Neurology of ciguatera

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Abstract
Ciguatera is a widespread ichthyosarco-
toxaemia with dramatic and clinically
important neurological features. This se-
vere form of fish poisoning may present
with either acute or chronic intoxication
syndromes and constitutes a global health
problem. Ciguatera poisoning is little
known in temperate countries as a poten-
tially global problem associated with
human ingestion of large carnivorous fish
that harbour the bioaccumulated cigua-
toxins of the photosynthetic dinoflagellate
Gambierdiscus toxicus. This neurotoxin
is stored in the viscera of fish that have
eaten the dinoflagellate and concentrated
it upwards throughout the food chain
towards progressively larger species, in-
cluding humans. Ciguatoxin accumulates
in all fish tissues, especially the liver and
viscera, of “at risk” species. Both Pacific
(P-CTX-1) and Caribbean (C-CTX-1)
ciguatoxins are heat stable polyether tox-
ins and pose a health risk at concentra-
tions above 0.1 ppb. The presenting signs
of ciguatera are primarily neurotoxic in
more than 90% of cases. Such include the
pathognomonic features of postigestion
paraesthesiae, dysaesthesiae, and height-
ened nociperception. Other sensory ab-
normalities include the subjective features
of metallic taste, pruritis, arthralgia,
myalgia, and dental pain. Cerebellar dys-
function, sometimes diphasic, and weak-
ness due to both neuropathy and
polyneuropathy may be encountered.
Autono-
mic dysfunction leads to hypotension,
bradycardia, and hypersalivation in se-
vere cases. Ciguatoxins are potent, li-
pophilic sodium channel activator toxins
which bind to the voltage sensitive (site 5)
sodium channel on the cell membranes of
all excitable tissues. Treatment depends
on early diagnosis and the early adminis-
tration of intravenous mannitol. The early
identification of the neurological features
in sentinel patients has the potential to
reduce the number of secondary cases in
cluster outbreaks.

Keywords: ciguatera; fish poisoning; neurotoxins; public
health

It was Galen who first said that Moray eels
were dangerous to eat.1 When European colo-
nists first settled in the islands of the Caribbean
they encountered the neurological conse-
quences suffered by gourmet victims who had
ingested the local gastropod, Livona, called
“cigua”. It was thought that all cases were due
to the ingestion of snails, although it is now
appreciated that most were in fact due to the
eating of ciguatoxic fish. Parra, in 1787 in his
“Description de Diferents Piezas” in the Anti-
illes, referred to the neurological symptoms of
the clinical intoxication which he called
“ciguatera”.1

The neurological manifestations of ciguatera
are dramatic and often enigmatic. Ciguatoxins
are some of the most potent biological toxins
known. Their neurotropic effects produce a
protein array of symptoms which are distress-
ing in the acute phase syndrome and which are
energizing throughout the often prolonged
progression of convalescence.

The detailed neurological effects of ciguatera
were first described by Surgeon Lieutenant
William Anderson RN, naval surgeon on
Cook’s Ship HMS Resolution, in the Pacific in
1786.2 Cook’s crew had caught fish which were
eagerly eaten by the sailors and the scraps fed
to the ship’s dogs. Anderson described the
neurological features of the consequent severe
intoxication in both human and canine victims.
He described the distressing skin tingling, the
“reversal” of tactile heat sensation, and the
accompanying nausea and prostration.

Ciguatera is a clinical intoxication1–5 caused
by the ingestion of ciguatoxic fish.5 Human
victims are the end link in a food chain
cascade.1 The primary toxins are manufac-
tured in the benthic (bottom dwelling) dino-
flagellate Gambierdiscus toxicus;3 and are con-
centrated successively in the flesh and viscera
of small piscine herbivores, small carnivorous
fish, and ultimately in larger fish, many species
of which are prized gourmet species. “At risk”
fish include some species of mackerel (Scomb-
ermorus sp) and barracuda (Sphyraena sp)3 and
many of the tropical reef species such as coral
trout (Plectropomus sp);6 and in some parts of
the world include the flesh and viscera of
Moray eels (Lycodontis sp).8 The disease is not
uncommon in many littoral populations of the
tropical and subtropical nations of the world.6
In some island nations in the Caribbean and in
the Pacific where the principal source of
protein is fish, the annual incidence of
intoxication may approach 10% of the population. Ciguatera poisoning is poorly understood as a potential global health problem in temperate countries, particularly in North America and Europe. The toxin is stored in the viscera of fish that have eaten the photosynthetic dinoflagellate; and is progressively concentrated upwards along the food chain. The toxin is stable in the tissue of living fish and does them no harm. Larger carnivores have higher concentrations of the toxin in their tissues. The practical consequence of this is that consumption of the largest carnivorous fish—often those gourmet specimens which are frozen and transported for intercontinental consumption—therefore forms the greatest risk of ciguatera intoxication for the consumer. Pacific ciguatoxins pose a health risk at concentrations (within ingested fish flesh) above 0.1 ppb.

Extensive international commerce in frozen fish, and especially that involving trade in gourmet reef species, means that victims of this dramatic intoxication may now be encountered in all countries. An estimated 10,000–50,000 victims have the disease annually. Cases have been reported in the past decade from the United States (Hawaii, and from Rhode Island), Madagascar, Hong Kong, Europe, and extensively from the South Pacific. Ciguatera is thus a global health problem from the perspective of preventive medicine and an acute challenge for the clinician treating individual cases.

Increased awareness of the neurotoxic effects of ciguatera will aid in earlier diagnosis. This in turn will facilitate earlier treatment and the shortening of convalescence. The earlier identification of sentinel patients has the potential to prevent secondary cases and thus reduce the clinical clusters or micro-epidemics of victims.

Ciguatoxins
Ciguatoxins are potent heat stable, non-protein, lipophilic sodium channel activator toxins that bind quasi-irreversibly to the voltage sensitive sodium channel at site five. The molecular targets are found on all membranes of excitable tissues but with varying tissue specific affinity. The receptor site overlaps the receptor site for brevitoxin, another food chain paralytic toxin. Both Pacific and Caribbean ciguatoxins have as their basic structure unique molecular chains of 13 and 14 joined ether rings (C_{62}H_{92}O_{19}) respectively. Nine of these transfused rings form a ladder which is very similar in all ciguatoxins (figure). The toxins are tasteless and odourless and are relatively heat stable to the temperatures usually employed in cooking. Both Pacific ciguatoxins (P-CTX-1) and Caribbean ciguatoxins (C-CTX-1) are stable for at least 6 months at commercial freezing temperatures.

Clinical evidence suggests that the toxin binds to sodium channel receptor sites of both somatic and autonomic nerves. The chronicity of symptoms (months or years in some victims) and the exquisite sensitivity of convalescent victims accidentally subjected to rechallenge suggests that the sodium channel receptors are inactivated permanently; and that convalescence from severe intoxication may depend on the generation of new receptors.

Extensive experimental studies of Pacific ciguatoxins, using rat dissociated dorsal root ganglion neurons in whole cell patch clamp techniques, have shown that P-CTX-1 causes tetrodotoxin sensitive (TTX-S) sodium channels to open closer to their normal resting membrane potential. By contrast, tetrodotoxin resistant (TTX-R) sodium channels recover from inactivation more quickly, enabling earlier
The neurological symptoms, subjectively the neuronal membranes, explain, at least in part, the chronic nature of the neurological symptoms. In particular, such experiments provide a basis for understanding the pathogenesis of sensory neurological disturbances caused by ciguatoxic fish poisoning.

**Acute ciguatera: neurological symptoms and signs**

The full syndrome of ciguatera involves neurological, musculoskeletal, dermatological, gastrointestinal, and psychological symptoms. The neurological symptoms, subjectively always the most distressing, are listed in the table.

Neurological features may include peripheral sensory or motor symptoms, central symptoms such as severe prolonged distorting headache, or autonomic features. In severe intoxications, autonomic dysfunction may present as bradycardia or hypotension.

Mortality is region specific, and in the case of the Pacific ciguatoxins is less than 0.5%. The pathognomonic symptoms of acute ciguatera poisoning are paraesthesiae and dysaesthesiae. The paraesthesiae spread centrifugally, dependent on ingested dose, from cirumoral origins. The pathophysiological basis for the centrifugal spread of symptoms has not been determined. It has been proposed informally that this may be due to a disproportionate concentration of sodium channel receptors along the peripheral nerves; or may be due to a primary neurotoxic selectivity acting on the cell bodies of sensory nerves initially with subsequent intraneural spread of the toxin along both axons and dendrites. Several hours after consuming a fish meal, victims awake at night, perlexed and distressed. The paraesthesiae last for a minimum of several days and in severe cases persist for many weeks. The slow regression of such paraesthesiae often causes secondary anxiety or depressive symptoms. In my experience these secondary symptoms may be accentuated in victims who have been severely poisoned in miniepidemics; and who see themselves chronically ill by contrast and may be reduced to shocked weeping in the context of unbearable distress during minuteurition or breast feeding. Cerebellar signs and a late presenting tremor are well described in the unpublished reports of victim support associations. Because these cerebellar signs may appear after the subsidence of paraesthesiae and are themselves self limiting, they have not been reported in detail.

**Chronic ciguatera: neurological features**

The chronic effects of ciguatera have been recognised in Pacific littoral communities for centuries. Studies in the United States Virgin Islands showed that more than half of the victims poisoned by Caribbean ciguatoxins had chronic dysaesthesia with a median duration exceeding 2 weeks after initial poisoning.

The intractable fatigue, experienced by some 3%-20% of severely intoxicated victims, is perplexing to patients and frustrating to doctors. The persistent fatigability and weakness is often accompanied by depression. It is not known whether the depression—which in some victims can be a major feature of the prostrating fatigability of chronic ciguatera—is due primarily to residual toxic effects, or secondary to the organic debilitation which may follow the primary episode of poisoning. In patients presenting with the constellation of symptoms

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**Table 1 Acute neurological symptoms and signs seen by ciguatera victims**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Paraesthesiae</td>
<td>One of the first signs of ciguatera intoxication. Occurs within hours of toxic fish ingestion. Symptoms last for days or weeks. Centrifugal spread from circumoral and glossal focus.</td>
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<tr>
<td>Dyseaesthesiae</td>
<td>A combination of hyperesthesia; heightened nociperception; peripheral dysaesthesia with possible central element of perverted sensation.</td>
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<td>Other sensory signs</td>
<td></td>
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<tr>
<td>Pain</td>
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<tr>
<td>Headache</td>
<td></td>
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<tr>
<td>Weakness</td>
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<tr>
<td>Autonomic signs</td>
<td></td>
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<tr>
<td>Sensory signs</td>
<td></td>
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<tr>
<td>Motor symptoms and signs</td>
<td></td>
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<tr>
<td>Cerebellar signs and tremor</td>
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and signs which comprise the chronic fatigue syndrome it is always important to include the possibility of chronic ciguatera in the differential diagnosis. In rare cases ciguatera may cause peripheral neuropathy and polymyositis.

The insomnia of the acute ciguatera syndrome may gradually change into the hyper-somnolence which is a common feature of chronic ciguatera, and is cognate to that experienced by victims of chronic fatigue syndrome. In cases of chronic fatigue syndrome in which ciguatera can confidently be established as the cause, there is no need—indeed it is counterproductive—to embark on open ended extensive investigations and a continuum of pathological tests. A milieu of optimism, with confidence about the success of long term convalescence, is the best approach during long term clinical surveillance of such victims over ensuing months.

**Differential diagnosis**

The ichthyosarcotoxaemias include maaitoxaemia, fugu (tetrodotoxin poisoning), scombroid (histamine) fish poisoning, clupeoid poisoning, elasmobranch (shark liver) poisoning, mercury fish poisoning, and bacterial fish despoilment. None has the peculiar dramatic features of dysaesthesiae so characteristic in some 80% of victims of ciguatera. Fugu may produce rapid onset paraesthesiae and a generalised numbness with the subjects describing a feeling of “floating on air”—a transient state which may progress to life threatening acute paralysis. Clupeoid poisoning may follow the eating of herring-like fish and presents with abdominal pain, itching, coma, and convulsions. Scombroid poisoning (histamine poisoning) may follow the eating of spoiled tuna, bonito, mackerel, and skipjack. Scombroid or histamine fish poisoning is now the most prevalent form of seafood borne disease in the United States. Histamine production in these stored fish is a consequence of the free histidine content of the fresh fish which is broken down by the bacterial enzyme histidine decarboxylase. The most common symptoms of scombroid poisoning include flushing, urticaria, hypotension, and headache—always associated with vomiting, diarrhoea, and abdominal cramps. Itching may be intense and be associated with urticarial lesions.

Currently there is no secure, commercially pragmatic test for ciguatoxins in fish flesh. The traditional method of detecting the presence of ciguatoxins in fish flesh involves testing lipid extracts by mouse bioassay. Recent research has shown that cytotoxicity, radioligand binding, and antibody based methods have the potential to be developed into cost effective screens for ciguatoxic fish in the market place or restaurant. The toxin is so potent that high performance liquid chromatography and mass spectroscopy are not sufficiently sensitive to detect clinically relevant concentrations of ciguatoxin in crude extracts of fish. Bioassays are available in various research centres. The diagnosis is essentially a clinical one, made particularly in the context of a detailed history of the type of fish species ingested, the rate of onset of symptoms, and a knowledge of the characteristic neurological features.

Nerve conduction studies may be abnormal. In experimental animals neurophysiological studies have demonstrated slowing of both mixed and motor nerve conduction velocities with reduction of depolarisation amplitudes. It is important to appreciate that many toxins produce dysaesthesiae as an important “sentinel” symptom of clinical poisoning. In the context of differential diagnosis, paraesthesia is a non-specific feature in itself; and the point should clearly be made that both sodium ion channel “openers” (for example, ciguatoxin, pyrethroids) and sodium ion channel “closers” (for example, tetrodotoxin and the clinical syndrome of fugu poisoning) produce similar, early onset “sentinel” circunural distribution of paraesthesia.

**Treatment**

Hyperosmotic mannitol infusions may reduce Schwann cell oedema which is a feature of acute ciguatera. Although not yet tested by double blind trials, most case series report that more than 60% of victims have their symptoms reversed by mannitol infusion provided that this is administered within 48 hours of the onset of symptoms. No other therapy, other than non-specific supportive management, has been shown to be of benefit. The neurological symptoms, however chronic, always resolve gradually. Some 5% of severely intoxicated victims complain of residual symptoms, particularly overwhelming chronic fatigue, for many months or even years after the acute episode.

Lipid storage and slow release of toxin has been proposed as the basis for the persistence and recurrent nature of the symptoms. Many victims report that relapses are triggered by other agents such as alcohol. However, it is known that relapse of symptoms may be initiated by the ingestion of chicken or pig meats from commercially raised animals which have been fed on fish meal; with the implication that such commercial feedstocks contain ciguatoxins in otherwise subclinical concentrations.

Intravenous mannitol infusion is the only therapy known to reverse the sensory symptoms and autonomic signs of ciguatera. The dose of mannitol which is recommended is 10 ml/kg of the standard 20% solution, infused slowly over not less than 30–45 minutes. If dehydration has developed due to vomiting as part of the acute phase syndrome, this should be corrected before mannitol infusion is instituted. If symptoms are reduced, a second dose can be given within 3–4 hours; and repeated on the next day. The pharmacological basis for the use of mannitol remains speculative. Its effect is thought to be due to osmotic reduction of neuronal oedema, but a “scavenger” property of the molecule has been suggested. No ill effects have yet been reported from its use and I have not experienced ill effects from its use in personal unpublished cases. There is no accumulated...
evidence to suggest that the blood-brain barrier is opened to larger concentrations of ciguatoxin.

The pleomorphic nature of ciguatera, the subjectivity of many of its symptoms in the absence of any definitive laboratory diagnosis for clinical cases make this condition one of the most challenging in clinical medicine.

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