Clinical and neurophysiological features of tick paralysis

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Summary

The clinical and neurophysiological findings in six Australian children with generalized tick paralysis are described. Paralysis is usually caused by the mature female of the species Ixodes holocyclus. It most frequently occurs in the spring and summer months but can be seen at any time of year. Children aged 1–5 years are most commonly affected. The tick is usually found in the scalp, often behind the ear. The typical presentation is a prodrome followed by the development of an unsteady gait, and then ascending, symmetrical, flaccid paralysis. Early cranial nerve involvement is a feature, particularly the presence of both internal and external ophthalmoplegia. In contrast to the experience with North American ticks, worsening of paralysis in the 24–48 h following tick removal is common and the child must be carefully observed over this period. Death from respiratory failure was relatively common in the first half of the century and tick paralysis remains a potentially fatal condition. Respiratory support may be required for >1 week but full recovery occurs. This is slow with several weeks passing before the child can walk unaided. Anti-toxin has a role in the treatment of seriously ill children but there is a high incidence of acute allergy and serum sickness. Neurophysiological studies reveal low-amplitude compound muscle action potentials with normal motor conduction velocities, normal sensory studies and normal response to repetitive stimulation. The biochemical structure of the toxin of I. holocyclus has not been fully characterized but there are many clinical, neurophysiological and experimental similarities to botulinum toxin.

Keywords: tick paralysis; cranial nerve involvement; reduction of compound muscle action potentials; botulinum toxin

Abbreviations: Ach = acetylcholine; CMAP = compound muscle action potential

Introduction

Ticks are arachnids and thus related to spiders and scorpions. During the late Palaeozoic or early Mesozoic era they became parasites and they can only obtain nourishment by sucking blood from mammals, birds or reptiles (Stone, 1988). They have been regarded as malevolent creatures from antiquity. Pliny (AD 77) described the tick as ‘most disgusting . . . living on blood with its head always fixed and swelling; being one of those animals which has no exit for its food, it bursts with over-repletion and dies from actual nourishment’ (Arthur, 1962).

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salivary glands into the preoral canal, and water is directly absorbed from subsaturated atmospheres. The salivary glands are also the source of the paralysis toxin. The digestive process is mainly intracellular and blood taken into the tick’s midgut remains largely undigested for long periods except in the female, at the time of egg-laying. The undigested blood remains a food reserve and is consumed gradually. Pathogens are thus not subject to digestive juices and can thrive in this nutritious environment. Finally, they have ‘phenomenal fecundity’ producing large numbers of eggs; *Amblyoma nuttalli*, for example, can produce up to 22 000 eggs.

Ticks of medical importance are divided into two families: *Argasidae* (soft ticks) and *Ixodidae* (hard ticks) (Sonenshine, 1991). There are ~170 species of argasid ticks. They have a soft, ‘leathery’ body and feed for a relatively short period of time, usually 5–25 min. There are ~650 species of ixodid ticks which are characterized by a hard body plate and a prolonged period of feeding, sometimes as long as 11 days. This prolonged period of feeding is in striking contrast to the feeding strategy of other blood-feeding ectoparasites such as mosquitoes (<3 min), kissing bugs (<20 min), vampire bats (<30 min) and leeches (~2 h) (Bowman *et al.*, 1996).

Human infections transmitted by ticks include diseases caused by protozoa (babesiosis), rickettsiae (Queensland tick typhus, Rocky Mountain spotted fever), spirochetes (Lyme disease, relapsing fever) and viruses (Russian spring–summer encephalitis, Colarado tick fever, Crimean–Congo haemorrhagic fever). Multiple organisms may be present in the one tick, e.g. *Ixodes ricinus* may harbour tick-borne encephalitis virus, *Borrelia burgdorferi* and *Rickettsia helvetica* simultaneously (Aeschlimann and Freyvogel, 1995).

Ticks may also provoke hypersensitivity reactions including anaphylaxis (Banfield, 1966). Granulomas may result from retained mouth parts after forcible attempts at removal (Stone, 1988).

Tick paralysis is caused by ixodid ticks. It was probably first recorded in 1824, in the explorer Hovell’s diary of his journey with Hume to Port Phillip Bay (Melbourne). He noted a ‘tick which buries itself in the flesh and would in the end destroy either man or beast if not removed in time’ (Scott, 1921). The first medical descriptions of generalized paralysis in humans were at the turn of this century from Canada (Todd, 1912) and Australia (Cleland, 1912). It was subsequently recognized that local paralysis restricted particularly to facial muscles, can also occur (Foster, 1931).

Despite the huge population of ticks in Australia, generalized paralysis in humans is uncommon. A search of the medical records of The Royal Alexandra Hospital for Children, the largest Children’s Hospital in New South Wales, revealed only two cases of children with generalized weakness between 1983 and 1995; one required ventilation. The impact of ticks on other species is enormous. It has been estimated that, each year, tick paralysis affects 20 000 domestic animals in Australia and in northern New South Wales alone, causes the death of 10 000 calves (Stone, 1988).

In North America, tick paralysis in humans is usually caused by *Dermacentor andersoni* or *D. variabilis* (Schmitt *et al.*, 1969). In Australia, *Ixodes holocyclus* is responsible for most cases. It seems to be the most potent of all the world’s paralysing ticks, and has produced paralysis in dogs, cats, sheep, calves, foals, pigs, chickens and mice, as well as humans (Malik and Farrow, 1991). The clinical course of paralysis produced by this tick is different from that of ticks in other continents. The neurophysiology in paralysed humans has not been reported previously. We describe the clinical and neurophysiological findings in six affected children.

**Case histories**

An abstract discussing Patients 3 and 4 has previously been published (Ouvrier, 1974). All children lived in the Sydney metropolitan area.

**Patient 1**

A previously well 23-month-old girl presented in April 1993 to Westmead Hospital with a 24-h history of lethargy, vomiting and poor fluid intake. She had stopped talking and had become unsteady, requiring assistance to walk.

On examination, she was drowsy, irritable and mildly dehydrated. Her temperature was 37.8°C. Her right pupil was dilated and reacted sluggishly to light, but there were no other focal neurological signs and her general examination was normal. The full blood count and biochemical profile was normal apart from borderline elevation of the urea concentration. She was found to have a metabolic acidosis with pH 7.3, carbon dioxide 23 mmHg, bicarbonate 11 mmol/l and base excess –14. Her creatine kinase was elevated at 452 U/l (range 0–200 U/l) and on the following day her urine was positive for myoglobin. The cerebrospinal fluid, electrocardiograph, cerebral CT scan and chest X-ray were normal.

It was felt she was suffering from some form of acute metabolic encephalopathy or poisoning, and she was rehydrated with 0.5 N saline and given intravenous cefotaxime. That evening both pupils were mid-position and unreactive to light. On the following morning, a member of the nursing staff discovered a tick behind her right ear. She had deteriorated overnight despite improvement in her acid base and electrolyte status. She remained drowsy and irritable. Her pupils were mid-size and unreactive to light. There was bilateral ptosis and paralysis of ocular movements with only minimal horizontal movement present. There was bilateral facial weakness, a poor gag reflex and little response to suction of her oropharynx. Limited movements of her hands and feet were noted, but she was not able to hold her limbs against gravity. She was hypotonic with absent deep tendon reflexes. The Babinski reflex was negative and sensory testing to pain was normal. An EEG showed diffuse slowing of basic rhythms. That evening she was intubated for airway protection.
Soon after discovery, the tick was carefully removed using forceps to the mouth parts and identified as *I. holocyclus*. Tick antitoxin was given (10 ml as a slow infusion) but there was no immediate response. On the following morning (day 3 of hospitalization) a further 20 ml of antitoxin was given. Her temperature increased to 39°C but this may have been due to a chest infection. By that evening the pupils had begun to react to light, the left being brisker than the right. Her cough in response to suction was better and she was moving all four limbs.

By day 4 she was more alert, responding to her mother and making purposeful movements. She was extubated on day 6, but developed signs of obstructed breathing and had to be reintubated. She was finally extubated on day 13. By day 8, she had a full range of ocular movements, her gag reflex was present and she was able to lift her arms and legs off the bed. By day 16 she could stand briefly and feed herself. A repeat EEG still showed some mild slowing of basic rhythms. By day 18 she was walking with assistance and by day 20, she was walking unaided. Four months later she had returned to normal.

An urticarial rash associated with intense pruritus developed on day 7. This worsened despite intravenous hydrocortisone. A skin biopsy showed no evidence of vasculitis. Blood cultures grew an Enterobacter species which was treated with timetin and subsequently gentamicin.

**Patient 2**

A 4-year-old boy was admitted in October 1995 to The Prince of Wales Children’s Hospital, intubated and ventilated, following a cardiorespiratory arrest. He had been well until 2 days previously when he was noted to be ‘off colour’ at his preschool and had an episode of urinary incontinence. That evening, his mother felt he looked a little ‘drunk’ and his eyes were not focused. The following morning, he was more unsteady and not able to get up off the floor to stand. He was seen by a general practitioner and a tick removed from the occipital region. It was subsequently identified as *I. holocyclus*. Over the day he continued to deteriorate, began drooling and was unable to walk.

Overnight he slept in his mother’s bed. When his breathing became laboured she took the child to the emergency department of a district hospital. On arrival, he was bradycardic and cyanosed with an oxygen saturation of 67% in room air. Asystole soon followed. He was intubated, given cardiopulmonary resuscitation and atropine and a normal rhythm was established within 2 min. He was then transferred to The Prince of Wales Children’s Hospital.

Examination showed that he could open his eyes on command and that his pupils were large and unreactive to light. There was total external ophthalmoplegia. He had a weak grasp but anti-gravity elbow flexion, hip flexion and ankle dorsiflexion were present. Deep tendon reflexes were preserved in the upper limbs but absent in the lower limbs.

He was given 20 ml of tick antitoxin intravenously. Later that day, lateral and vertical eye movements returned and his grasp was stronger. His right knee jerk became just elicitable. A further dose of antitoxin was given. On day 2 he had more spontaneous anti-gravity movements in his arms and legs. Both pupils were now reacting, the left still sluggishly. By day 4, the pupils were briskly reactive to light and both gag and cough reflexes were present. There were a number of unsuccessful attempts at extubation and this was not finally achieved until day 14. On day 16, he was walking alone on a rather broad-based gait and was able to stand on one leg. His mother discharged the child from hospital on day 18.

**Patient 3**

A 12-year-old boy presented in November 1972, with a 48-h history of sleepiness, fatigue and nausea. During the day prior to admission he was unsteady whilst walking. On the day of admission he developed diplopia and could neither stand nor walk without assistance. An engorged tick, subsequently identified as *I. holocyclus* was found on his scalp and removed by his general practitioner. That evening he was admitted to the Royal Alexandra Hospital for Children.

On admission, he was drowsy but rousable. He was ataxic and had mild weakness of his arms and legs but the deep tendon reflexes were brisk. By the next day he had deteriorated. Ocular convergence was poor and there was coarse horizontal and slight vertical nystagmus. He had bilateral ptosis and bifacial weakness. There was poor palatal elevation and mild weakness of jaw closure. Finger–nose ataxia was present which seemed out of proportion to the degree of weakness. He could not lift his head off the bed, nor flex his hips against gravity whilst lying supine. The triceps and ankle jerks were now absent and the other tendon reflexes were sluggish.

He was given 20 ml of tick antitoxin intravenously after a test dose and remaining mouth parts buried in the wound. On the day of admission he developed diplopia and could neither stand nor walk without assistance. An engorged tick, subsequently identified as *I. holocyclus* was found on his scalp and removed by his general practitioner. That evening he was admitted to the Royal Alexandra Hospital for Children.

**Patient 4**

A 12-year-old boy presented in November 1972, with a 48-h history of sleepiness, fatigue and nausea. During the day prior to admission he was unsteady whilst walking. On the day of admission he developed diplopia and could neither stand nor walk without assistance. An engorged tick, subsequently identified as *I. holocyclus* was found on his scalp and removed by his general practitioner. That evening he was admitted to the Royal Alexandra Hospital for Children.

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Fig. 1 Patient 3: the recurved teeth of the hypostome can be seen penetrating the upper dermis with extensive surrounding inflammatory response. Haematoxylin and eosin; magnification ×16 objective.

pupil was fixed and dilated. Nystagmus was present on lateral gaze to the left and right and convergence was impaired. A variable ptosis was present. There was right facial weakness and weak jaw closure. His gag reflex was depressed and there was pooling of secretions. His voice was hoarse. He was unable to walk but could hold his legs above the bed. There was mild weakness of his upper limbs. His deep tendon jerks were absent.

He was closely observed and given feeds, initially intravenous and then nasogastric. There was no definite improvement for 3 days, at which point he seemed more active and had a stronger voice and cough. By the fourth day after admission his left pupil reacted sluggishly to light but 3 days later, he was still unable to lift his head from the bed. He was discharged after 2 weeks in hospital. At review 3 weeks later his neurological examination was normal.

**Patient 5**

An 11-year-old girl presented in July 1977. She had been unwell with headache for 3 days. On the day before admission her lower limbs became weak, she had difficulty walking and then developed diplopia and dysarthria. She was admitted to the Repatriation Hospital, Concord.

On examination, she was well looking, alert and orientated. Her pupils were dilated with minimal reaction to light on the
right. She had bilateral abducens and facial palsy. She was generally hypotonic with weakness of all limbs but most marked distally in the lower limbs. The only deep tendon reflexes present were the biceps jerks. She was thought to have the Miller–Fisher variant of Guillain–Barré syndrome and was admitted to the intensive care unit where prednisone 40 mg/day was started. Over the next week she progressively became weaker and could no longer swallow or chew. Urinary incontinence developed. Her vital capacity dropped below 1 litre but she did not require ventilation. Her cerebrospinal fluid was normal and a Tensilon test was negative.

At that time, a tick identified as *I. holocyclus* was found in her scalp and removed. She made a slow recovery and was not able to walk unassisted until 2 weeks later.

**Patient 6**

A previously well 2-year-old girl presented in December 1992. Her mother noted that she seemed tired, her eyes were droopy and her head control was poor. Her gait was unsteady. The following day she was worse. Her voice had become high pitched, her speech was slurred and when she tried to walk, she fell over. Her mother, remembering similar signs in her pet dog who had suffered tick paralysis 20 years earlier, found a tick in the right parietal region. Removal of the tick was attempted with forceps by their general practitioner but proved difficult and the mouth parts were left in situ. These were subsequently removed with a scalpel.

The next morning (day 3) she was worse and was sent to Westmead Hospital. On examination she seemed quiet and slightly drowsy. There was a mild ptosis but her gag reflex and the rest of her cranial nerves were normal. She was unable to walk. She was hypotonic and her deep tendon reflexes were depressed.

By day 4 she was weaker and had now lost the reflexes in her legs. By day 5 she was unable to sit up, had poor head control and little movement in her legs. She was able to elevate her arms only to shoulder level. She began to have difficulty drinking and, briefly, was given only intravenous fluids. By day 10, her speech had improved, she could lift her arms above her head and sit unsupported. By day 11, she was able to stand with assistance with hyperextended knees and she was discharged. She has subsequently made a full recovery, although it was several months before her mother felt her running had completely returned to normal.

**Neurophysiology**

The results of the nerve conduction studies of the six cases are shown in Tables 1 and 3; normal values are given in Table 2. The initial studies were performed in the first week of the illness in all cases. Repetitive nerve stimulation was performed on the ulnar nerves of Patients 1, 3 and 4 and was normal in each. In Patients 1, 2 and 6, the effect of cooling was examined by initially recording at room temperature and then cooling the limb. In Patient 5, the limb was first cooled and measurements made with rewarming. The effect of cooling was examined at the time of the initial nerve conduction studies in Patients 1, 2 and 6. It was studied 2 weeks after the initial examination in Patient 5.

**Discussion**

In contrast to the dramatic, life-threatening symptoms that follow soon after snake or spider bite, tick paralysis evolves slowly but it can be equally deadly. Two of our patients would have died without modern intensive care. Each required prolonged ventilation and Patient 2 was lucky to survive a cardiorespiratory arrest on arrival in hospital. In New South Wales, tick paralysis caused 20 deaths between 1900 and 1945 (Sutherland, 1983a). Children aged between 1 and 5 years were mainly affected but there were also three adults whose ages ranged from 30 to 75 years. By comparison, in New South Wales from 1910 to 1981 there were 81 deaths due to snare bite (White, 1995). Ticks have caused more deaths than the greatly feared funnel web spider, *Atrax robustus*, which was responsible for 13 deaths from 1927 to 1981 (Sutherland, 1983b). Other notorious predators which have caused fewer fatalities than ticks include the red back spider, *Latrodectus mactans hasselti*, responsible for 14 deaths Australia wide (Sutherland, 1983c) and the blue-ringed octopus, *Hapalochlaena* sp., which has caused two deaths (Sutherland, 1983d).

**Clinical features**

There have been few reviews of the clinical findings in tick paralysis in humans in Australia (Ferguson, 1924; Hamilton, 1940; Taylor and Murray, 1946; Pearn, 1977; Sutherland, 1983a). These papers described the essential features. A prodrome is followed by unsteadiness of gait and then ascending, symmetrical paralysis which can take days to develop fully. Maximal weakness may not be reached until ~48 h after the tick has been removed or has dropped off. Death is due to respiratory paralysis. In those children who survive, recovery is slow, several weeks usually passing before their strength returns to normal.

Cranial nerve involvement was noted in previous studies, particularly bulbar and facial weakness but the frequency of ocular involvement was not emphasized. Four of our patients had pupils which were unreactive or minimally reactive to light (unilateral in one). Abnormalities of external ocular movements were noted in all patients except Patient 6. Total external ophthalmoplegia was present in Patients 1 and 2. The ocular signs were present early and give a warning that the problem may not be Guillain–Barré syndrome which is the major differential diagnosis. Fixed dilated pupils associated with ascending paralysis have also been described following snake (Sutherland, 1983e) and blue-ringed octopus bite (Sutherland, 1983d) but the evolution of signs is much more rapid. Infant botulism can produce a similar picture but
<table>
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<tr>
<th>Subject (age)</th>
<th>Nerve of distal CMAP (mV)</th>
<th>Latency of distal CMAP (ms)</th>
<th>MCV (m/s)</th>
<th>SNAP (µV)</th>
<th>SCV (m/s)</th>
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<td>Patient 1 (23 months)</td>
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Table 1 Summary of nerve-conduction studies in six patients with tick paralysis

CMAP = compound muscle action potential; MCV = motor conduction velocity; SNAP = sensory nerve action potential; SCV = sensory conduction velocity.

usually occurs in the first months of life (Thomas, 1993), whereas tick paralysis usually occurs in the older, mobile child. Interestingly, although fixed dilated pupils and ophthalmoplegia are considered characteristic signs of botulism, they are relatively uncommon. For example, in two recent series, fixed pupils occurred in only two of 14 adult cases (Cherington, 1974) and two of six infants (Thomas, 1993). None of the infants had ophthalmoplegia.

Deterioration despite removal of the tick and slow recovery are important features differentiating paralysis caused by *I. holocyclus* from that of the North American ticks *D. andersoni* and *D. variabilis*. Removal of these ticks usually results in improvement in 1 h and recovery within a day (Garrettson, 1984). After removal of *I. holocyclus* in a child showing any signs of paralysis, increased weakness should be anticipated. In four of our patients the tick was removed and the child sent home only to become worse. This deterioration is part of the natural history of *I. holocyclus* paralysis but the possibility of other undetected ticks should also always be considered.

Rarer complications of tick paralysis in humans include myocarditis (Pearn, 1966) and myositis (Boffey and Patterson, 1973; Sutherland, 1983a). Mild transient elevation of creatine kinase associated with myoglobinuria occurred in Patient 1 but there were no subsequent renal problems.

Although the toxin seems to mainly act at the neuromuscular junction, there is human and animal evidence of autonomic and possibly central involvement. The frequency of pupillary involvement in our patients has been discussed. Cooper (1976) found fixed dilated pupils in three of seven experimentally paralysed dogs, unilateral in one case. He also noted that mice frequently develop a severe ileus.
Tick paralysis

Table 2 Nerve-conduction data from normal children

<table>
<thead>
<tr>
<th>Reference</th>
<th>Nerve</th>
<th>Age range</th>
<th>Amplitude of CMAP (mV)</th>
<th>MCV (m/s)</th>
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<td></td>
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<td>1–3</td>
<td>5.88 ± 2.51</td>
<td>52.7 ± 4.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1–3</td>
<td>7.66 ± 2.23</td>
<td>53.8 ± 4.83</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1–3</td>
<td>6.42 ± 1.92</td>
<td>48.7 ± 4.86</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1–3</td>
<td>15.71 ± 1.79</td>
<td>44.9 ± 4.44</td>
</tr>
<tr>
<td>CMAP: mean ± SD</td>
<td>Posterior tibial</td>
<td>1–3</td>
<td>15.71 ± 1.79</td>
<td>44.9 ± 4.44</td>
</tr>
<tr>
<td>Ouvrier et al. (1990)</td>
<td></td>
<td>4–6</td>
<td>15.75 ± 2.16</td>
<td>48.6 ± 4.25</td>
</tr>
<tr>
<td></td>
<td>Posterior tibial</td>
<td>7–14</td>
<td>15.75 ± 1.77</td>
<td>48.2 ± 2.76</td>
</tr>
</tbody>
</table>

CMAP = compound muscle action potential; MCV = motor conduction velocity.

Table 3 Temperature related changes in four patients with tick paralysis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Nerve</th>
<th>Before cooling</th>
<th>After cooling</th>
<th>Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CMAP (mV)</td>
<td>Latency (ms)</td>
<td>CMAP (mV)</td>
</tr>
<tr>
<td>1</td>
<td>R posterior tibial</td>
<td>1.0</td>
<td>3.8</td>
<td>2.1</td>
</tr>
<tr>
<td>2</td>
<td>R common peroneal</td>
<td>0.5</td>
<td>4.4</td>
<td>1.0</td>
</tr>
<tr>
<td>5</td>
<td>L common peroneal</td>
<td>4.3</td>
<td>5.4</td>
<td>4.1</td>
</tr>
<tr>
<td>6</td>
<td>R median</td>
<td>0.9</td>
<td>2.7</td>
<td>1.2</td>
</tr>
</tbody>
</table>

CMAP = compound muscle action potential. *In Patient 5, the proximal latency was measured. In the other patients, latency refers to distal latency.

Urinary retention has been described in dogs (Gordon, 1972). Ilkiw et al. (1988) demonstrated alteration in cardiovascular sympathetic and parasympathetic activity, independent of hypoxia, in dogs. Our first patient had repeated vomiting, obtundation and slow wave EEG activity suggesting central involvement. Vomiting was also a feature of Patient 4. Vomiting is a common sign of tick envenomation in dogs where it may be intractable and associated with loss of voice, but without obvious limb weakness. This can be secondary to poor oesophageal motility and the development of mega-oesophagus, but a direct effect of the toxin on medullary chemoreceptors has also been suggested (Malik and Farrow, 1991).

Why do some ticks paralyse their host?
Most species of tick do not paralyse their host. On a worldwide basis only 46 species are known to have this capability (Stone, 1988). *Ixodes*, with 217 species, has the largest number of species of any tick genus, yet paralysis is reported to be caused by only seven of these species. Not all ticks in a species known to cause paralysis, will produce it (Cooper, 1976). Paralysis usually develops as the tick becomes fully engorged and the host may die after the tick has fully fed and detached itself. In dogs, fatal paralysis may not even commence until after the tick has detached (Cooper, 1976). There is no obvious survival advantage for the tick and in human terms, this seems a perverse, if not malicious action.

The ability to paralyse may be an accident of nature, an unexpected toxic effect superimposed on a function such as local anaesthesia or anticoagulation which had evolved to enhance attachment and feeding (Stone, 1989). However, the ability to paralyse is common to many predators including snakes, the blue-ringed octopus and the close relatives of ticks, spiders and scorpions. It is possible that all ticks at
one point paralysed their prey but with the change to the parasitic lifestyle, this power was lost in most but not all species.

In the wild, paralysis is usually not a problem for the common native hosts for *I. holocyclus*. Bandicoots, possums, kangaroos, and koalas are mostly immune as adults. The immunity seems to be acquired and short lived. Bandicoots which are heavily infested with *I. holocyclus* when captured, after being confined free of ticks for several months, may be subsequently killed by a single adult female tick (Clunies Ross, 1926).

In Australia, there are 70 tick species with 22 species of *Ixodes*. Only three cause paralysis: *I. holocyclus*, *I. cornuatus* and *I. hirsti* (Stone, 1988). In humans, all cases where the tick has been identified have been due to *I. holocyclus* except one instance where a 3-year-old boy required ventilation after being confined free of ticks for several months, may be subsequently killed by a single adult female tick (Clunies Ross, 1926).

The life cycle of *I. holocyclus*

*Ixodes holocyclus* has few natural predators but the engorged larvae and, to a lesser extent, engorged nymphs are extremely susceptible to desiccation. The high temperatures and lack of hosts away from the coastal fringe limit its domain to a narrow coastal strip usually no more than 20 km wide (Cooper, 1976). However, this extends thousands of kilometres from North Queensland south to Victoria.

The development from egg to adult tick takes ~1 year (Clunies Ross, 1924; Cooper, 1976). It is a three-host life cycle with four stages. Variations in moisture or temperature can hasten or delay any stage. The eggs incubate in moist leaf litter or under bark for 40–60 days, then hatch into larvae. The six-legged larva attaches to host number 1, usually a native animal such as a bandicoot, possum or kangaroo and sucks blood for 4–6 days. The engorged larva then drops to the ground and moults into the eight-legged nymph. The nymphs crawl up vegetation and then attach to host number 2 which may be any animal, including humans. After feeding 4–7 days they drop to the ground and moults into the eight-legged adult tick.

The unfed adult female is oval shaped and ~3 mm long and 2 mm wide. It clings vegetation and attaches to host number three which may be any animal, including humans. When engorged it can be up to 13 mm long and 10 mm wide. It drops to the ground and spends 3 weeks in moist vegetation before laying 2500–3000 eggs, and then dying. Overall survival of the eggs is as low as 0.08% (Stone, 1988). Males wander about on hosts looking for females to mate with but usually do not suck blood from the host. They die after mating. They may paralyse partly fed females by piercing their cuticle on the ventral surface and feeding on haemolymph (Cooper, 1976). Adult females can survive for >70 days without feeding and adult males >140 days (Clunies Ross, 1924).

There is one dominant generation each year and the adults are most abundant in spring and early summer which consequently is the most common time for tick paralysis. However, the presence of all stages can be detected at most times during the year and in our series, Patient 1 presented in autumn and Patient 5 in winter.

**Formation of the feeding lesion**

Once on the host, the tick must attach itself, neutralize the host defence and local haemostatic systems and prepare itself for a massive increase in body size as blood is sucked from the host. This complicated process is described in detail in Sonenshine (1991b) and will only be discussed briefly here. It is dependent on the specialized mouthparts of the tick and its remarkable salivary glands. After a site for feeding has been chosen, the tick begins to lacerate the epidermal layers using the horizontal action of its cheliceral digits (Fig. 2). These are paired appendages for cutting, ripping and tearing skin. The hypostome which also has a cutting edge is inserted, enabling the tick to remain attached. Often, however, it will detach itself and repeat the process elsewhere on the skin of the host as though seeking the most favourable location. In humans, the scalp behind the ear seems to be a preferred site.

Once the tick is firmly attached, as blood flows into the wound site, the tick begins feeding and the buccal canal becomes a common duct for the intake of host tissue fluids and the output of tick saliva (Kemp et al., 1982). The three components of the host defence system which have to be overcome are haemostasis, the inflammatory response and cell mediated immunity. Anticoagulants and anti-inflammatory agents secreted in the ticks saliva counter the first two problems but cell mediated immunity is more difficult to deal with and many ticks succumb or depart without feeding when attempting to attach to previously exposed hosts.

Feeding is spasmodic for several days whilst the cuticle growth, which is necessary for rapid expansion of body size, is completed. The rapid feeding phase then commences and comparatively huge volumes of blood are taken up over a 12–24-h period, with the body weight of the tick increasing 100–200 times. To concentrate the blood meal, ixodid ticks use their salivary glands periodically to secrete excess water back into host and the tick may actually consume 2–3 times as much blood as its engorged weight. This phase of rapid feeding and intense salivation coincides with the time of peak production of toxin (Kemp et al., 1982).

The toxin

Clunies Ross (1926, 1935) provided the first definitive evidence that paralysis was due to a toxin secreted by the tick. Kaire (1966) was able to obtain a partially purified toxin by homogenizing 350–400 replete ticks. Subsequent
work by Stone et al. (1988) has suggested that it is a protein neurotoxin with a molecular weight of 40 000–80 000. It has been named holocyloctoxin but its chemical structure has not been fully identified.

There is a delay from the time of attachment of the tick to the onset of symptoms. Clunies Ross (1934), experimenting on >100 dogs, found that symptoms of paralysis never appeared until the fifth day after attachment of *I. holocyclus*. Even when over 30 ticks were placed on puppies weighing 3–4 kg, symptoms did not appear until day 4. Murray and Koch (1969) showed that an *I. holocyclus* female having killed one mouse could be transferred to a second mouse which was killed more quickly than the first. This could be repeated until as many as five mice had been paralysed and the time required to kill the final mice had been reduced from 72–92 h to 12–18 h. This and the work of Cooper (1976) and Kaire (1966) which will be discussed later, suggests that the delay has two components. First, several days pass before the tick salivary glands begin to secrete significant quantities of toxin. Secondly, the toxin once secreted does not act immediately.

The most complete study of the action of tick toxin was performed by Cooper (1976) who studied its effect on dogs and a rat phrenic nerve–hemidiaphragm model. The neuromuscular junction was identified as the site of the paralysis. An intriguing finding was the discovery that the paralysis was temperature dependent. With the phrenic nerve–hemidiaphragm preparation removed from paralysed mice, at 35–36°C there was usually no response to stimulation of the nerve. As the temperature of the preparation was lowered, the response of the diaphragm to phrenic nerve stimulation progressively increased and reached a peak between 14 and 18°C. The effect was completely reversible and the response of the muscle could be varied at will simply by manipulating the temperature. Direct stimulation of the muscle produced a normal contraction irrespective of the temperature.

No change in the post-synaptic sensitivity to acetylcholine was demonstrated. There was normal spontaneous release of acetylcholine (ACh), but a temperature dependent inhibition of evoked ACh release from nerve terminals. The action potential seemed to invade the nerve terminal normally but there was failure of ACh release. It was concluded that there was an abnormality of the excitation–secretion mechanism possibly due to reduced calcium availability.
Clinical neurophysiology

We have only been able to find six previous case reports of nerve conduction studies in tick paralysis (Cherington and Snyder, 1968; DeBusk and O’Connor, 1972; Haller and Fabara, 1972; Swift and Ignacio, 1975; Morris, 1977; Donat and Donat, 1981). Each report was limited to a single patient and in three of them only one nerve was studied. All cases were from North America and in two, the tick was identified as *D. variabilis*. Each study demonstrated a reduction in size of the compound motor action potentials (CMAPs) except that of Haller and Fabara where they were not measured. There was variation in the other findings with some nerves showing mild slowing of motor nerve conduction and of distal motor latencies. Sensory studies and repetitive stimulation were normal. After removal of the tick, nerve conduction studies rapidly returned to normal reflecting the clinical response. The exception was Donat and Donat’s 1981 case where >50 (unidentified) ticks were found on a child’s back. There was a very slow clinical response and 6 months after presentation, low amplitude CMAPs in his lower limbs and denervation on EMG were still present.

Ideally all neurophysiology laboratories should have their own normal ranges for nerve conduction studies in children. However, there is an understandable reluctance to submit normal children to an often distressing procedure and most laboratories use values derived from the relatively small number of studies performed on normal children. These have been summarized by Oh (1984) and Ouvrier *et al.* (1990). Most studies are >20 years old, the only recent study is from China (Cai and Zhang, 1997) (see Table 1). All demonstrate changes with age but there is variation between the studies in the values obtained and the nerves examined. This makes interpretation of what may be mild abnormalities difficult and results are regarded as abnormal only when they deviate markedly from these values. Our studies were performed in four different laboratories over a period of >20 years. There were technical difficulties with the children being ill and studied mostly in intensive care units rather than in a neurophysiology laboratory. Nevertheless there was a remarkable uniformity in the results. The most striking feature was the extremely low CMAP amplitudes present in 14 of the 17 nerves studied. The three exceptions were the ulnar nerve of Patients 5 and 6, and the posterior tibial nerve of Patient 2, where values of around 4 mV were obtained. This is probably also a low figure, judging from the normal values in Table 2 and the fact that in Patient 5, the ulnar CMAP had increased to 18 mV when repeated 3 weeks later. Motor nerve conduction velocities were in the normal range in 12 of the 16 nerves studied. Borderline or slightly low values were found for the common peroneal and posterior tibial nerves of Patient 1, for the posterior tibial nerve of Patient 2 and the ulnar nerve of Patient 5. Patients 1 and 2 were the sickest in the study and the temperature of the common peroneal nerve at the time was 30°C. We feel these borderline low conduction velocities were due to technical problems such as cooling rather than indicating a peripheral neuropathy. Sensory studies were normal in all cases as were responses to repetitive nerve stimulation in the three cases where it was performed.

In an attempt to duplicate Cooper and Spence’s (1976) experimental observations in the human, cooling of the limbs was performed in four of our patients. There was no change in amplitude of the CMAP in Patient 2 but in the other three, increases were noted. The change was most marked in Patient 1 where there was a doubling in amplitude of the CMAPs of both the common peroneal and tibial nerves. However, the initial values were very low and the test–retest variability is large when analysing such low amplitude potentials.

Denys (1991) has reviewed the multiple, complicated effects of cooling on nerve conduction studies. In normal nerves, cooling slows nerve conduction velocity, increases distal latency and increases the amplitude or ‘area under the curve’ of the M wave. The last effect is felt to be due to cooling having less influence on initial sodium permeability than on the recovery process, i.e. on the subsequent inactivation of sodium permeability and increase in potassium permeability (Louis and Hotson, 1986). Cooling also decreases both quantal release of ACh and its rate of hydrolysis. It slows the muscle contraction–relaxation cycle.

Denys (1990) demonstrated an increase in amplitude of the CMAP in normal subjects of up to 18% with cooling. Much greater changes were produced by cooling in disease states such as myasthenia gravis, myasthenic syndromes and amyotrophic lateral sclerosis.

There are formidable technical difficulties in studying the effects of cooling in humans. Focal cooling, at the recording site only, has a different effect from generalized cooling. Different results are found from recordings during the warm-up phase after cooling than during the cooling-down phase. There are variable temperature gradients in a limb from proximal to distal and from superficial to deep layers. Halar *et al.* (1980) found that cooling of the skin temperature from 32.5 to 26.8°C decreased the intramuscular temperature only from 35.9 to 32.7°C. We were able to cool the limbs to skin temperatures of ~25°C but the temperature at the neuromuscular junction is likely to have been considerably higher, particularly in the lower limbs. In Cooper’s (1976) study, marked increases in the CMAP of the rat phrenic nerve–hemidiaphragm preparation were not seen until temperatures of <24°C were achieved. The relatively small changes seen in our patients may be due to a failure to produce a sufficiently low temperature.

Similarities between tick toxin and botulinum toxin

Tick toxin and botulinum toxin seem to have much in common. With botulinum toxin, the same questions have been asked about the ‘riddle of origin’ of a toxin which seems to have neither a predatory nor protective function...
Tick paralysis

I. holocyclus

Clinically, both act principally at the neuromuscular junction and autonomic ganglia. Neurophysiologically, both produce low amplitude CMAPs with normal nerve conduction studies. Repetitive stimulation performed in three of our patients was normal. Variable results have been reported with repetitive stimulation in botulism; an incremental response is often, but not always, seen (Cornblath et al., 1983; Graf et al., 1992). This may be related to the quantity of toxin present (Graf et al., 1992). Gutierrez et al. (1994) believe that post-tetanic facilitation is the characteristic electrophysiological feature of botulism, but this was not performed on our patients. Experimentally, both tick and botulinum toxins have been found to act presynaptically at the neuromuscular junction. Moreover, Lundh (1983) demonstrated the same temperature dependence in rats paralysed with botulinum toxin as Cooper (1976) had found with tick toxin. A dose of botulinum toxin was given which caused complete paralysis of the extensor digitorum longus muscle at 35–37°C. When the temperature was reduced to <25°C, muscle twitches appeared, and below 20°C, the muscles twitched vigorously.

Little is known about the pharmacological mechanism of the action of tick toxin, but that of botulinum has recently been described (Simpson, 1996). After binding with high affinity to receptors on nerve endings, the toxin penetrates the cell membrane by receptor-mediated endocytosis and then crosses the endosome membrane by pH-dependent translocation. When it reaches the cytosol, the toxin acts as a zinc-dependent endoprotease to cleave polypeptides that are essential for exocytosis. Without these polypeptides, nerve action potentials are unable to trigger the release of ACh. This last step is thought to be enzymatically mediated (Simpson, 1986). Cooling slows the internalization step and also increases the availability of intracellular calcium, allowing more ACh to be released (Coffield et al., 1994).

Cooper (1976) found that mice injected with I. holocyclus toxin did not develop paralysis for some 8–12 h after the injection. Kaire (1966) found that symptom onset was ~48 h after toxin injection in dogs. This delay suggests that the toxin may need to undergo a similar sequence to that of botulinum toxin, where binding and internalization precede intracellular poisoning. The characteristic deterioration seen after tick removal may be due to the continued action of internalized toxin.

**Treatment**

The first step in treatment is finding the tick and then removing it. Hamilton (1940) stressed that multiple ticks may be attached and a careful search of body crevices should be made, including the auditory meatus, natal cleft, the vulva and nose. In each of our patients, the tick was attached to the scalp usually behind the ear. In Sutherland’s review of 20 tick deaths (1983a), the site of attachment was recorded in 15 cases and was in the scalp of 10 of these. Not uncommonly a swelling is noted but its significance is not appreciated. In our first patient, the mother had noticed a lump in the child’s scalp but did not think it relevant, and its true identity was not discovered until the day after admission. Patient 5 was in the intensive care unit for almost 1 week before the tick was found. Taylor and Murray (1946) describe an infant in whom the diagnosis of poliomyelitis was revised at post-mortem when adhesive tape applied by the doctor of first contact was found to conceal a tick. Sutherland (1983a) was sent a tick which had been excised by a surgeon who felt it might be a malignant melanoma.

Many methods of tick removal have been advocated but traditional methods such as the application of a lighted match, alcohol or petroleum jelly are not effective (Needham, 1985). It has been recommended that the tick be grasped close to the skin with curved forceps and removed with steady pressure. However, as seen from our patients, it may be difficult to remove the tick intact and without local trauma. Stone (1988) has suggested that forcible removal of the live tick may lead to rapid dispersal of the toxin which had been partially contained by the host immune response. Rather than attempting to remove the live tick, he has proposed that it be rapidly killed using a pyrethrin based insecticidal spray (Stone, 1990). The dead tick would then shrivel and drop out spontaneously or after a gentle touch.

Anti-toxin, a hyperimmune serum prepared from dogs, first used in 1935 is the usual treatment for paralysed animals (Malik and Farrow, 1991). In humans it has been used sparingly and only in severely ill patients because of the risk of acute reactions and of serum sickness. Pearn (1977) described rapid reversal of paralysis in a 3-year-old girl. The results have not been as impressive in other studies including those of Hamilton (1940) and Tomkins (1963) where there was a high incidence of reactions. The variation in efficacy could be the result of different toxins secreted by different ticks but it is also possible that the toxin may have become internalized and inaccessible to the circulating antitoxin.

Among our patients, the antitoxin may have halted the rapid downhill course of Patient 1. The child subsequently developed a fever and rash which was probably a reaction to the anti-toxin. Patient 2 improved without adverse effects but Patient 3 showed little improvement and developed a marked urticarial response. Unfortunately the usefulness of antitoxin in humans is unlikely to be resolved by a controlled trial, given the relatively small number of children ill enough to be candidates for its use.

**Summary**

Tick paralysis is a relatively rare but potentially fatal condition. On the east coast of Australia, it should be considered in all cases of apparent Guillain–Barré syndrome, particularly if there is early pupillary involvement. The toxin is secreted from the highly adapted salivary glands of the tick and is of great biological interest. It has many similarities to botulinum toxin but its biochemistry and pharmacology...
have not yet been fully discovered. It is worth further study as it may have a similar therapeutic role to botulinum toxin.

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