

Eosinophilic meningitis: cause of a chronic pain syndrome

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Abstract

Three tourists developed eosinophilic meningitis after visiting the Fijian Islands. Two had a severe and long lasting illness with chronic intractable pain. In one patient electrophysiological studies and MRI scan of the brain were abnormal and provided evidence of both radicular and cerebral parenchymal involvement by the most likely causative agent, *Angiostrongylus cantonensis*.

By 1965 eosinophilic meningitis was well recognised as occurring on many Pacific Island groups.¹ The disease characteristically follows a self limiting course lasting several weeks with headache, meningism, and cerebrospinal fluid eosinophilia. In addition, an acute sensory disturbance, fever and cranial neuropathy may be present.²⁻⁴ Recent reports have described a more severe illness with delirium, limb weakness and occasional fatality.⁵⁻⁷ The only causative agent described in the Pacific in such cases has been the rat lung worm *Angiostrongylus cantonensis*. Infection by this agent is usually acquired by the consumption of poorly cooked snails, freshwater prawns and, rarely, unwashed lettuce.^{2,8} The fully mature nematodes live in rat pulmonary arteries. Snails eat rat faeces containing the first stage larvae. Not only rats but other hosts such as crabs, frogs or freshwater prawns ingest the snails or slugs which carry the immature larvae.

Following human ingestion larvae migrate to the central nervous system where they are unable to complete their life cycle and the larvae die.⁹ The human disease is caused by both the effects of larval migration and the inflammatory reaction that occurs when larvae die in the nervous system.^{10,11} Neither corticosteroids nor antihelminthics have been of any benefit in alleviating this illness.²

Three patients who developed eosinophilic meningitis after visiting the Fijian Islands are described. Two had a severe form of the illness.

Case reports

CASE ONE

A 44 year old woman became ill on 15 September 1987, three days after returning to Australia from a week's holiday in Fiji. During her stay the patient recalled eating a meal of snails and prawns. The initial symptoms were malaise, anorexia, abdominal discomfort

and lower limb myalgia. Several days later she developed a left lower motor neuron facial palsy which was treated with a two week course of prednisone. A CT scan performed on 21 September 1987 was normal. On the 8 October 1987 the patient was admitted to Concord Hospital, Sydney, complaining of persistent lower limb myalgia, abdominal pain and nausea. For the preceding three days she had been vague and slightly confused. She was afebrile and normotensive. She perseverated and was unable to write a sentence or perform a constructional task adequately.

Examination demonstrated left lower motor neuron facial palsy but no other abnormal neurological sign. Full blood count, eosinophil count, chest radiograph electrolytes and creatinine were normal. Liver transaminases were elevated, AST 43 U/L and gamma glutamyl transferase 53 U/L. An EEG demonstrated temporal slow wave activity more prominent on the left with several left temporal sharp waves. A lumbar puncture was recommended but the patient refused and discharged herself.

On 28 October 1987 the patient complained of ten days of headache, horizontal diplopia for one week and persistent trunk and limb paraesthesiae. Mental state assessment was normal. Neurological examination showed bilateral abducens palsies, left papilloedema, slight neck stiffness and minor right arm weakness. The previous left facial weakness had resolved. Her right arm weakness involved intrinsic muscles of the hand, extensor digitorum communis, extensor carpi radialis and the triceps. The right triceps and supinator jerks were reduced. Sensation to pin, temperature and light touch were normal even in areas where the patient experienced paraesthesiae. Proprioception was intact. An LP showed turbid cerebrospinal fluid (CSF) with a pressure of greater than 30 cm H₂O. CSF protein was 0.7 g/l and CSF glucose 1.8 mmol/l (serum glucose 4.5 mmol/l). CSF cell count was 509 white cells/mm³ and cytological examination showed 82% lymphocytes, 13% eosinophils, 4% plasma cells and 1% basophils consistent with eosinophilic meningitis. Visual and brainstem auditory evoked responses and a cerebral CT scan were all normal.

An MRI scan of the brain was obtained two months after the onset of the illness and showed multiple discrete white matter lesions in both cerebral hemispheres and the cerebellum (fig). No ova, cysts or parasites were seen on stool examination. Nerve conduction studies of the right median, ulnar and radial nerves were normal. Electromyography

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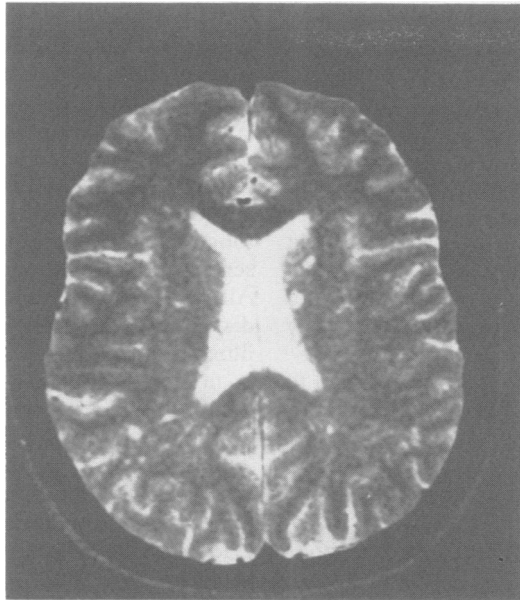
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Figure MRI scan in Case 2 illustrating multiple areas of high signal in the white matter (T2 weighted Image).



(EMG) provided evidence of denervation with profuse fibrillation and reduced recruitment in right first dorsal interosseous, extensor carpi radialis and triceps muscles. Upper limb ulnar nerve somatosensory evoked potential study showed absence of Erb's (N9) cervicomedullary (N13) and thalamocortical (N/P 19) potentials on the left. Right ulnar nerve somatosensory evoked potential demonstrated an absent Erb's point potential and cervicomedullary and thalamocortical potentials were normal in latency with low amplitudes. Serum was collected at two and three months of the illness for enzyme linked immunosorbent assay (ELISA) for *Angiostrongylus cantonensis*. Both showed an antibody ratio of 2:1 relative to a negative control while a concurrently tested positive control showed a ratio of 4:1. This result was inconclusive.

During the next three months the patient's sixth nerve palsies and papilloedema slowly resolved. Her right arm weakness has persisted and she continues to be troubled by persistent painful parasthesiae involving the trunk and left leg. At times the sensory disturbance is radicular in character with bandlike or vicelike sensations around the trunk. Trials of paracetamol, codeine phosphate and clonazepam gave no relief. She now requires amitriptyline 100 mg daily for partial pain relief and continues to experience chronic leg and trunk pain twenty months after her acute illness.

CASE 2

In June 1984, two weeks after returning from a holiday in Fiji, a 54 year old man developed right sided low back pain radiating to the right groin. Over the next few days the pain progressed to affect the left forearm and leg. He was troubled by headache, malaise and had difficulty in concentrating. Pain involving the toes and inner aspect of the left leg was sufficiently severe to require admission to hospital for narcotic analgesia.

Neurological examination in July 1984

showed an absent left knee jerk and patchy sensory loss to pin and light touch over the anterior aspect of the left leg. Investigations including full blood count, serum electrolytes and liver function tests, viral titres and cerebral CT scan were normal. Lumbar puncture demonstrated elevated CSF protein 1.14 g/l, normal CSF glucose and 405 white cells/ m^3 , 58% lymphocytes, 12% monocytes and 27% eosinophils consistent with eosinophilic meningitis. CSF cryptococcal antigen, VDRL and culture for bacteria, fungi and AFBs were negative. Eosinophilic meningitis with characteristic sensory disturbance acquired in Fiji was assumed to be due to *A cantonensis*. Serum ELISA tests for antibodies to *A cantonensis* performed at two different laboratories gave conflicting results with significant and non-significant titres reported.

Over the next six months the patient continued to be troubled by pain over the lateral aspect of the left thigh and both sides of the left calf. The skin of the left leg was sensitive to touch. In addition hyperalgesia with patchy sensory loss to pin and light touch over the dorsal forearm, and left index and middle fingers remained. Serial lumbar puncture showed progressive resolution of the CSF abnormalities. Nerve conduction studies, EMG, posterior tibial and median nerve somatosensory evoked potentials performed at six months were normal. In February 1985, following an acute exacerbation of left leg pain a lumbar myelogram was performed and was normal. MRI scans of the brain and lumbar spine performed during 1987 were normal.

Various combinations of non-narcotic analgesics, benzodiazepines, antihistamines, tricyclic antidepressants and thioridazine have failed to control residual dysaesthesia and pain over the left forearm and left leg. A two week trial of high dose prednisone and a trial of transcutaneous electrical stimulation gave no benefit. During 1987 nerve blocks were performed on both the left femoral nerve and left lateral cutaneous nerve of the thigh. The femoral block produced minor relief of his thigh pain. An epidural corticosteroid injection at the L4 level resulted in no alleviation of pain. A trial of clonazepam precipitated an episode of acute depression. A programme of tricyclic antidepressant therapy has provided partial symptom relief.

CASE THREE

A thirty year old yachtsman presented to Dunedin Hospital, New Zealand on 23 January 1984 after a two month illness. In November 1983 while in Fiji the patient ate freshwater prawns from the Sikatoka river. Several days later he developed fatigue, shooting pains in the head, neck and legs as well as cramping abdominal pain. He was confined to bed for three weeks with leg weakness and paraesthesiae, tinnitus and abdominal pain. Full blood count showed eosinophilia with white cell count 9,600/ mm^3 with 53% neutrophils, 29% lymphocytes and 17% eosinophils.

By mid December 1983 the patient's symptoms had improved but he continued to

experience leg weakness, dysaesthesiae and horizontal diplopia. Liver enzymes, urea, creatinine, electrolytes and chest radiographs were normal. However, eosinophil count on 22/12/83 remained elevated at 1920 cells/mm³. The patient was able to leave Fiji in January 1984 but remained troubled by both upper and lower limb pain. Throughout his illness there was no fever or meningism. On examination at Dunedin Hospital, two months after the onset of the illness, the patient's neurological and general physical examination were entirely normal.

The blood eosinophil count had returned to normal. A lumbar puncture performed on 24/1/84 showed normal CSF pressure, glucose 3.3 mmol/l (serum glucose 5.9 mmol/l) and protein 0.75 g/l. The CSF cell count was 15 red cells/mm³ and 98 white cells/mm³ with 59% lymphocytes, 36% neutrophils and 5% eosinophils.

CSF culture for bacteria, fungi and protozoa was negative. Stool examination for cysts, ova and parasites was negative. The clinical history, blood and CSF eosinophilia were consistent with eosinophilic meningitis. As the disorder was acquired in Fiji the probable cause for eosinophilic meningitis was *A. cantonensis*. The illness was self limiting and no further treatment was required.

Discussion

Several parasites including *A. cantonensis*, *Gnathostoma spinigerum*, *Paragonimus westermani* and the cysticerci of *Taenia solium* (cysticercosis) have been described from various parts of the world as causing a neurological illness with CSF eosinophilia.¹² Both clinical and necropsy evidence suggests *A. cantonensis* as the likely cause of eosinophilic meningitis in the Pacific Islands. Diagnosis is difficult as the organism is rarely isolated from the CSF during life and a presumptive diagnosis is usually made on the basis of appropriate clinical criteria combined with CSF eosinophilia.^{2,3} The introduction of serological testing for *A. cantonensis* has provided further indirect evidence of its role in the aetiology of eosinophilic meningitis in the Pacific.^{6,13}

The spread of the illness throughout the Pacific Islands may be related to the migration of rats via inter-island shipping as well as the introduction by the Japanese during World War II of the giant African land snail, *Achatina fulica*, which carries large numbers of the nematode. An extensive epidemiological survey of Pacific Island rats in 1963 failed to find any evidence of *A. cantonensis* on several Pacific Islands including Viti Levu, in the Fijian Islands group, despite large numbers of rats carrying *A. cantonensis* on other island groups.¹ The subsequent occurrence of eosinophilic meningitis in the Fijian islands provides further evidence of its spread.¹⁴ Our three patients highlight the dangers posed to tourists to Fiji of eating poorly cooked snails, shellfish, and unwashed salad vegetables.

Eosinophilic meningitis may result in a persistent pain syndrome. All three patients were

initially troubled by a sensory disturbance that is reported by up to 54% of patients in the acute stage of the illness as an ill-defined, evanescent pain or paraesthesiae involving the limbs and trunk. This disturbance may not be clearly dermatomal in distribution, often only involving small areas of skin. Hyperaesthesia may be very marked and extreme sensitivity to light touch may be present. Despite this, formal sensory testing in many patients is normal.^{2,3} Although some authors have noted that this disturbance may not resolve with the rest of the illness, the longterm evolution of the syndrome is not well documented.² Patients 1 and 2 illustrate that the condition can induce pain that is severe, prolonged and difficult to treat. The evanescent and often localised nature of the sensory disturbance, the presence of hyporeflexia, and animal and human necropsy evidence suggest that the sensory disturbance is primarily due to spinal nerve root involvement.^{2,6} EMG and somatosensory evoked potentials performed during the acute phase of the first patient's illness showed segmental acute denervation and ulnar nerve somatosensory evoked potential findings of absent Erb's potentials confirmed spinal nerve root involvement.

Patient 1 provides the first neurophysiological evidence for radicular damage in eosinophilic meningitis. The chronic pain in patients 1 and 2 may be related to residual periradicular granuloma formation following the death of the nematode. Because of the nature of the sensory disturbance and the presence of lower motor neuron signs a thalamic origin for the pain appears unlikely.

All three patients satisfied the clinical criteria for eosinophilic meningitis caused by *A. cantonensis* as described by Punyagupta *et al*, and yet in the two patients in whom Enzyme-Linked Immunosorbent Assay (ELISA) testing was performed the results were inconclusive.² ELISA is the most recent and promising test for angiostrongyliasis. Like all serological tests the results only add to the presumptive diagnosis.^{15,16} A recent Taiwanese study of ELISA in eosinophilic meningitis reported a high sensitivity but further series reflecting the usefulness of ELISA testing are awaited.¹⁶ In two reports the lowest titres on ELISA testing in presumed cases of *A. cantonensis* related eosinophilic meningitis have been in patients with more severe symptoms and signs. It is suggested that a sufficiently large antigen load may reduce levels of circulating free antibody.^{6,13} A test for the antigen would provide a more definite diagnosis.

Radiological abnormalities in eosinophilic meningitis have rarely been described. Ko *et al* in two separate reports outlined five patients in whom lesions were visible on cerebral CT scan during an episode of eosinophilic meningitis caused by *A. cantonensis*.^{17,18} The size and location of the lesions varied and probably relate to the number and movement of the worms involved. One of their patients was followed with serial scans and the lesions resolved fifty nine days after the onset of the illness. CT scan was unhelpful in patients 1 and

2 but in patient 1, in whom MRI scanning was performed during the acute phase of the illness, MRI showed multiple abnormal areas on T₁ and T₂ images. The greater anatomical resolution of MRI may help in detecting lesions during the acute phase of the illness.

- 1 Wallace GD, Rosen L. Studies on eosinophilic meningitis: (1) Observations on the geographic distribution of *angiostrongylus cantonensis* in the Pacific Area and Its Prevalence in Wild Rats. *Am J Epidemiol* 1965;81:52-61.
- 2 Punyagupta S, Jutlijdata P, Bunnag T. Eosinophilic meningitis in Thailand: clinical studies of 484 typical cases probably caused by *Angiostrongylus cantonensis*. *Am J Trop Med Hyg* 1975;24:921-31.
- 3 Kuberski MD, Wallace GD. Clinical Manifestations of Eosinophilic Meningitis due to *Angiostrongylus cantonensis*. *Neurology* 1979;29:1566-70.
- 4 Yii CY. Eosinophilic meningitis and meningoencephalitis caused by *Angiostrongylus cantonensis* on Taiwan. *Am J Trop Med Hyg* 1976;25:233-49.
- 5 Reid JR, Wallis WE. The chronic and severe forms of eosinophilic meningitis. *Aust NZ J Med* 1984;14:163-5.
- 6 Kliks MM, Kroenke K, Hareman JM. Eosinophilic radiculomyeloencephalitis: an angiostrongyliasis outbreak in American Samoa. *Am J Trop Med Hyg* 1982;31:1114-22.
- 7 Bowden DK. Eosinophilic meningitis in the New Hebrides: two outbreaks and two deaths. *Am J Trop Med Hyg* 1981;30:1141-3.
- 8 Rosen L, Loison G, Louigret J, Wallace GD. Studies on eosinophilic meningitis (3). Epidemiological and clinical observations on Pacific Islands and the possible etiologic role of *Angiostrongylus Cantonensis*. *Am J Epidemiol* 1967;85:14-7.
- 9 Scrimgeour EM. Angiostrongyliasis in Port Moresby, Papua New Guinea. *Aust NZ J Med* 1983;13:644-6.
- 10 Tanchai P, Nye SW, Beaver PC. Eosinophilic meningoencephalitis is caused by angiostrongyliasis in Thailand. Autopsy report. *Am J Trop Med Hyg* 1967;16:454-61.
- 11 Nye SW, Tanchai P, Punyagupta S. Lesions of the brain in eosinophilic meningitis. *Arch Pathol* 1970;89:9-19.
- 12 Jaroonvesama N. Differential diagnosis of eosinophilic meningitis. *Parasitology Today* 1988;4:262-6.
- 13 Beck MJ, Cardina TM, Alicata JE. Eosinophilic meningitis due to *Angiostrongylus cantonensis* in American Samoa. *Hawaii Med J* 1980;39:254-7.
- 14 Welch JS, Dobson C, Campbell GR. Immunodiagnosis and seroepidemiology of *Angiostrongylus Cantonensis* in man. *Trans Soc Trop Med Hyg* 1980;74:614-23.
- 15 Chen SN. Enzyme-linked Immunosorbent Assay (ELISA) for the detection of antibodies to *Angiostrongylus cantonensis*. *Trans R Soc Trop Med Hyg* 1986;80:398-405.
- 16 Jaroonvesama N, Charoenlapp K, Buranasin P, Zaraspe GG, Cross JH. ELISA testing in cases of clinical angiostrongylis in Thailand. *Southeast Asian J Trop Med Pub Hlth* 1985;16:110-3.
- 17 Ko RC, Chiu MC, Kum W, Chan SH. First report of human angiostrongyliasis in Hong Kong diagnosed by computerised axial tomography and enzyme-linked immunoassay. *Trans R Soc Trop Med Hyg* 1984;78:354-5.
- 18 Ko RC, Chan SW, Chan KW, et al. Four documented cases of eosinophilic meningoencephalitis due to *Angiostrongylus cantonensis* in Hong Kong. *Trans R Soc Trop Med Hyg* 1987;81:807-10.