The "Irukandji Syndrome" and Acute Pulmonary Oedema.

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ABSTRACT

Envenomation by jellyfish that cause the "Irukandji syndrome" must now be regarded as life-threatening. Three cases are reported of acute pulmonary oedema that developed in previously healthy adults after envenomation by a jellyfish that produced the "Irukandji syndrome". Direct myocardial depression and pulmonary capillary leakage are suggested as the possible causes of the acute pulmonary oedema. Probably, this is venom mediated, as are the severe muscular pains and symptoms of catecholamine excess that have been reported previously. Serum immunoglobulin levels were measured on several occasions after envenomation. A positive result of testing for the presence of *Carukia* antigen was obtained in the most recent case but the test was not available for the earlier cases; however, the possibility of envenomation by a number of other venomous species of jellyfish that were present in the waters at this time was excluded. A jellyfish that is similar to *Carukia barnesi*, and possibly was responsible for these envenomations, was captured later in an area adjacent to the one in which one patient was stung. Experiments with the nematocysts of this animal showed that their discharge was inhibited by vinegar (41%-6% acetic acid). In the current state of knowledge, a treatment plan for a severe case of "Irukandji syndrome" involves pain relief; the management of apparent endogenous catecholamine excess; and the aggressive treatment of pulmonary oedema and hypoxia, which should include oxygen, Swan-Ganz catheterization and consideration of early intubation with intermittent positive -pressure ventilation, together with standard drug support.

The first description of the "Irukandji syndrome" appeared in the medical literature in 1952, in this Journal.' A jellyfish that caused this syndrome was identified positively first by Barnes in 1964' and later was classified by Southcott as *Carukia barnesi.1* However, Barnes believed that more than one jellyfish was capable of causing this syndrome. He was also the first to recognise the occasional association between envenomation and systemic hypertension; he suggested the use of a-receptor blockade therapy, but was unable to publish this idea before his untimely death.

The medical significance of the "Irukandji syndrome" after a sting by a jellyfish of the class Cubozoa is now well documented. 1,2A.5 Currently, it is unknown how many different species cause this syndrome in humans although, as Barnes predicted, it appears likely that it may involve several other species in addition to *Carukia barnesi,* and may not necessarily be confined to Australian waters.`

The chemistry and pharmacology of *Carukia* venom is unknown at present and, although its potency is well appreciated clinically," it has not been perceived yet as life endangering. We present here a report of two of three recent cases of "Irukandji syndrome" in which rapidly developing pulmonary oedema produced acute respiratory failure in previously -healthy young adults. The results of more detailed investigations into a third, previously reported case," are also presented.

Clinical records

Case 1

While snorkelling in clear water off a small islet near Shute Harbour, north Queensland at 3.00 p.m. on January 9, 1987, a fit, 18-year-old man felt a stinging sensation on his chest, arms and the back of his neck. The water was clear with an incoming tide in a sheltered bay and a 2-knot current. The ambient temperature was 31 'C and the wind speed was 15 knots in a north-easterly direction; the water was calm as it was in the lee of the islet.

At the site of envenomation on the patient's neck a small (2-cm x 2-cm) area of erythema was present and he had a red line that was 4-cm long on his right shoulder. Vinegar was applied immediately to these areas, which was followed by a suspension of aluminium sulphate (20% wt/vol; Stingose), neither of which reduced the mild stinging sensation of the skin. Within five minutes of the sting, the patient developed stomach cramps and low back and chest pain that was followed five minutes later by severe pain "all over". Twenty minutes after the sting, he developed nausea and vomiting, and during the following 10 minutes the pains became "too severe to bear" - the patient was convinced of his impending death. Then followed profuse, drenching sweats and continuous muscular spasms.

At a doctor's surgery, some 45 minutes after the original envenomation, the patient complained of severe muscle pains in his abdomen, chest and all four limbs. He was vomiting, shaking and sweating profusely, and had mild peripheral cyanosis. His blood pressure was 180/90 mm Hg, and he had a regular pulse of 100 beats per minute. Pethidine (100 mg) and metoclopramide (10 mg) were administered by the intravenous route with little effect. Five minutes later, another 100 mg of pethidine and 10 mg of diazepam were administered intravenously, again with little effect. Finally, promethazine (50 mg) was administered intravenously and the patient was transferred by ambulance to hospital, some 30 kin away.

At the hospital, some 90 minutes after the original envenomation, the patient was distressed and in pain. His extremities were cold and he was sweating profusely. His blood pressure was 180/100 mm Hg, and his pulse was regular at 100 beats per minute. He was not cyanosed, his heart sounds were normal, his chest was clear and his abdomen was soft to palpation. Pethidine (50 mg) was administered intravenously and this dose was repeated 90 minutes later. The muscular pains finally abated some four-and-a-half hours later, eight hours after the original envenomation. At this time his blood pressure was 140/90 mm Hg, his pulse was 100 beats per minute, his respiratory rate was 28 breaths per minute and his temperature was 35.6 °C.

At 1.30 a.m. the following morning (10.5 hours after the original envenomation), the patient developed respiratory distress with bilateral pleuritic-type chest pain on inspiration which radiated to his back and abdomen. On clinical examination, he was distressed and was producing pink, frothy sputum although clinically he was not cyanosed and he was afebrile. His respiratory rate was 32 breaths per minute, his pulse rate was 120 beats per minute and his blood pressure was 120/90 mm Hg. The jugular venous pressure was not raised and ankle and sacral oedema were absent. Widespread coarse inspiratory and expiratory crepitations were heard on auscultation of the chest.

A chest x-ray film showed hazy opacification of both lung fields that was compatible with interstitial pulmonary oedema, and the electrocardiogram showed a tachycardia with T-wave inversion in leads I, aVL, V I and V2.

Forty per cent oxygen was administered by way of a facemask, in conjunction with intravenously administered frusemide (40 mg) and naloxone (0.8 mg). Two tablets of glyceryl trinitrate were administered sublingually, after which the patient's condition settled slowly.

Seven hours subsequently, although the patient's condition had improved greatly, the pleuritic pain continued and his urine output remained low (20 ml/h). The patient remained afebrile with a clear chest and normal chest x-ray film and electrocardiogram. Later that morning, the patient became febrile (38.2°C) for 24 hours; this was treated with paracetamol every six hours.

The next day, January 11, the patient was discharged from hospital; he was prescribed soluble aspirin for the pleuritic chest pain. Severe lassitude persisted for another three days.

Case 2

Another similar, but more severe case, happened near Seaforth Island on the Great Barrier Reef on December 26, 198611 - two weeks before Case 1. This patient was a fit 28-year-old man who was stung on the neck and face by an unseen jellyfish while snorkelling. Within five minutes he had developed an "Irukandji syndrome" almost exactly the same as that which is described above. He was admitted to the Mackay Base Hospital and was treated with very high doses (250 mg) of pethidine by intravenous infusion, as well as intravenously -administered hydralazine (20 mg) for control of his blood pressure, diazeparn (10 mg) for anxiety, and hydrocortisone (100 mg) and promethazine (50 mg).

In spite of adequate control of his blood pressure, which had been elevated on admission to hospital, this patient also developed severe respiratory distress and a chest x-ray film (Figure 1) showed marled pulmonary oedema. In this case, the blood gas concentrations altered to such an extent that intubation and intermittent positive-pressure ventilation were necessary and had to be continued for a total of 50 hours before extubation was possible.

Case 3

A very fit 47-year-old man, with a history of transient cardiac arrhythmia five years previously, was in knee-deep ocean water on Hinchinbrook Island, north Queensland, wearing a T-shirt over swimming-trunks. The weather was fine and hot on the morning of December 27, 1987.

He felt a sudden sting on the skin of his abdomen under his billowing T-shirt, which was repeated more severely on the front of his chest and then on his left cheek. He left the water immediately, but apart from general redness in the sting areas, no skin lesion or adherent tentacular material was seen. He saw nothing in the water. Within 10 minutes he had developed chest pain and "tightness", dyspnoea, nausea and headache. Over the next hour, the additional development of severe muscular and joint cramps in all limbs, and particularly his lower back, together with lower limb paraesthesiae, caused his transfer by boat and ambulance to the nearest mainland hospital.

He arrived there at 11.00 a.m. in severe distress, pale and sweating profusely. His pulse rate was 110 beats per minute, his blood pressure was 170/100 mm Hg rising to 190/105 mm Hg; he had multifocal ventricular premature contractions, and non-sustained ventricular tachycardia was seen once on his electrocardiogram. His lung fields were clear on auscultation and skin in the sting areas showed only a diffuse erythema. Pethidine, which was administered intravenously (25 mg), and intramuscularly (150 mg), led to only partial analgesia, but his ventricular premature contractions reduced in number.

Seven hours after envenomation, and still in distress from his back and limb pains, he developed acute pulmonary oedema with the production of blood-stained frothy sputum. His response to oxygen administration by way of a face-mask, nebulized salbutamol and intravenously-administered frusemide (20 Ng), aminophylline (250 mg) and morphine (5 mg),

was incomplete; he was transferred to a coronary care unit in Townsville with a presumptive diagnosis of an acute myocardial infarction.

Thirty hours after envenomation he arrived at Townsville General Hospital with clinical pulmonary oedema. His respiratory rate was 38 breaths per minute, his heart rate was 120 beats per minute, he had crepitations throughout the lung fields, and he was producing pink, frothy sputum. Blood gas concentrations showed marked hypoxia and Swan-Ganz catheterization showed elevated left ventricular filling pressures. A presumptive diagnosis of a myocardial infarction was made.

On arrival at hospital, blood gas measurements (on air) were: PAO2, 4.67 kPa; and PACO2, 4.27 kPa. The full blood count was: haemoglobin, 191 g/L; white cell count, 33.4 x 101/L (neutrophils, 83%) and platelets, 352 x 101/L. All biochemical tests gave normal results apart from a reduction in bicarbonate levels to 19.9 mmol/L.

Two hours after admission to hospital, Swan-Ganz right heart catheterization was performed. The initial readings were: central-venous pressure, zero; right-ventricular pressure, 3.47/1.20 kPa; mean pulmonary-capillary wedge pressure, 2.27-2.40 kPa. Over the next 36 hours the arterial diastolic pressure or pulmonary-capillary wedge pressure varied from 2.67-4.13 kPa. The cardiac output was not measured. Although these readings were taken by staff members with limited experience in this area, they do show elevated left-heart filling pressures that are consistent with left ventricular failure.

He was treated with intravenously administered morphine (5 mg), frusemide (20 mg), and ampicillin (500 mg); the sublingual administration of glyceryl trinitrate (one tablet); and one dose of captopril (12.5 mg) by mouth. His condition improved steadily over the next 48 hours. Serial electrocardiograms showed transient T-wave inversion in leads I and aVL; his creatine kinase levels did not become elevated.

Forty-eight hours after envenomation, discussion among us established the diagnosis of "Irukandji syndrome"; by this time the patient had developed visible, desiccated, vesicular lesions on his sternal skin at the site of the most painful swelling. Diazeparn by mouth was added to his therapeutic regimen and most other medications were ceased. His tachycardia and mild subjective chest discomfort persisted, but his condition continued to improve and clinically he was well by the fifth day after envenomation. At this time his haemoglobin level and white cell count gave normal results.

Echocardiography that was performed 57 hours after envenomation showed moderate dilation of all chambers of the heart with moderately severe diffuse hypokinesis. The valves were normal and a pericardial effusion was not present (Figure 2). Repeat echocardiography on the 24th day showed normal heart size and function.

RESULTS

Immunological studies

In our study of Case 1, serum that was collected 20 days after envenomation did not contain specific immunoglobulin (Ig)G antibodies against *Chironex fleckeri, Physalia physalis, Cyanea capillata, Cassiopea xamachana, Chrysaora quinquecirra* or *Aurelia aurita.*

In Case 2, serum that was collected on the day of envenomation, as well as two, six and 23 days subsequently, did not show significant changes in IgG concentrations against antigens to *Chrysaora quinquecirra, Cyanea capillata,* "Morbakka"," and *Cassiopea xamachana,* although borderline elevated titres against *Chironex fleckeri* were detected in the sera at Days 0 and 2 which had fallen by Days 6 and 23.

In Case 3, blood that was drawn two days after envenomation (almost a year after the previous two cases) showed an extremely high (one in 3600) and significant titre to *Carukia* (the "Irukandji"). Raised titres were also found to *Physalia physalis, Chrysaora quinquecirrha, Aurelia aurita, Cyanea capillata,* and *Cassiopea xamachana,* although these were not at significant levels. This specimen showed no IgG titre to *Chironex fleckeri* which suggests that there is no cross-reactivity between *Carukia* and *Chironex,* although there is among many other species of jellyfish.

It is believed that these later results were more accurate as the serum was freeze-dried immediately after collection from the patient; this was not possible in the previous cases. It is hoped that this procedure can be arranged for IgG studies of jellyfish envenomations in the future.

Collection of jellyfish specimens

Three days after the sting at Shute Harbour (Case 1), one of us (P.J.F.) went to the area at the same state of tide and similar weather conditions to try to catch a specimen of the offending jellyfish.

A fine net, with floats to hold the top on the surface and weighted on the bottom to hold it as vertically as possible in the water, was secured to the shore on the islet near the area where Case 1 was stung. The other end was attached to a boat that was anchored 15-m offshore in 12 m of water. As the tide started to flood, the net billowed out in the current and, by swimming behind it – fully protected with a Lycra "stinger-suit" - it was possible to watch the net.

During the next four hours, two small jellyfish were trapped in the net and transferred to specimen bottles. These were "box-shaped" with one tentacle at each "corner". They had a bell diameter of only 1.5 cm and a tentacular length of only 5 cm. Macroscopically, they resembled *Carukia bariiesi.3* The tentacles had to be removed while they were still fresh and they were freeze-dried and sent to the laboratory of one of us (J.W.B.) in Baltimore for venom analysis. One tentacle was retained for experiments with the nematocysts.

Both jellyfish specimens were caught near the top of the net: one in only 5 cm of water and the other in 30 cm of water. This corresponds with the theory that many jellyfish stings occur to humans who are at or near the surface of the sea;' -Irukandji are likely to swim close to and just below the sea surface.

Experiments with the nematocysts
In an experiment that was similar to those that previously have been reported vinegar, methylated spirits and aluminium sulphate (20% wt/vol) were applied to isolated tentacular segments. The nematocysts of this carybdeid were inhibited completely by vinegar and 20% aluminium sulphate, whereas methylated spirits resulted in mass discharge, similar to that which has been reported for *Chironex.* `

DISCUSSION

The clinical picture of a full-blown Irukandji syndrome' 1,2,3,4,5 presents many of the features of unchecked catecholamine release, and preliminary experimentation in rats by one of us (J.W.B.) suggests that this may be one of the causes. Thus, the previous suggestion of the use of phentolamine as an effective agent has been reinforced pending further investigations.

The use of calcium-channel blocking agents in the therapy of this syndrome is speculative and needs further study, although its success in other animal experimental cardiotoxic problems already is documented. Ataraxic drugs, such as chlorpromazine, or the butyrophenones (droperidol and haloperidol), which are also catecholamine antagonists, might help to allay the anxiety that is associated with the syndrome and would potentiate the effects of any analgesic agents that are necessary; at present they are untried. Evidence already exists that the Commonwealth Serum Laboratories' specific box-jellyfish *(Chironex fleckeri)* antivenom largely is ineffective in the "Irukandji syndrome".'

"Irukandji" venom is in short supply as the collection of specimens of *Carukia barnesi* presents formidable difficulties due to the animal's minute size (maximum bell diameter, approximately 2.5 cm), and its scarcity, due to its usual open-ocean habitat."' The clinical features of these reported cases are compatible with *Carukia barnesi* envenomation, although firm identification of this species was not made at the time of the sting in each case.

The specimens that were caught the day after envenomation of Case 1 macroscopically were similar to *Carukia barnesi,* and this was confirmed later on examination of the bodies of the two jellyfish by Dr Robert Hartwick of James Cook University. However, the tentacles did not have the characteristic "tails" that have been described by SouthCott3 and, although these could have been variants in the life-cycle, it suggests that the jellyfish may have been a new, and perhaps more venomous, species.

Other cases of presumed "Irukandji syndrome", including one from Hawaii, have involved respiratory distress;6.7 the syndrome may be more widespread in the Pacific region than believed previously.6-8 Barnes' suspicions that more than one type of jellyfish is responsible for the syndrome appear to be gaining credence.

Both vinegar and 20% aluminium sulphate are effective in preventing the discharge of any unfired nematocysts that remain on the skin, although in an "Irukandji" sting no remaining adherent tentacles are visible usually. However, if skin scrapings are taken from the envenomated area, by the method that has been described previously, undischarged nematocysts can be seen. In spite of such a small envenomated area, the syndrome is so severe that any prevention of further nematocyst discharge has to be recommended. Vinegar is now an accepted treatment for the inhibition of nematocysts of cubozoans (including the lethal *Chironex fleckeri),* and as it is economical and often present near swimmers in north Australian waters, it has to be recommended as the treatment of choice. Aluminium sulphate (20%), although more expensive, is as effective, but often it is less-readily available.

Serological diagnosis of jellyfish envenomation is becoming more accurate 16, and we believe that our serological results enabled us to exclude the other venomous jellyfish that are found in these waters at the time of these stings. Definitive testing with *Carukia* antigen is now possible technically, but is untried largely due to the scarce supply of the venom.

The pathophysiology that underlies the clinical pulmonary oedema in these patients is uncertain. Clarification would require further haemodynamic and left-ventricular functional assessments, and both serum and urinary catecholamine estimations. In the clinical setting, haemodynamic measurements are made most easily by way of a Swan-Ganz pulmonary-artery catheter (Case 3) that measures right atrial, pulmonary artery, and pulmonary-capillary wedge pressures. The cardiac output can also be measured and, hence, the pulmonary and systemic resistances can be derived. At the bedside, cardiac chamber size and function can be measured accurately and serially by echocardiography (Figure 2) or by radionuclear techniques. Comparison of the pulmonary-oedema fluid and plasma would provide further evidence of whether such oedema is a result of the increased permeability of pulmonary capillaries or of increased hydrostatic pressure - whether it be cardiogenic, or due to blood volume redistribution.

The observed pulmonary oedema is not explained fully by acute left-ventricular failure. All our subjects were fit, healthy men with no known cardiac disease. The poor response to diuretic agents, nitrates and opiate drugs is unlike that which is seen in cardiogenic pulmonary oedema. When pulmonary oedema is secondary to acute fulminant myocarditis, there usually is a rapid progression to death of pump failure. In Case 3, definite reversible left-ventricular dysfunction with elevated filling pressures was documented. However, the left-ventricular filling pressures were not would be expected for the severity of the clinical state hypoxia.

It is unclear whether the toxin in "Irukandji" envenomations is toxic directly to the myocardium and lungs. Non-cardiogenic pulmonary oedema accompanies a wide variety of toxic insults, which include endotoxaemia.11 Venoms, especially from jellyfish, have been shown to cause membrane destabilisation with associated ionic transport defects."," When low doses of the toxin of *Chironex* fleckeri are injected into rats, pulmonary oedema occurs. At higher doses, increasing impairment in the diastolic relaxation of the ventricle occurs until death results with the heart paralysed in systole.

Many of the features of the "Irukandji syndrome" could be explained by massive catecholamine release. The symptoms of severe abdominal and chest pain, vomiting, profuse sweating, hypertension and tachycardia also are seen together in patients with phaeochromocytoma when a sudden release of catecholamines from the tumour has occurred. Reversible severe left-ventricular dysfunction also has been described recently in this disordil. In animal studies, infusions of catecholamines (in doses that are used clinically) can dilate poorly-contracting ventricles within hours. The acute cardiomyopathy appears to be, in the large part, related to a1-adrenoceptor-mediated mechanisms .29

Sympathetic over-activity also has been postulated to be a major cause of non-cardiogenic pulmonary oedema, especially in some central nervous system disorders. Possible mechanisms include a shift of blood volume into the pulmonary circulation and alterations in capillary membrane permeability.

Investigations into the relative importance of the toxins that act directly, or indirectly by way of massive catecholamine release, are just commencing. Plasma catecholamine and urinary metabolite levels will need to be measured to confirm the strong clinical impressions.

Clearly, the occurrence of this syndrome in its severe form in a patient with pre-existing cardiopulmonary disease would give cause for concern. All the severely affected patients

who have been treated to date have been fit persons. "Irukandji" envenomation, once diagnosed, must be regarded seriously, and treated early and aggressively under hospital supervision (see box). Signs of cardiovascular and/or respiratory stress should be monitored, and assisted ventilation may be needed, as based on the usual clinical and blood-gas indications. The specific control of pulmonary capillary leakage awaits more understanding and the appearance of an antivenom.

Suggested treatment of "Irukandji syndrome"

Pain relief
Fifty milligrams of pethidine as an immediate intravenously-administered bolus dose, followed by a pethidine infusion at a rate of 30 mg per hour (or morphine, 5 mg as an intravenously-administered bolus dose and 2.5 mg increments of morphine as necessary every five minutes) is suggested as the most-effective regimen for pain relief. This 'should be carried out only with respiratory resuscitation facilities available immediately

Treatment of excess catecholamine release'
An intravenous injection of 5 mg of phentolamine followed by 10 mg of phentolamine that is administered intravenously when necessary is recommended until a favourable reduction in hypertension, shaking and sweating becomes evident

Management of pulmonary oedema or cardiopulmonary complications Treated as usual with the intravenous administration of diuretic and opiate agents, together with the sublingual administration of nitrates. Swan-Ganz right-heart catheterization is recommended to monitor pressures and to administer nitroprusside, dopamine or dobutamine. Endotracheal intubation and intermittent positive-pressure ventilation may be necessary in the face of increasing pulmonary oedema which does not respond to the above therapy, or if the pulmonary oedema is non-cardiogenic

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