Review article

Irukandji syndrome: a widely misunderstood and poorly researched tropical marine envenoming

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Abstract

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Irukandji syndrome is a poorly defined set of symptoms that occur after envenoming by certain species of jellyfish, primarily cubozoans or 'box jellyfish'. Envenomed victims can show symptoms ranging from headaches, severe pain, nausea and vomiting to pulmonary oedema, cardiac failure and severe hypertension resulting in death. Historically, this syndrome appears to have been misdiagnosed and reported cases are undoubtedly a significant underestimation of the prevalence of this syndrome. The variation in symptoms has resulted in a myriad of treatments though none has been established as definitive. Effective pain relief with opioids is the most immediate priority. Although the annual numbers of envenomations are generally low, the associated financial costs of this envenomation may be comparatively high, with suggestions that it could run to millions of dollars per season in northern Australia alone. The syndrome has been well documented from many areas along the east coast of northern Australia, leading to the belief that it is an Australian oddity. However, with an increase in medical knowledge and improved diagnosis of the condition, it appears that envenomations causing Irukandji syndrome are an increasing marine problem worldwide.

Key words
Marine animals, jellyfish, envenomation, clinical toxicology, toxins, first aid, pain, treatment, epidemiology, review article

Introduction

The expression 'Irukandji syndrome' (a disease caused by envenomation from certain marine cnidarians) first appeared in the early 1950s to describe a set of debilitating symptoms that had been documented in Australian bathers since the 1920s. Although not considered a major health priority in Australia, the syndrome does represent a substantial cost, not only to public health, but also to tourism through fear and potential misinformation to visitors to the tropical regions.

The definition of Irukandji syndrome has varied widely over time because of the diverse range of symptoms and severity experienced . While this syndrome may be fairly innocuous to some, others have experienced severe symptoms and complications as a result of envenoming. In general, mild pain is felt at the sting site at the time of initial contact, which fades with time and when overshadowed by the delayed onset of severe systemic symptoms, especially pain, and including hypertension, tachycardia and, in extreme cases, pulmonary or cerebral oedema. There have been two recorded deaths associated with Irukandji syndrome.[1–12] Why patients experience a difference in the severity of stings is unknown; however, theories related to the extent of exposure and the species responsible have been suggested. Despite symptoms resolving in a matter of hours in most sting victims' reports of continued complications lasting days and even weeks have been published.[5,7,13]

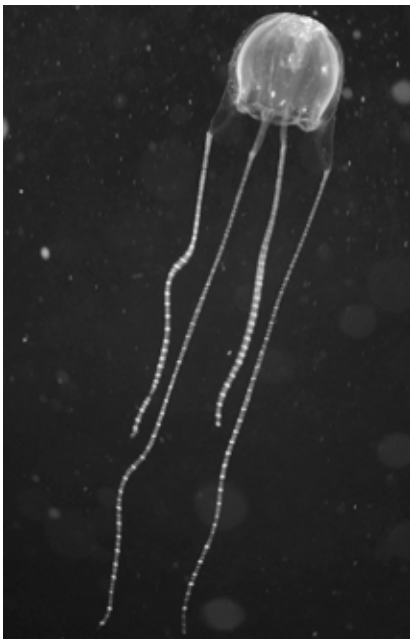
In 1964, the first causative agent of the syndrome was identified in northern Australian waters by pathologist Jack Barnes, namely *Carukia barnesi*, a small carybdeid species (Figure 1). Since then, other species have been shown to give rise to the syndrome and the term 'Irukandji' is now used to describe all carybdeids whose sting may result in Irukandji syndrome.[14] To date, seven carybdeid species are recorded as causing the syndrome.[14] However, with up to 17 species implicated in various parts of the world, not all of which are members of the carybdeid family, confusion has surrounded exactly which species do give rise to this syndrome.

The appropriate first aid for the Irukandji syndrome is constantly debated, with treatment varying between physicians and treatment centres. However, the control of pain is the immediate and main priority with Irukandji patients as pain is a major, and often severe symptom.[7] Additional to the confusion in treatment is the potential for misdiagnosis of such a cryptic condition. No definitive test is available to confirm Irukandji syndrome and, as such, misdiagnosis can include a variety of conditions displaying similar symptoms.

Once thought to be geographically confined, the actual distribution of this syndrome has never been fully defined. There have been reports from various Australian locations as well as from other tropical and a few temperate locations worldwide. The species responsible and timing of these

events, like so many areas relating to this syndrome, remain poorly researched. This paper aims to distinguish fact from fiction in Irukandji syndrome and to review the research associated with it in Australia and throughout the world.

Figure 1
Carukia barnesi



History of Irukanji syndrome

The term 'Irukandji syndrome' was coined by Hugo Flecker in 1952 to refer to his earlier-described Type A stings, first recorded in 1945 and, at that time, of unknown origin.[3,4,6,15,16] 'Irukandji' was the name of an indigenous tribe that formerly inhabited the coastal regions around Cairns, Australia, from the Mowbray River in the north to Trinity Inlet in the south.[17] Members of this tribe knew that at certain times of the year people often left the water displaying debilitating symptoms. However, what is not well known is that these symptoms were first described much earlier in the Philippines.[18] In a series of eight cases, what is now termed 'Irukandji syndrome' was documented in swimmers bathing off a wharf in Manilla, with the offending organism suggested to be a jellyfish. This also seems to be the first report of the use of vinegar as a first-aid treatment for the syndrome, although its first-aid potential here appears to have been limited.[18]

Since its discovery, the occurrence of Irukandji syndrome has been regularly recorded in the literature. When in 1945 several cases presented simultaneously from beaches around the Cairns region, northern Australia, it was surmised that the causative agent was an unknown organism producing non-severe local symptoms but severe systemic symptoms.[19] However, not all beaches in the region recorded Irukandji syndrome even though well patronized by bathers.[17] By 1964, no further progress had been made in finding the causative agent, but it was hypothesised that Irukandji syndrome was caused by an organism that was:

- small;
- colourless and transparent;
- must at times be present in considerable numbers;
- motile.[4]

In an attempt to uncover the identity of the agent, Barnes conducted the first published controlled envenoming by an unknown species of cubozoan jellyfish. He tested two specimens, one on himself and his son, the other on a lifeguard. The initial sting was described as feeling like the envenoming of a small Bluebottle (*Physalia* sp.) which could be caused by the tentacles or the bell.[4] Within a short space of time, all three subjects developed Irukandji syndrome. The species in question was later named *Carukia barnesi*, ('Car' from carybdeid and 'ukia' from Irukandji, 'barnesi' from Barnes).[20,21]

Although a great deal of time and effort was placed into elucidating additional causes of the syndrome, none were found. As such, the term 'Carukiosis' was proposed instead of Irukandji syndrome or 'Type A sting' to better reflect the causative agent of the disease.[22] However, with later work implicating further species, the term Carukiosis was abandoned.[21] It was 40 years before evidence was produced of a second species of cubozoan causing Irukandji syndrome with an additional five species being shown in the following three years to cause the syndrome.[14,23] Although it has been suggested that yet more species may be implicated, there is presently no direct evidence to support these claims.[24–26] The term 'Irukandji' is now routinely used to encompass any jellyfish that causes the set of systemic symptoms characteristic of the syndrome.

Cost to the community

Although Irukandji syndrome is of minor concern to medical practitioners, it represents a major cost to northern Australian communities in terms of public health, leisure and tourism.[27,28] However, attribution of a direct monetary cost to this syndrome is highly problematic. There is little doubt that Irukandji syndrome presents a significant workload to emergency departments in presentations, retrievals and admissions: approximately half of stings resulting in Irukandji syndrome require admission, whilst a significant amount of time and resources are required to retrieve envenomed patients, many of whom are offshore and require helicopter assistance.[27–29] For example, in northern Australia in the 1998–99 Irukandji season there were 30 helicopter retrievals for Irukandji stings from remote locations such as offshore islands on the Great Barrier Reef at an average cost of AUD2,000–4,000 per patient (approximate total cost of AUD90,000).[27] In total, it is thought that the direct costs of retrieving and treating patients with Irukandji syndrome in northern Australian waters are AUD1–3 million per year.[27]

Additional to these direct costs are the indirect effects that media reports have on tourism. Like many marine animal injuries, there has been a disproportionate amount of media attention given to the Irukandji syndrome with much of it being inaccurate and poorly substantiated.[29] This often gives the impression that the waters are unsafe, which may have a direct negative impact on tourism.[30]

Definition of the syndrome

The majority of Irukandji stings are initially innocuous, with very little pain at the sting site. Unlike the majority of other cnidarian envenomings, the markings at the site of envenomation are usually not in accordance with the physical characteristics of the bell or tentacles of the medusae.[21] It has been suggested that most stings occur by contact with the bell and stings from tentacles are less frequent; however, there are few data to support this.[31] Sting sites are often an oval area of erythema with a series of irregularly spaced papules, often referred to as "*goose pimples*", which may be up to 2 mm in diameter.[32] These papules usually develop within about 20 min from the time of the sting and fade soon after; however, the erythema may persist for some time.[4,17,27,32] Unlike many cnidarian stings, Irukandji stings do not give rise to dermo-necrotic lesions.[33]

LOCAL PAIN

Variability in both the initial response and the later systemic reaction is a characteristic feature in Irukandji syndrome. Initial pain ranges from "*quite severe*" to absent.[4,10,13,17,31,34–36] Local pain is said to diminish, with mild discomfort occasionally persisting until it is overshadowed by more dramatic symptoms.[4]

LATENT PERIOD

Unlike the majority of cnidarian envenomings, there is generally a delay from the time of the sting to the onset of systemic symptoms. This has been reported to range from 5 to 120 minutes with an average of 25–40 minutes.[4,13,17,19,36]

RANGE OF SYMPTOMS

Patients with Irukandji syndrome routinely show systemic symptoms, which may include headache, backache, nausea, vomiting, abdominal cramps, overall body pain, hypertension, tachycardia, feelings of impending doom, pulmonary and/or cerebral oedema and death (Table 1).[1–12] However, presently there exists no universally accepted definition of the syndrome.

DISTINCT DIFFERENCES/VARIATION

The large variation displayed between envenomed casualties has led to many theories for these differences. For example, a positive correlation between the severity of the sting and either the duration of jellyfish contact, or the time to first-aid administration has been postulated.[4,21] Similarly, thicker skin regions or presence of body hair may provide partial protection from an Irukandji sting, leading to differences in sting severity depending on the envenomed area of the victim.[4] Geographical variations have also been proposed to account for these disparities, suggesting different potential causative agents.[1,5,7,8,11,27]

SEVERE SYMPTOMS

Severe envenomings do occur, often resulting in cardiac complications.[1,7,12,40–43] In one study, 30% of patients experienced some degree of heart failure, while 22% experienced elevated troponin levels in another.[7,27] Severe cardiac dysfunction has been reported in several cases.[7,40–42,44] Pulmonary oedema has been recorded but is considered to be rare.[2,40,41,45,46] There are no published data on repeat envenomings over time with the same victim; however, what few reports do exist suggest that there is no additional risk from subsequent encounters.[4,15]

DEATHS FROM IRUKANDJI SYNDROME

The first reported death in Australia from Irukandji syndrome was in January 2002 at Hamilton Island; however, the cause is speculative as no supporting evidence of envenoming (for example the presence of nematocysts on the victim) was obtained nor was a post-mortem performed.[11,47,48] This patient had a pre-existing cardiac condition with a history of an aortic valve replacement and was taking warfarin.[11] Because of these factors, it has been suggested that death may have been due to this pre-existing condition and not a direct effect of the envenoming.[48]

The second recorded death occurred on the outer Great Barrier Reef in April 2002.[7,11,12] This patient, a 44-year-old male, suffered a sting to his chest while snorkelling 25 km north of Cairns. Within 15 minutes he displayed signs of Irukandji syndrome and was evacuated to Cairns Base Hospital. A cranial CT was performed and an intracerebral haemorrhage was discovered in the right frontal lobe. The patient underwent a craniotomy, but died 13 days post sting. Nematocysts removed from the sting site were identified as those from a large (> 20 mm) *Carukia barnesi*, making this the first definitive death reported from this species.[12]

DURATION OF THE SYNDROME

While some Irukandji stings appear to resolve within a matter of hours, it is estimated that around 10–70% of patients require hospital admission and treatment for 24–72 hours with full resolution of symptoms after a maximum of several days.[4,5,7,21,34–36,45] However, continued complications have been reported as lasting anywhere from weeks to months.[1,7,35,38,42,49,50]

Table 1

Symptoms from Irukandji syndrome patients recorded in the literature

Symptoms	Description	Reference
Local	Profuse sweating, generalised hyperhydrosis	3,4,10,11,17,21,35
	Initial sting site sweating with entire body sweating later	34
	No sweating of sting site	3
	Tremor	9
	Erythema or welts, diaphoresis or flushing	3,4,8
	Moderate to severe pain	1,5
	Mild discomfort at sting site persisting until overshadowed by more severe symptoms; 5 minutes post sting the site marked by patch of erythema typically oval in shape, 5 by 7 cm wide	4
	Acute pains in affected part, minimal rash at sting site with slight redness and raised vesicles	3
	Small insignificant puncture	17
	Absence of swellings	17,19
Musculoskeletal	Violent cramps and muscle pain	5,9,17
	Long-lasting joint pain	3,4
	Cramping and spasms of intercostals and diaphragm	4,10,31
	Severe and boring pain in sacral or lower back area	4,10,31
	Muscle pains and cramps in all four limbs, abdominal pains and cramping, rigid abdominal wall	3
	Hyperactive deep reflexes	3
	Lie prostrate	37
Gastrointestinal	Painful vomiting and retching, excessive vomiting, nausea	2–5,8,9,17,19
	Colicky pains in epigastrium	3,19
Neurological	Distressed on presentation, anxiety	5,8
	Anxiety with feeling of impending doom, restlessness	10
	Severe frontal or global headache, mild headache	2,4,36,37
Cardiac	Hypertension, tachycardia and systolic hypertension in 50%	7–10
	Global cardiac dilatation with left ventricular dysfunction	11
	Elevated troponin levels, T-wave inversion and ST-segment depression, mild to moderate impairment of systolic function with segmental hypokinesis	7
	Irregular heart beats	3
	Myocardial infarction	38
	Cardiogenic shock	36
Miscellaneous	Oliguria, renal impairment	11
	Priapism, allergic reactions, expiratory wheeze	11,27
	Localised piloerection (sometimes generalised), uncontrolled tremor, hyperventilation	10
	Difficulty in breathing, dry mouth, burning eyes, sharp prickling sensation, cold, violent shivering, marked neutrophil leucocytosis within first hour, cough in 57%	4,10
	Squirting redness of sting sites	34
	Raised temperature, pyrexia	3
	Shock, collapse	37
	Over-stimulated sympathetic system	39
	Periorbital oedema	27
	Pulmonary oedema	36

First aid

In the initial treatment of Irukandji syndrome the main hindrance to first-aid measures is the often minor initial nature of the sting.[45] There is a plethora of untested and ineffective first-aid treatment for Irukandji patients including, but not restricted to meat tenderiser, fresh water, aluminium sulphate, figs, mustard, manure, urine and papin.[51–54] A pressure immobilisation bandage (PIB) was once thought to be appropriate first-aid treatment with little

if any evidence to support its introduction.[36] Data now exist that suggest that the application of a PIB may actually have the potential to worsen patients' symptoms by increasing the venom load.[12,42,43,46,55] Similarly, the use of ice packs is now believed to have no effect on the management of the Irukandi syndrome.[45] Conversely, there is mounting evidence that the use of heat is beneficial for cubozoan envenomed victims.[9,35,51,53–56]

Vinegar

Possibly the most misunderstood first aid for Irukandji syndrome is the use of vinegar. Reports exist that dousing the envenomation site with vinegar is of little benefit, contradicting a theory that vinegar alters the pH of the protein toxin thus rendering it less biologically active.[36,54] However, there are no data to support either of these assumptions. The use of vinegar originated from studies on the first aid for the large box jellyfish, *Chironex fleckeri*.[57] This study showed that vinegar caused permanent de-activation of all undischarged venom-containing nematocysts but was not effective in decreasing the pain displayed by an envenomed victim, nor did it de-activate the venom.

Further studies have shown that vinegar is effective in nematocyst inactivation in a least five species of carybdeids.[13,32,58,59] Given the small area of envenomation in most victims (and hence the small number of nematocysts employed) compared to the potential severity of the syndrome, any prevention of nematocyst discharge is likely to be advantageous.[40] Presently, the accepted first-aid treatment for Irukandji syndrome is the application of vinegar for a minimum of 30 seconds, then monitoring the patient and treating symptomatically.[46] Victims should not re-enter the water as delayed effects may impair breathing, muscle power and co-ordination, increasing the risk of drowning.[34]

Medical care

Evidence into the most efficient treatment for control of Irukandji syndrome has been described as anecdotal at best with no standard protocol which gives consistent and effective control of pain, and with treatment varying with attending physician.[28,60] Historically, treatment has included the use of trichlorethylene, sodium phenobarbital, calcium chloride and calcium levulinate, calcium gluconate, systemic antihistamines, corticosteroids, frusemide, dobutamine, hydralazine, sodium nitroprusside, glyceryl trinitrate, streptokinase, aspirin, propanolol administered with nitrates and morphine infusions, ataraxic drugs such as chlorpromazine and butyrophenones, phentolamine and diazepam.[13,20,35,36,38,40,41,44,45,61,62] Although substantial debate exists over the best treatment, it is widely accepted that the control of pain in the envenomed victim is the immediate major priority.[5,46]

Intravenous morphine and pethidine have been the predominant opioids used over the years.[13,34,38,40,46] However, concerns have been raised over the use of pethidine because of its direct myocardial and respiratory depressant effects, and the toxic metabolite (norpethidine) produced when used in humans.[41,46,47,60] As a result, fentanyl has been suggested as the opioid of choice rather than morphine or pethidine.[5,41,46,63] Early application of promethazine had reportedly displayed potential for reducing the amount of narcotics required; however, a more recent retrospective analysis of hospital patients records spanning over 20 years did not support this.[5,46,63]

To date, the most novel approach to the treatment of Irukandji syndrome has been the use of magnesium. Its use is based on its ability to decrease vascular resistance in hyperadrenergic states and its potential to suppress catecholamine release, inhibit calcium influx, noradrenalin and possibly acetylcholine release, decrease sympathetic terminal receptivity to catecholamines and reduce catecholamine-induced myocardial necrosis.[32,64–66] However, much variation in its effectiveness has been reported; authors generally agree that the use of magnesium infusions should not be regarded as routine treatment until further definitive evidence is collected or until other treatment approaches have failed.[62,64,66]

At present, no antivenom exists for Irukandji envenomings; however, there has been some investigation into the use of *Chironex fleckeri* (the large box jellyfish) antivenom in envenomed victims.[39,67] Although there appeared to be some reduction in the symptoms and opioid requirements when this antivenom was administered in one study, the overall effects were not deemed beneficial,while in another it was ineffective.[39,67]

MISDIAGNOSIS

Historically, the poor understanding of the Irukandji syndrome and its possible complications, coupled with the minimal or absent sting marks at the site of the envenoming and its initial mildness have led to it being misdiagnosed.[11,36] These misdiagnoses have included acute appendicitis, decompression illness, gastric poisoning, peptic ulcer, ruptured spleen, ruptured ectopic pregnancy and myocardial infarction.[1,4,16,27,34,60,62,68] Similarly, Irukandji syndrome may, in fact, have indirectly caused deaths that have been attributed to drowning. Victims may conceivably drown if in deep water at the onset of Irukandji syndrome because of cramps and respiratory muscle spasm severe enough to cause death from asphyxia and water inhalation.[11,18,34–36]

WHY THE DELAY?

The delay in manifestation of symptoms is one of the most significant indicators of the syndrome, but one of the

least understood. Current theories for this delay include the possibility that a period of time is required before the toxins are metabolised in an envenomed victim or that the already active venom requires time to travel from the site of initial deposition to the toxin target site.[34] Simple logic would suggest that if the toxins need time to metabolise, this delay would be mirrored in prey items; however, this does not appear to be the case. Although the literature on feeding ecology is scarce, in one species, *Carukia barnesi*, the toxic effects of the venom on prey items is rapid with envenomed fish usually succumbing within minutes.[69] Additionally, intravenous injection of the Irukandji venom causes hypertensive crisis and death in rats in a similar time frame to that caused by *Chironex fleckeri* venom, namely within minutes.[65,70,71] Thus, the delay in symptoms would not appear to be caused by a latent period of time for the venom to become active.

Alternatively, the reason for the delay has been linked to the path the venom travels to reach its target. It is known that the venom components in *C. barnesi* venom are large (50–100 kiloDaltons, kDa) and, therefore, may travel via the lymphatics, similar to the pathway for snake venoms, thus causing the characteristic 20–30 minute delay in the expression of symptoms.[46,69]

Causative agents

As mentioned earlier, it has become evident that the Irukandji syndrome may be caused by a various of species of jellyfish and in both hemispheres.[7,10,18,35,38,39,48,49,59,62,65,72–74] Unfortunately, as these cnidarians are often relatively small in size and difficult to identify precisely even when creatures are seen, accurate identification of an envenoming is relatively rare.[75] Evidence of species causing the symptoms range from speculative to definitive evidence where the victim collected the specimen at the time of envenoming.[14,25] Presently, 17 species of cnidarians, including 14 different carybdeids, have been implicated in causing Irukandji syndrome (Table 2); however, the data supporting many of these claims are speculative. Not all carybdeids are capable of causing Irukandji syndrome. For example, no systemic symptoms have been caused by envenomings from *Carybdea sivickisi, Carybdea rastoni, Carybdea marsupialis* or *Tripedalia binata*.[4,15,72–74,80–83]

Table 2
Species implicated in the Irukandji syndrome

Physalia physalis, "Bluebottle"[35,61]
Cyanea sp., "Lion's mane"[15,76]
Carukia barnesi[3]
Rhizostoma sp.[15]
Gonionemus oshoro[77]
Unidentified "Morbakka" carybdeids[10]
Gerongia rifkinae, aka "Darwin Carybdeid"[78]
Unnamed carybdeid[23]
Carukia shinju[26]
Malo maxima[14,26]
Alatina rainensis[79]
Alatina nr *mordens*[14]
Carybdied spp "Fire jellies"[14]
Carybdea alata[14,51]
Carybdea xaymacana[14]
Unknown jellyfish, Thailand[50]
Malo kingii[24]

Distribution of Irukandji syndrome

Generally, Irukandji syndrome is thought to be a tropically based disease, found around coral reefs in northern Australia; however, no real research has been conducted into the true distribution of the syndrome. Irukandji syndrome has been recorded from many locations in Australia, Torres Strait, Hawaii, Fiji, coastal Thailand, Puerto Rico, Manilla Bay

Figure 2
Global distribution of documented Irukandji syndrome stings

in the Philippines, the Gulf Sea, Key West Florida, the French West Indies, Bonaire in the Carribean, Timore Leste, Papua New Guinea, Japan, North Wales in the United Kingdom and throughout the Indonesian archipelago (Figure 2).[4,8,9,14,15,18,21,27,34,35,37,38,40,45,50,51,59,62,75,77,84–86] Within geographic locations, near-shore reefs and islands may influence the presence or absence of animals causing the syndrome. For example, there is a higher than expected incidence of stings for particular beaches in far northern Australia that have closely located near-shore islands.[4]

At the northern and southern extremes of this distribution, the season usually occurs only in a few of the warmer months of the year, increasing with proximity to the equator where it may be present all year round.[2,7,15,21,46] Also, marked differences in trends of occurrence may occur with location. In Hawaii, cases of Irukandji syndrome increase dramatically in conjunction with the monthly aggregation cycle of *Carybdea alata*, a carybdeid linked to the syndrome, at approximately eight to ten days after the full moon.[51] Similar reports of lunar cycles coinciding with cubozoans that have the potential to produce Irukandji syndrome have been recorded from Puerto Rico, Kiribati, and around the Gilbert Islands but the syndrome has not yet been recorded from these regions.[87–89]

In Australia, Irukandji syndrome may be present throughout the year except for July and August.[4,8,21,34,36,39,45,46,76,90,91] Peak times appear to be from December to February on the east coast of Australia, and January to May in the Northern Territory. Some bimodality to envenomings is evident, including on the west coast with various meteorological conditions linked to these occurrences.[2,8,13,36,37,44,46,78,91,92] Maximum incidences have been reported as the last and first two weeks of each year, often with multiple stings occurring over only a few days.[4,13,17] However, this may reflect increased beach usage by swimmers at these times.[4,17] Numbers of cases may also vary between seasons within locations, some years experiencing large numbers of envenomings while in others no cases may be recorded.[7,17,21,46] These variations in sting incidence may also reflect the ecology of the envenoming animals and their propensity for different areas at different times.[5] With so little known about the ecology and life history of these animals, this remains speculative at best.

Venom components

Research into the venom components of cubozoans responsible for the syndrome have been hampered by the relatively low numbers of animals collected and the low yields of venom acquired from these animals compared to that of the larger, multi-tentacled chirodropids.[93] Research conducted into extracted venom has shown a large number of different proteins. As many as 60 proteins were present in the venom extracted from nematocysts on mature bells of animals (SDS-PAGE gel analysis), and at least 45 different proteins in the venom extracted from tentacular nematocysts, with proteins ranging in size from 25–250 kDa in size, the majority being less than 100 kDa.[69] There are also distinct differences in venom protein profiles between mature and immature specimens as well as venom extracted from bell nematocysts as compared to tentacles.[69] The large number of proteins found in *C. barnesi* venom is far greater than previous studies into the components of cubozoan venom, which saw only three major protein bands present.[86]

Laboratory studies

Laboratory studies into the components of Irukandji venom have predominantly revolved around the cardiac responses of extracted venom on both whole and isolated vertebrate models including on pigs, guinea pigs and rats.[43,49,65,70,71,86] Initial studies on the effects of *C. barnesi* venom have shown that serum levels of endogenous adrenaline increase as well as heart rate and blood pressure, with widening pulse pressure and a positive inotropic effect when injected into rats.[49] Similarly, studies utilising crude blended whole specimens of *C. barnesi* injected into mechanically ventilated pigs saw a 200- and 100-fold increase in serum noradrenaline and adrenaline respectively, with sustained tachycardia and systemic and pulmonary hypertension.[43,65] The effect of the venom may not only be causing the release of catecholamines but may also cause direct vasoconstriction.[65]

Crude venom extracts on isolated rat and guinea pig right atria caused tachycardia in the presence of atropine.[65] However, this effect was almost abolished in an *in vivo* pig model by the prophylactic addition of tetrodotoxin and restricted to peripheral post-ganglionic sympathetic sites and possibly the splanchnic nerve innervations and the adrenal medulla. This suggests that this venom extract functions as a neural sodium channel activator.[65] However, as crude venom extract and not pure extracted venom was used in these studies, and as subsequent research has found toxic components in tentacle extract devoid of nematocyst material, as well as cardiac responses to this same material, these results must be viewed with some reservation.[65,70,71]

Subsequent laboratory studies have utilised a refined venom extraction technique.[69,94] These investigations showed some comparable cardiac effects, including severe pressor responses from venom of *Carukia barnesi* and *Alatina* nr *mordens* (approximately 3–5 times less potent than that of *C. barnesi*), supporting the theory of a venom-induced catecholamine release after intravenous venom administration.[70,71] Interestingly, pressor responses do not appear to be dose-dependent, suggesting that the venom may be inducing a release of catecholamine into the circulation and not actually contain a direct vasopressor itself.[70,71]

In one of these studies, the administration of prazosin (an α-1 adrenoreceptor antagonist) in envenomed test

animals both reduced the venom-induced pressor response and inhibited the tachycardia, supporting the hypothesis that this is an indirect rather than a direct effect on the peripheral vasculature, and also not a direct α-adrenergic effect.[71,95] Conversely, cardiovascular collapse in envenomed animal models does appear to be dose related, indicating the toxins may also be acting directly on the myocardium.[71] Salivation and urination in envenomed animals is also seen, which suggests parasympathetic stimulation resulting again from the venom-induced catecholaminaemia.[70,71]

Climate change and human interaction

Studies of jellyfish abundance and frequency are under-researched; however, the few studies that do exist seem to implicate an increase in jellyfish numbers over time.[96] Various potential factors for this have been cited, from anthropocentric practices such as over fishing and pollution, to climate change and ocean acidification.[96–98] Climate models combining factors of increased ocean temperatures have led researchers to surmise that jellyfish numbers as a whole will increase over the next 100 years.[96] Additional to oceanic conditions are the reports of seasonal expansions and blooms of gelatinous species, possibly because of increased global temperatures, and introduction into new areas through changing ocean currents and human activity.[99,100] What is abundantly clear is that when it comes to jellyfish trends worldwide, more information is needed on the life cycles and ecology of these animals.[100]

Conclusions

Irukandji syndrome has historically been considered a problem for the waters of northern Queensland; however, a literature search has revealed that its reach extends much further than originally thought. Whether this increased global reporting is owing to heightened awareness, reflects changing ocean conditions or is indicative of the increased number of people utilizing the oceans remains unclear. The possibility of this syndrome becoming a more widely distributed phenomenon adds weight to the need for further understanding and this can no longer be perceived as simply an Australian problem but, rather, a global phenomenon. The Irukandji syndrome needs further research and a clearer definition both in terms of the specific species and their toxins causing it and its geographic and temporal distribution.

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