Non-infectious illness after tick bite

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Tick bites are common and may have non-infectious complications. Reactions range from local reactions to systemic syndromes, tick paralysis, mammalian meat allergy and tick anaphylaxis. Management revolves around prevention with vector avoidance and immediate removal of the tick if bitten. Treatment of bite reactions is usually symptomatic only with anti-histamines or corticosteroids. Adrenaline may be indicated for severe cases.

Ticks are ubiquitous arthropods which incidentally bite humans during outside activities (i.e. exposure to burrows and caves in regards to Argasid (soft) ticks, and exposure to vegetation for Ixodid (hard) ticks)[1]. Seventy species of ticks have been recorded in Australia[2]. Common Argasid ticks that bite humans include *Argas* and *Ornithodoros* species, whereas Ixodid ticks include *Amblyomma*, *Dermacentor*, *Haemaphysalis*, *Hyalomma* and *Ixodes* species[1]. Human-biting ticks in Australia include *A. triguttatum*[3] and Ixodes genus ticks (predominantly *I. holocyclus and I. cornuatus* but include *I. fecialis, I. tasmani, I. australiensis)*[2]. Two biting seasons have been described in south-eastern Australia, the predominant one peaking in October/November with a secondary peak in April[4].

Accurate data about the prevalence of post tick-bite illness are hard to find, but as many as 10% of tick-bite victims may experience illness overseas[5]. This includes local reactions (57.6% of total reactions in Polish patients)[6], systemic syndromes, tick paralysis and anaphylaxis.

Studies of tick saliva

Tick saliva is injected during a bite and contains a complex mix of chemicals. These neutralise host protective mechanisms such as pain, haemostasis, inflammation (which can reduce transmitted infections) and immune reactions[7]. Transcriptome analysis has characterised the sialotranscriptome of specific ticks[8], which changes depending on life stage and feeding status.

Of the human biting ticks, *Ixodes* spp. saliva contains proteins encoded by a metalloproteinase family of genes that inhibit wound healing and facilitate prolonged feeding via anti-haemostatic agents[7].

Boophilus (previously *Rhipicephalus*) bites differentially induce acute phase proteins in infested cows (increased haptoglobin in sensitive and serum amyloid A in resistant strains)[9]. Cows have varying genetic susceptibilities to *Boophilus* tick bite that may be mediated by induction of inflammation (via leukocyte adhesion modulated by ICAM-1, VCAM-1 and P-selectin)[10]. Downregulation of host immunity via regulatory dendritic cells in murine bone marrow[11] and bovine leucocyte recruitment (eosinophils, basophils) have been reported[12]. Cows resistant to tick bite express more E-selectin[12] and downregulate genes encoding production of volatile compounds that attract tick larvae[13].

Local reactions

These can have an erythaematous, nodular, pustular or plaque-like appearance[14]. Local reactions are minimised by immediate removal of the tick[14] with symptomatic treatment (i.e. anti-histamines or corticosteroids).

Gauci divided allergic reactions to *I. holocyclus* into six classes using skin-prick tests and radioimmunoassay (RIA). All systemic hypersensitivity (class 3) and atypical reactions (class 4) were IgE-mediated. 73% of the large local reactions (class 2) and only 12.5% of the small local reactions (class 1) were associated with IgE specific for tick allergens. Heavy exposure to tick-bite was associated with positive RIA values. There was an association between atopic status and tick allergy[15].

Biopsies of tick bites in humans demonstrate deep perivascular and interstitial infiltrates of lymphocytes, neutrophils and eosinophils. Late biopsies show vascular eosinophilic hyaline thrombi which can mimic Type 1 cryoglobulinaemia[16]. Retention of tick mouth parts may drive this inflammatory reaction[17]. Other local reactions include foreign body granuloma, tick bite alopecia (may be scarring or non-scarring[14]), intermediate cell histiocytosis and cutaneous lymphoid hyperplasia[18]. Chronic papular urticaria due to *A. reflexus* has been reported[19].

The local immune response to early tick bite lesions in humans (predominance of macrophages and dendritic cells with elevated mRNA for macrophage and neutrophil chemoattractants as well as IL-1β and IL-5) differs from those with longer tick attachment times (increased lymphocytes and decreased macrophages and neutrophils)[20]. Antibodies directed against components of tick saliva can be detected in humans and used to determine the epidemiology of specific tick activity in certain regions[21].

Systemic syndromes

These include headache (10.8%), fever (5.4%), lymphadenitis (5.9%) and arthralgia (4.3%)[6]. No *in-vivo* physiological studies in humans with systemic symptoms induced by tick bite exist, but systemic toxicosis was demonstrated in an animal model[22]. After *Ornithodoros* ticks fed on rats, hyperaemia of oral mucosa and ocular mucosa, pilo-erection, tachypnoea, ocular and nasal discharge was observed in association with local haemorrhagic lesions. Increased bleeding times, eosinophilia and basophilia, raised creatinine kinase (total and MB) and LDH were noted. Myocardial myocyte degeneration and necrosis was also documented.

In-vitro studies of blood collected from humans previously bitten by ticks, when stimulated with *Ixodes* antigens, was shown to induce basophilia[23].

Symptomatic treatment with anti-histamines or corticosteroids are usually sufficient for this syndrome.

Tick paralysis (TP)

Tick paralysis is caused by several neurotoxins that vary according to tick species and (therefore) region of the world[24]. The best characterised is a 5 kDa protein contained in the saliva of gravid females that interferes with acetyl choline release[25]. Bancroft described the first human case of tick toxicosis in Australia in 1888[14]. TP can be induced by 69 tick species worldwide but Ixodes ticks (*I. holocyclus* or *I. cornuatus*) are usually implicated in Australia[26] and *Dermacentor* (*D. andersoni* and *D. variabilis)* in North America[24]. Widespread reports of TP have subsequently come from Spain, Turkey, Egypt, Ethiopia, Thailand, and Argentina[24]. Cases acquired in Australia but presenting elsewhere have been reported[24], and may delay the diagnosis. Aside from humans, dogs and cats are the most commonly affected animals but sheep, cattle, goats, pigs and horses may also be involved.

Tick attachment sites are predominantly on the head in the US but vary in different regions. Ectopic sites (such as intra-aural[26]) are often associated with delayed diagnosis. Most US cases occur in young girls (possibly due to long hair obscuring the attached tick) but adults are also affected. A flu-like prodrome followed by development of weakness, ascending symmetrical paralysis, ataxia, dilated pupils, slurred speech and depressed deep tendon reflexes is described. Laboured breathing, bradycardia and asystole may develop requiring supportive care. Myocarditis, diplopia and facial palsy may also occur. The duration of illness is very short in American cases after tick removal but is often longer in Australian cases[26]. The differential diagnosis includes Guillain–Barre syndrome, spinal cord lesions, myaesthaenia gravis, botulism, poliomyelitis, organophosphate or heavy metal poisoning and diphtheria. Rapid recognition enables prompt tick removal and avoids inappropriate therapy such as plasmaphoresis[26].

Treatment requires immediate removal of the tick, which may be associated with temporary worsening of the paralysis. In order to not facilitate envenomation, the tick must be killed before removal, which is most readily achieved by freezing with ether-containing agents (i.e. Wart-Off, Tick-Off)[15]. The tick may be removed with narrow forceps applied as close to the skin as possible (which is the most common method used in the USA)[26].

Tick anaphylaxis (TA)

This may due to a direct IgE–mediated reaction against components of tick saliva, or an indirect IgE reaction against galactose-α-1,3-galactose (α-gal, a saccharide found in all non-primate mammalian cells, but not in humans[15]) injected by the tick. It was first reported in Australia in 1940[27] and has since been recognised overseas after *Ixodes*[15] *Rhipicephalus*[28] and *A. reflexus* (in 8%)[29] tick bites.

Management includes prevention with vector avoidance (i.e. application of diethyltoluamide (DEET) to skin, permethrin impregnation of clothes, tucking trousers into socks and daily tick checks), immediate removal of the tick, anti-histamines and corticosteroids and adrenaline for severe cases.

Mammalian meat allergy (MMA)

Red meat allergy triggered by tick bite was first recognised in Sydney in 2007[15] when 25 cases related to *I. holocyclus* bites were reported. Subsequent cases were recognised in eastern Australia and Costa Rica, South-east USA, France, Spain, Germany, Switzerland, Sweden, Italy, Korea, Japan, and China[20]. Aside from *I. holocyclus* and *I. cornuatus*, ticks triggering these events have included *A. americanum*, *I. ricinus* and *H. longicornis*. The author's laboratory recently diagnosed a case of MMA that

was acquired in the Kimberley region, demonstrating that this condition is also found west of the Nullabor Plain. Another subsequent case in WA, possibly related to *I. australiensis* has confirmed this observation[15].

In 2009, delayed anaphylaxis triggered by consumption of mammalian meat was found to be associated with the presence of α-gal-specific IgE antibodies[15] and it was noted that >80% of these patients had a history of tick bite. Subsequently α-gal IgE antibodies were prospectively shown to develop in response to tick bite. α-gal has now been definitively identified in the gastrointestinal tract of *I. ricinus*[15] completing the pathogenetic puzzle. These reactions have been described after eating beef, lamb and pork[15]. Anaphylaxis has also occurred after eating kangaroo meat, but the patient's tick bite status was not known[30]. As well as meat, cetuximab (a mouse-human chimeric antibody)[15], gelatine[15] or milk products can also trigger MMA.

Clinical manifestations, including a delay of 3–6 hours after oral exposure, can range from gastrointestinal upset to angioedema and frank anaphylaxis[15]. Skin prick testing (SPT) typically gives weak reactions (<5 mm) to commercial preparations of mammalian meats but stronger reactions with fresh meat extracts. Patients always have elevated specific IgE levels (>1.0 IU/mL) to the relevant meat, cow's milk, cat and dog reagents as well as to α -gal. SPT and specific IgE levels are always negative to poultry or fish reagents. Management of MMA revolves around avoidance of meat and tick exposures with ready availability of adrenaline (i.e. Epi-Pen) for severe reactions[15].

Australian Multisystem Disorder (AMD)/ 'Debilitating Symptom Complexes Attributed to Ticks' (DSCATT)

Recently a number of Australians have become convinced that a protean illness, which may or may not be associated with tick bite, is a manifestation of locally acquired Lyme Disease (cited in Boyle *et al*.[31]). Enquiries by the Chief Health Officer (cited in Boyle *et al*.[31]) and both houses of Parliament (cited in Boyle *et al*.[31]) were unable to identify convincing proof of this concept. I have proposed that a non-controversial name for the syndrome, 'Australian Multisystem Disorder', should be adopted[32]. The Australian Senate has counter-proposed with the title 'Debilitating Symptom Complexes Attributed to Ticks'[33].

Appropriate management of this syndrome relies on development of adequate research funding to identify the aetiology and efficacious protocols.

Conclusion

Non-infective complications of tick bites are common and may have potentially fatal consequences. Prevention of tick bites is crucial and prompt removal of ticks will limit their adverse effects.

Conflicts of interest

The author declares no conflicts of interest.

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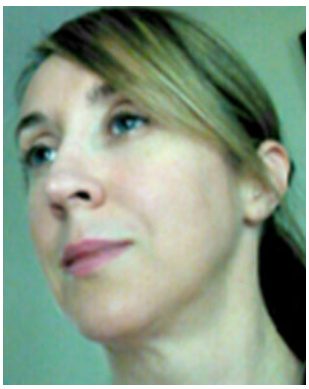
Biography

Professor Beaman graduated from the University of Western Australia and trained in Clinical Microbiology and Infectious Diseases at Sir Charles Gairdner Hospital. He completed a Post Doctoral Fellowship at Stanford University under Professor Remington and then established the first Infectious Diseases Department in Western Australia at Fremantle Hospital. He joined Western Diagnostic Pathology in 2002, where he was Medical Director and Deputy CEO until recently. He is currently an Infectious Diseases specialist at Joondalup Health Campus in Perth.

Bovine theileriosis in Australia: a decade of disease



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Theileriosis refers to the clinical disease caused by organisms from the genus *Theileria*, tick-borne haemoprotozoans infecting a diverse range of mammalian hosts. In Australia, *Theileria* spp. have been identified in both domestic and wildlife species but the bovine parasite, *Theileria orientalis*, has received the most attention due to the emergence and spread of clinical disease over the past 12 years, particularly in cattle herds on the east coast. At an estimated $20 million per annum, the burden to cattle production is significant but despite over a decade of disease, there are still no effective chemotherapeutic treatments or vaccines available in Australia. Recent insights from genome sequencing studies reveal species level diversity within *T. orientalis*, which may help direct efforts at disease control.

Clinical presentation

Theileria orientalis is an apicomplexan parasite that requires both a bovine and a tick host in order to complete its lifecycle (Figure 1).