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Introduction

Human consumption of shell sh and certain n sh contaminated with the neurotoxin domoic acid causes Amnesic Shell sh Poisoning (ASP), a syndrome that results in preventable morbidity and mortality [1-5]. Although the incidence of ASP is rare around the world due to careful monitoring by government agencies since the original incident in 1987, patients can still present with clinical symptoms (Table 1) that may not be known to physicians. Hence, the goal of this report is to provide information to clinicians, along with relevant background material about the biological source of the neurotoxin.

History of the Event

ASP was rst described in late 1987, in eastern Canada, when at least 153 human cases of intoxication and four deaths of elderly patients were reported, along with signi cant morbidity in other patients [6-8]. All were determined by Health Canada to have consumed aquacultured blue mussels (Mytilus edulis) from Prince Edward Island, eastern Canada.

Identi cation and Source of the Toxin

e toxin in the mussels was discovered to be domoic acid, a small (311 g/mol) polar amino acid [9]. Surprisingly, this toxin was identical to the one reported in Japan in 1959, from a marine red macroalga, Chondria armata. Seaweed extracts containing domoic acid had been used as an e ective anthelminthic to treat intestinal worms in Japanese children. However, in the case of the Canadian outbreak, an order of magnitude higher dose (~290 mg) was consumed, compared to the "therapeutic" anthelminthic dose (~20 mg) used by the Japanese in treating for parasites [3,10]. Moreover, the elderly Canadian patients were more vulnerable and at a higher risk of mortality due to reduced renal function, as well as having a compromised blood-brain barrier [11]. e poisoning led to serious and potentially life-threatening neurological sequelae, including primarily serious and protracted generalized convulsions and seizures, as well as memory loss (hence the name of the syndrome) and even death [7,8]. e toxin also resulted in dermatologic, pulmonary, ophthalmic, as well as gastrointestinal and neurologic manifestations (Table 1) [12,13].

e biological source of domoic acid in the 1987 poisoning event was not seaweed, but rather species of phytoplankton, the marine pennate diatom Pseudo-nitzschia multiseries (Figure 1) [6]. At present, 45 species of the genus Pseudo-nitzschia have been discovered, of which 19 produce domoic acid [14]. ese toxigenic species are found worldwide [3,4]; another diatom, Nitzschia navis-varingica, also produces domoic acid [15]. Mounting global research has discovered that repeated seasonal harmful algal blooms (HABs) of toxigenic Pseudo-nitzschia species exposed birds (e.g. pelicans, cormorants; [16]), marine mammals (e.g. sea lions, seals, dolphins, whales; [17]) and marine sh [18,19] to toxic and sublethal doses of domoic acid. Blooms of toxigenic Pseudo-nitzschia have become more prevalent along coastal waters worldwide. e 2015 toxic bloom along the entire west coast of North America resulted in numerous harvesting closures and human health concerns. It is not known why this diatom produces domoic acid, as this biotoxin does not appear to harm its immediate predators.

Humans become poisoned a er consuming molluscan shell sh (e.g., mussels, clams, oysters, scallops, cockles) that have ltered the toxic diatom cells out of the water, therefore concentrating the toxin in their digestive system (Figure 2). e toxin can be present at very high in bivalve shell sh, particularly within the viscera and intestinal tracts [6]. Humans can also become poisoned by eating planktivorous sh (e.g., anchovies, sardines) that have fed on the toxic diatoms, recreational sh (e.g., white croaker, staghorn sculpin, coho salmon) that feed on other contaminated pelagic sh, or benthic organisms (e.g., Dungeness crabs) (Figure 3). e serious impact of chronic low doses of domoic acid on human health are not understood, compared to what is known about exposure to high doses [10,19,20]. is is especially problematic for coastal indigenous populations that consume molluscan shell sh on a regular basis.

ASP is one of several marine biotoxin poisonings, along with Paralytic Shell sh Poisoning (PSP; saxitoxin and derivatives), Diarrhetic Shell sh Poisoning (DSP; okadaic acid and derivatives),

Symptom	Percent
Acute Symptoms and Signs	
Dizziness	80
Nausea and vomiting	76
Abdominal cramps	51
Severe headache	43
Diarrhea	42
S D O S L W D W L R Q V	35
Agitation	<25

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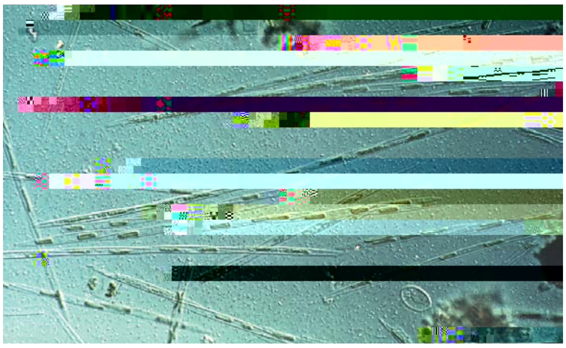

Figure 1: 3KRWRPLFURJUDSK RI Pseudo-nitzschia multiseries FHOOV IURP WKH &DUGLJDQ 5LYHU HVWXDU\ 3ULQFH (GZDUG ,VODQG &DQDGD GXULQJ
Pseudo-n2 T5chia m8.6<0035200B00336d ( )Tj1d ( )Tj44005>

Azaspiracid Shell sh Poisoning (AZP; azaspiracid and derivatives), Neurotoxic Shell sh Poisoning (NSP; brevetoxins) and Ciguatera Fish Poisoning (CFP; ciguatoxin), caused by another group of marine phytoplankton, dino agellates [21-23]. Other biotoxins include pectenotoxins, spirolide toxins and yessotoxins, produced by other species of dino agellates [23].

Pathophysiology of Amnesic Shell sh Poisoning

Domoic acid and its 11 natural isomers (some with less toxicity) act as potent excitatory neurotransmitters. e molecule is heat-stable and binds strongly to the same receptor sites as its biochemical analogues, glutamic acid and kainic acid. However, domoic acid is three times more potent than kainic acid and 30-100 times more so than glutamic acid [24].

An acute neuronal hyperexcitation syndrome is caused by toxic levels of domoic acid in humans. As well, peripheral neurons are a ected, followed by a chronic loss of function in neurological systems [11,12,25,26]. ese are most susceptible to excitotoxic degeneration, especially in the hippocampus amygdala and anterior horn cells of the human spinal cord.

Neurotoxic synergism is postulated to occur by voltage-dependent magnesium block at the NMDA receptor channel, followed by domoic-acid-mediated activation of non-NMDA receptors. is leads eventually to chronic loss of function in short-term memory, as well as certain cognitive functions, and has even been associated with dementia [27,28]. A rat model has shown the sequence of events leading to damage caused by domoic acid (Figure 4) [29]. Mice exposed to domoic acid in the laboratory get limbic seizures, gait abnormalities and demonstrable degeneration of their hippocampus [26]. e e ects of domoic acid on the nervous system and memory have triggered interest in those studying Parkinson's disease, Huntington's chorea, Alzheimer's disease, and other dementias.

Clinical Manifestations, Symptoms and Signs

Extensive research on patients of the 1987 intoxication revealed a wide range in the onset time of symptoms: 15 min to 38 hrs (mean, 5.5 hrs) a er ingestion, depending on the amount and cumulative absorption of ingested toxins [7,8]. e maximal neurologic de cits were observed, four hours post-ingestion, in patients exhibiting the

least e ect, versus 72 hours in patients most a ected by domoic acid. A summary of the symptoms is given in Table 1.

Patients presented with permanent neurologic sequelae, amnesia and cognitive abnormalities, including coma, mutism, seizures, and purposeless chewing and grimacing. e cognitive dysfunction occurred in patients manifesting neurologic signs and symptoms within 48 to 72 hrs. Some patients were described with hiccups and emotional lability, with uncontrolled crying or aggressiveness [7]. In addition, patients exhibited seizures, myoclonus, hemiparesis, hypore exia, profuse respiratory secretions, and hemodynamic instability with labile blood pressure. Patients had a predominantly anterograde memory disorder. However, some severely a ected patients also had retrograde amnesia, extending several years prior to the mussel-induced intoxication [8]. Nearly a year a er the ASP event, an 84-year-old male survivor re-experienced severe seizures and was diagnosed with temporal lobe epilepsy caused by domoic acid intoxication [29,30].

ose most a ected were males, older patients (>60 years of age), as well as immunocompromised younger patients. ose <65 years of age had pre-existing illnesses, such as insulin-dependent diabetes, chronic renal disease, autoimmune conditions requiring chronic steroid therapy, hypertension with a history of TIA's, chronic hepatic dysfunction and alcoholic liver disease. Animal studies have demonstrated that the placental barrier is unable to prevent fetal exposure to domoic acid and that the toxin can transfer to neonatal rats during lactation [31]. us, pregnant women, infants and children must remain particularly vigilant to avoid consuming high-risk shell sh.

Diagnosis

Patients can be diagnosed by: CBC; EKG (cardiac dysrhythmias); EEG (if seizures); CMP (Comprehensive Metabolic Panel), focusing on Mg, Ca and K; and stool sample testing (C & S, Gram stain, ova and parasites). Motor testing can identify unsteadiness, generalized weakness, symmetric transient hyperre exia, and Babinski signs. As well, patients can be observed for fasciculations and distal atrophy, hypore exia, loss of distal sensitivity to pain and temperature changes [8]. Neuropsychological testing identi es confusion, disorientation, and memory loss. In extreme cases involved amnesia lasting ve years. Long-term testing can be carried out using enhanced CT, MRI and PET scans of the brain to assess structural changes to hippocampus and amygdala.

Testing for the presence of domoic acid in seafood consumed by humans is carried out by government agencies. However, the toxin can also be detected in blood by competitive ELISA [32].

Treatment

Currently, the only approved therapies for humans intoxicated with domoic acid are anticonvulsant drugs and maintenance therapy; although a number of glutamatergic antagonists are in preclinical development [26]. Treatment for domoic acid toxicity therefore consists of supportive symptomatic therapies, including:

1. I.V. hydration with Lactated Ringer's solution/normal saline.
2. Antiemetics for nausea, vomiting; properistaltic/prokinetic to increase transit time through GI tract such as metoclopramide.
3. Analgesics for headache, abdominal pain (parenteral toradol, dicyclomine).
4. Administration of intravenous anticonvulsants, e.g., Diazepam and/or Phenobarbital, to treat seizures (but seizures in these cases are resistant to treatment with Phenytoin).
5. Clinical management of cardiac dysrhythmias; these are typically exacerbated by massive electrolyte disturbances as we as shi s in Mg and Ca.
6. Continuous ECG monitoring, along with correction of underlying electrolyte abnormalities, infusion of I.V. magnesium sulfate if necessary; also therapeutic for seizures and/or cardioversion if patient is hemodynamically unstable and exhibits organ hypoperfusion.

Some neurons undergo excitotoxic cell death very quickly a er exposure to domoic acid. However, toxicity may also develop over time, during which domoic acid can initiate a "neurotoxic cascade" [33], long a er the toxin is gone. Treatments could therefore catch patients during the early stages of toxicity, preventing them from experiencing some of the later e ects, notably seizures that intensify over time and are responsible for memory loss. Promising research indicates that administration of troxerutin (a avanol) [34], as well as ursolic acid (a natural triterpenoid) [35], to domoic-acid-treated mice results in reversal of memory impairment. Both are potential agents for prevention and treatment of cognitive de cits resulting from domoic acid toxicity. Furthermore, guidance for developing other treatments can be gained from experimental animal studies [26].

Contacts in the Event of Amnesic Shell sh Poisoning

In the USA, contact Poison Control (1-800-222-1222; http://www.poison.org/). In Canada, contact Health Canada (1-866-225-0709; http://www.hc-sc.gc.ca/fn-an/securit/chem-chim/toxin-natur/index-eng.php) or the Canadian Food Inspection Agency (1-800-442-2342; http://www.inspection.gc.ca/food/information-for-consumers/fact-sheets/speci c-products-and-risks/ sh-and-seafood/toxins-in-shell sh/eng/1332275144981/1332275222849).

Report the following information:

1. Age, weight and condition of patient.
2. Type of shell sh or n sh ingested.
3. Amount of shell sh or n sh ingested.
4. Where the shell sh or n sh was eaten.
5. Where the shell sh or n sh was harvested.
6. Time of ingestion.
7. Patient's medication list (which may impact G.I. transit time and absorption).

Prevention

Patients with multiple co-morbidities, hepatic and renal dysfunction, and compromised immune systems should avoid raw seafood (especially in endemic coastal regions in late summer and early fall) and heed posted public service announcements posted during HABs.

Do not eat shell sh sold as bait. Bait products do not meet the same food safety regulations as seafood for human consumption. Be careful of anchovies and sardines harvested in late summer and early fall (especially in endemic coastal regions) and most importantly during reported HABs. Check with local health o cials before collecting shell sh (especially mussels, oysters, clams, scallops and certain veritie