can accumulate different biotoxins, alternative hypotheses explaining the observed toxicity are postulated. For instance, histamine-production by psychrotrophic bacteria (e.g. *Enterobacter* spp.) isolated from refrigerated *Octopus maya* specimens can result in allergies in consumers which exhibit symptoms similar to those documented in the present study (Gullian Klanian *et al.* 2018). Such bacterial strains, have, to date, not been isolated from *Octopus vulgaris*. A second alternative feasible scenario involves the documented accumulation of Harmful Algal Bloom (HAB)-related toxins within cephalopods (Lopes *et al.* 2013), which lead to similar symptoms as those observed in the current study due to their neurotoxicity. The HAB-related toxins in question include domoic acid and its derivatives, saxitoxin and its derivatives and palytoxin and its derivatives. HABs have rarely been documented from Maltese waters, although they are not completely unknown from this part of the world.

The neuromuscular symptoms in our patients can tentatively be attributed to ingestion of octopus flesh. Being the first such episodes reported within the

Mediterranean Basin, where octopus is regularly consumed by the public, these cases highlight the need for increased awareness about such a typology of intoxication in humans, especially within the emergency department where prompt investigation and notification is paramount. The lack of comprehensive urine and blood sample analyses supporting the conclusions of this study precludes the conclusive identification of TTX as the source of the observed intoxication, which could have arisen through at least two alternative pathways.

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