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Neurologic Melioidosis

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Abstract. Melioidosis is an important cause of morbidity and mortality in northern Australia and Southeast Asia. Diagnosis is best made by isolation of *Burkholderia pseudomallei* from clinical specimens. A variety of clinical presentations are described, including neurologic disease. The aim of this study was to review admissions with confirmed neurologic melioidosis to a regional hospital in a region to which melioidosis is endemic during 1995–2011. There were 12 culture-confirmed cases of neurologic melioidosis, of which two were detected by analysis of cerebrospinal fluid. Four of these cases were in children. Significant clinical features were fever, headache, and ataxia. Common changes on magnetic resonance imaging T2-weighted scans included ring-enhancing lesions and leptomeningeal enhancement. There were four deaths and an additional four patients had significant long-term neurologic sequelae. When considering the etiology of undifferentiated neurologic disease, an awareness of the possibility of neurologic melioidosis is important in disease-endemic regions.

INTRODUCTION

Burkholderia pseudomallei is a gram-negative, facultative, soil saprophyte responsible for the disease melioidosis. Melioidosis is contracted by inoculated soil and water through wounds or inhalation and is particularly common during and after the wet season.[1] The disease is endemic to areas of southeast Asia, northern Queensland, and the Northern Territory of Australia. There is also increasing evidence that melioidosis may be endemic to the Indian subcontinent and Caribbean.[2,3] Melioidosis has a wide range of clinical presentations, including pulmonary and genitourinary infection, bone and soft tissue infection, severe sepsis, and neurologic complications.[4] Although comprising approximately 4% of all cases of melioidosis, neurologic melioidosis is of significant importance because it has a mortality rate of approximately 25% and survivors have significant morbidity.[5] Neurologic melioidosis has varying presentations that include symptoms mimicking Guillain-Barré syndrome, limb weakness, and cranial nerve palsies.[5]

MATERIALS AND METHODS

This report is a retrospective chart review of all patients admitted to the Townsville Hospital in Townsville, Queensland, Australia during 1995–2011 that had a diagnosis of culture-confirmed neurologic melioidosis. A total of 12 patients were identified; however, records for only 10 patients were available for review. Limited data were available for the remaining two patients. Ethical approval for the study was obtained through the Townsville Health Service District Human Research Ethics Committee. Specific clinical data extracted from the case records included demographics, risk factors, clinical presentation, investigations, treatment, and outcomes.

RESULTS

A total of twelve patients were identified. This represented 5.7% (12 of 211) of all patients with culture-confirmed disease seen in the region over this period. Patients ranged in age from 6 to 69 years (Table 1). Of these patients, four (33%) were children (age range = 6–14 years). Children (age range = 4–16 years) represented 4.7% (10 of 211) of all culture-positive patients with melioidosis during this period. Sex groups were equally represented (six patients of each sex). Four patients were Aboriginal or Torres Strait Islander. Five patients (Table 1) had no identifiable risk factors (diabetes, immunosuppression, high alcohol use, thalassemia, or exposure-prone activity). Two patients had diabetes and were receiving immunosuppressive therapy. Two patients had definitive wet soil contact and two had excessive alcohol use. Two patients had exposure-prone activity as outdoor workers. One patient had recently completed a home renovation. Eighty percent of cases occurred during the wet season (November–April).

Ninety percent of patients with neurologic melioidosis had a fever > 38°C. Most patients (70%) had a normal Glasgow Coma scale score and of the remaining patients two had a score of 14 and one had a score of 10 on presentation. Other vital signs were generally within normal limits. Of the presenting features (Table 2), headache was present in 70% of patients. Neck stiffness was detected in two patients at admission. Photophobia was present in 40% of patients. Fifty percent of patients had an ataxic gait. On presentation, lower limb power was reduced in three patients and abnormal sensation was observed in two patients.

Initial brain computed tomography (CT) was performed for four patients, and two showed evidence of neurologic disease. Of the two patients with initial normal brain CT scan results, all showed abnormalities on subsequent magnetic resonance imaging (MRI). Spinal CT was performed for two of three patients who had features suggestive of spinal disease. One patient (case 7) had a minor disc bulge and another patient (case 3) had a paraspinal collection. Spinal MRI abnormalities included transverse myelitis (case 7), ring-enhancing lesions (case 2), and an extradural collection (case 3).

Cerebrospinal fluid (CSF) analysis (Table 3) was performed for seven patients, and post-mortem CSF screening was performed for one patient (case 1). Glucose levels were within normal limits for all patients except one who had a reduced glucose level (case 8). All patients except two (cases 6 and 9) had elevated protein levels. All leukocyte counts except one

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TABLE 1

Demographics and risk factors of 12 patients admitted to Townsville Hospital, Townsville, Queensland, Australia with confirmed neurologic melioidosis*

Patient	Age, years	Sex	Location	Season	Risk factors	Isolation site	Outcome
1	37	M	Rural	Dry	Outdoor occupation	Tissue†	Death
2	23	F‡	Rural	Wet	None	Blood	Neurologic impairment
3	43	F‡	Rural	Wet	Diabetes	Epidural abscess	Full recovery
4	69	F	Rural	Wet	Diabetes	Tissue†	Death
5	12	F	Rural	Dry	Contact with sewage	CSF	Neurologic impairment
6	56	M	Urban	Wet	None	Respiratory aspirate	Death
7	41	M	Rural	Wet	Alcohol use, outdoor occupation	Respiratory aspirate	Death
8	62	F	Urban	Wet	Recent home renovation	CSF	Full recovery
9	43	M	Urban	Wet	Alcohol use, waterlogged soil contact	Blood	Neurologic impairment
10	14	F‡	Urban	Wet	None	Brain tissue	Neurologic impairment
11	6	M	Urban	Wet	None	Brain tissue†	Death
12	8	M‡	Rural	Wet	None	Blood	Death

*CSF = cerebrospinal fluid.
†Post-mortem sample.
‡Aboriginal or Torres Strait Islander.

(case 9) were elevated (range = 2–1,750 cells/mm^3). Mononuclear cells predominated in all except two patients (cases 5 and 8). Two CSF cultures were positive for *Burkholderia pseudomallei* (cases 5 and 8).

Positive cultures for *B. pseudomallei* were found for all 12 patients, two of which were obtained post-mortem. Of the remaining 10 patients, the time from admission to positive culture results ranged from 0 to 15 days (median = 4 days). In our case series, lung (1 of 1) and prostate (1 of 1) biopsy specimens, brain swab specimens (1 of 1) and pus (2 of 2) culture showed 100% sensitivity. Half of pleural fluid (1 of 2) and brain biopsy (1 of 2) samples were culture positive. Approximately 20% of blood (9 of 46), CSF (2 of 9), and sputum and respiratory aspirate (7 of 34) cultures were positive. Faeces (0 of 9), urine (0 of 31), and catheter tip (0 of 8) samples and eye (0 of 2) and vaginal (0 of 1) swab specimens were culture negative. Lung and prostate biopsies were performed post-mortem. Faecal samples were cultured for only three patients. Urine and respiratory samples of eight patients were cultured. Catheter tip samples of seven patients were cultured. These results should be interpreted with caution because of the small sample size and repeated use of individual tests in limited numbers of patients.

Serologic testing was performed for 10 patients. Positive indirect hemagglutination assay (IHA) results at initial testing were reported on day 1 (case 3, titer = 1: 640), day 5 (case 6, titer = 1:320), and day 17 (case 9, titer = 1:640). The IHA result was negative for three patients (cases 1, 4, and 5), who had titers ≤ 1:10. Two patients (cases 8 and 10) initially showed negative results but showed positive results after retesting and titers of 1:640 (case 8) and 1:320 (case 10). Borderline IHA results were observed for two patients (cases 2 and 7).

Appropriate inpatient intravenous antibiotic therapy included meropenem, imipenem, co-trimoxazole, and ceftazidime. Delay from presentation to appropriate antibiotic therapy ranged from one to six days. The median delay was 2 days. For six of ten patients, appropriate antibiotic therapy was begun before positive cultures for *B. pseudomallei* were obtained.

Two patients fully recovered and did not have long-term sequelae. Six patients died during their hospitalization. Four patients had significant long-term neurologic sequelae, including ataxia, and coordination and sensory deficits.

DISCUSSION

Risk factors for melioidosis are widely documented and include diabetes mellitus, alcoholism, renal disease, immunosuppression, and thalassemia.[6] Persons with these characteristics may be particularly susceptible because of a poor ability to develop a cell-mediated immune response secondary to these conditions, which causes poor neutrophil function.[7–10] However, neurologic melioidosis appears to have a different risk factor profile. Currie and others reported that patients with neurologic melioidosis were younger (mean age = 38 years), male, and more likely to be Aboriginal.[11] Consistent with these results, in our series eight patients were previously healthy without chronic disease or immunosuppression, and our mean patient age was 35 years. In contrast, 50% of patients were female and 67% were non-Indigenous. Although the numbers are small, children were overrepresented; 33% (4 patients) of all cases of neurologic melioidosis were in children, even though children accounted for only 4.7% of all culture-confirmed cases of melioidosis. The consumption of kava has been identified as an independent risk factor for neurologic melioidosis but this finding was not documented in our case series.[11]

In our series, half of initial CT scans performed did not show evidence of neurologic disease. This finding is consistent with previous results, which showed a lack of sensitivity of CT scanning in identifying neurologic melioidosis, particularly in initial stages of the disease.[11] In a case review of neurologic melioidosis by Currie and others, 8 of 11 initial CT scans showed normal results and in the remaining patients, only non-specific CT changes were observed. In the same study, MRI demonstrated abnormalities for all 9 scans performed.[11] Classical MRI signs of neurologic melioidosis include calvarial osteomyelitis, leptomeningeal enhancement, ring-enhancing lesions, edema, abscesses, and a predilection for brainstem involvement. In our series (Table 2), seven patients had ring-enhancing lesions and two had leptomeningeal enhancement. Overall, five patients had brainstem involvement.

Chadwick and others reviewed five patients with neurologic melioidosis and reported that four patients had sinusitis on CT, suggesting a possible causal link between sinusitis and neurologic melioidosis.[5] Sinusitis was not noted on any imaging

TABLE 2

Clinical presentation, radiologic findings, and daily antibiotic dosing for 10 patients admitted to Townsville Hospital, Townsville, Queensland, Australia with confirmed neurologic melioidosis*

Patient	Clinical details	Radiologic findings	Antibiotic dosing
1	37-year-old man. Fever, headache photophobia, ataxia, expressive aphasia.	No imaging performed, died day of admission to tertiary hospital.	CTZ: 2 g (D_2)
2	23-year-old Indigenous woman. Post partum. Leg abscess developed and leg weakness and ataxia during admission.	MRI spine (D_1): T2 scan: 6 mm ring-enhancing lesion at T12 level and edema	CTZ: 6 g ($D_{1–13}$); STX: 800/160 mg ($D_{1–12}$); IMI: 2 g ($D_{14–19}$)
3	43-year-old Indigenous woman. Diabetes, receiving prednisolone, fevers, back pain, abnormal leg sensation. Ataxia developed.	CT abdomen and chest: fluid collection right apex, Hypodense right paraspinal collection. MRI spine: posterior extradural collection (loss of subarachnoid space T6–9).	CTZ: (NA) ($D_{1–8}$), 6 g ($D_{18–29}$); STX: 1.2 g/240 mg ($D_{18–29}$)
4	69-year-old woman. Diabetes, receiving dexamethasone, fever, headache, and flank/back pain.	CT brain: left posterior parietal and occipital poorly defined area of reduced density within the deep white matter with some mass effect.	MER: 3 g ($D_{3–4}$)
5	12-year-old girl. GCS = 10, fever, headache, photophobia, neck stiffness, chest pain, and vomiting. Developed ↓ right power, ↑ left-sided tone.	CT brain: NAD. MRI brain (D_6): extensive vasogenic edema of medulla and dorsal pons with extension to midbrain, posterior extension to cerebellar peduncles. Ring-enhancing lesions in right medulla and pons.	MER: 4 g ($D_{2–4}$), 6 g (D_5), 8 g ($D_{7–9}$); CTZ: 6 g ($D_{10–14}$); STX: 7.2 g/1.4 g ($D_{6–12}$)
6	56-year-old man. Headache, flaccid paralysis of right arm and right leg, ataxia, expressive dysphasia, and fever.	CT brain (NA): left fronto-temporal area of low density (white matter predominance) and mild mass effect. CT brain (D_4): ring-enhancing lesion in left parietal subcortical white matter with vasogenic edema. MRI brain (D_7): left fronto-parietal lesion involving brainstem and brainstem and cortical spinal tract ring-enhancing lesions. MRI brain (D_{20}): more ring-enhancing lesions and pial enhancement in the cerebral peduncles and cortical spinal tract.	MER: 6 g ($D_{5–9}$), 8 g ($D_{10–27}$)
7	41-year-old man. Fever, back and leg pain, leg weakness and ataxia. Respiratory failure (D_7).	CT lumbosacral (D_1): disc bulge L_5–S_1. MRI spine (D_1): ↑ signal from $C_{3/4}$ with cord expansion to the cauda equine, central posterior placed high signal area (T2), some ↑ signal post-gadolinium, and transverse myelitis. CT brain (D_9): white matter hypodensity around brain stem, left basal ganglia and left fronto-parietal region, edema and mass effect on left lateral and fourth ventricle consistent with demyelinating process. MRI brain and spine (D_9): ill-defined enhancement of corticospinal tracks and adjacent white matter (left > Right), dorsal brain stem involvement, and enhancing lesions of conus medullaris and spinal cord.	MER: 4 g ($D_{7–21}$)
8	62-year-old woman. Headache, photophobia, neck stiffness, back pain, fevers, nausea, vomiting, and diarrhea, ischemic heart disease, chronic airways disease.	CT head (D_1): NAD. MRI head (D_6): linear high signal in right high frontal sulcal space and right high frontal region focal leptomeningeal enhancement.	MER: 6 g ($D_{3–14}$); CTZ: 6 g ($D_{15–45}$); STX: 1.6 g/320 mg ($D_{13–45}$)
9	43-year-old man. Fevers, headache, leg weakness, dyspnea, altered leg sensation, epigastric pain radiating to back.	MRI brain (D_{30}): ring-enhancing lesion left superior parietal lobe, ventral brainstem leptomeningeal enhancement, and subtle signal abnormalities in perirolandic region.	MER: 3 g ($D_{6–32}$), 6 g ($D_{33–35}$); CTZ: 6 g ($D_{36–37}$); STX: 3.2 g/640 mg ($D_{15–21}$)
10	14-year-old Indigenous woman. Sore throat, fever, photophobia, headache, ataxia, diplopia, tonsillitis, broad- based gait, cranial nerve V, VII, IX–XII palsies (D_2).	MRI brain (D_{18}): areas of swelling and enhancement around cerebellum and medulla, and ring-enhancing and punctate lesions.	MER: 6 g ($D_{2–5}$), 8 g ($D_{6–56}$); STX: 1.6 g/320 mg ($D_{4–78}$), 800/160 mg ($D_{79–240}$)

*CTZ = ceftazidime;D = day; MRI = magnetic resonance imaging; STX = co-trimoxazole; IMI = imipenem; CT = computed tomography; NA = not available; MER = meropenem; GCS = Glasgow coma scale; ↓ = decreased; ↑ = increased; NAD = no abnormality detected.

TABLE 3

Cerebrospinal fluid analysis for 12 patients admitted to Townsville Hospital, Townville, Queensland, Australia with confirmed neurologic melioidosis

Patient	Glucose (mmol/L) reference range = 2.2–3.9 mmol/L	Protein (mg/L) reference range = 150–500 mg/L	Leukocyte count ($\times 10^6$ cells/L) reference < 5 $\times$ 10^6 cells/L	Mononuclear cells(%)	Culture result
1	Not tested	Not tested	Not tested	Not tested	Negative*
2	Not tested	Not tested	Not tested	Not tested	Not tested
3	Not tested	Not tested	Not tested	Not tested	Not tested
4	3	1,400	115	70	Negative
5	4	520	190	18	*Burkholderia pseudomallei*
6	3.8	480	15	99	Negative
7	3.2	1,900	25	90	Negative
8	1.8	930	1,750	20	*Burkholderia pseudomallei*
9	3.9	420	2	No data	Negative
10	2.5	910	150	86	Negative
11	Not tested	Not tested	Not tested	Not tested	Not tested
12	Not tested	Not tested	Not tested	Not tested	Not tested

*Post-mortem screening.

in our series. Of the three patients with spinal pathologic changes, there were radiologic findings of transverse myelitis, ring-enhancing lesions, cord edema, and extradural collection.

It is well documented that the clinical and radiologic signs of neurologic melioidosis can mimic those of neurologic tuberculosis and arboviral encephalitis. Tuberculous meningitis is the most common form of neurologic tuberculosis and its radiologic features include hydrocephalus, basal meningeal enhancement, and infarctions of the supratentorial brain parenchyma and brain stem.[12] The typical MRI feature of arboviral encephalitis is bilateral hypointensity on T1 images and hyperintensity on T2 images of the thalamus. In addition, there may also be involvement of the basal ganglia, midbrain, pons, and cerebellum.[13]

There has been speculation over the pathogenesis of neurologic melioidosis; it has been suggested that direct seeding of the neurologic system or an exotoxin are the likely causes. Early research suggested an exotoxin-mediated pathogenesis caused by absence of central nervous system (CNS) involvement on imaging and sterile CSF cultures.[14] In our series, only two CSF cultures were positive for *B. pseudomallei*. However, more recent studies have suggested that direct seeding of the CNS is involved. Koszyca and others reported 29 cases in which appropriate imaging or histopathologic analysis had been performed, and there was evidence of direct invasion of the CNS by *B. pseudomallei* in 23 cases.[15] According to Currie and others, the presence of a mononuclear pleocytosis also supports the presence of direct neurologic invasion by *B. pseudomallei*.[11] Interestingly, in our series the two patients with CSF-positive cultures demonstrated polymorphonuclear cell changes. Acute infection with *B. pseudomallei* in other sites is frequently associated with a polymorphonuclear leukocyte response.

The sensitivity of IHA for detection of melioidosis is 56%.[16] The sensitivity of IHA in our series was 30% on initial testing. However, the overall sensitivity with repeated testing was 50% (two patients with initially negative results showed positive results at admission). Of the three patients with only negative IHA results, two were never retested and died within two days of initial IHA testing. In addition, the two patients with borderline IHA results were never retested. The rapid progression of disease seen in our case series may have resulted in this initial poor sensitivity because of inadequate time for antibody development. The two dry-season patients (cases 1 and 5) had negative serologic results, which reduced the likelihood of reactivation.

The most appropriate antibiotic of choice for the treatment of neurologic melioidosis is still being debated. Chadwick and others suggested intravenous ceftazidime or imipenem for the eradication phase of neurologic melioidosis.[5] Kandasamy and Norton identified ceftazidime or meropenem alone or with the addition of co-trimoxazole as the most active regimen.[17] In our series, patients who died during admission received monotherapy with either meropenem or ceftazidime only. Those who received dual therapy survived. Kumar and others suggested 6–8 months of oral maintenance therapy, including co-trimoxazole, doxycycline, or quinolones.[12] In our series, in which outpatient antibiotic therapy duration was noted, all but one patient received six months of maintenance therapy.

Neurologic disease is an uncommon manifestation of melioidosis. Difficulties encountered in making the diagnosis would include a relative absence of traditional risk factors, a lack of specific initial CT imaging findings, and the low recovery rate of the organism from CSF. A high clinical index of suspicion, particularly in children, is therefore essential in early assessment and management of this disease.

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REFERENCES

1. Guard RW, Khafagi FA, Brigden MC, Ashdown LR, 1984. Melioidosis in far north Queensland. A clinical and epidemiological review of twenty cases. *Am J Trop Med Hyg 33:* 467.
2. Dance D, 1991. Melioidosis: the tip of the iceberg? *Clin Microbiol Rev 4:* 52–60.
3. Dance DA, 2000. Melioidosis as an emerging global problem. *Acta Trop 74:* 115–119.
4. Brett PJ, Woods DE, 2000. Pathogenesis of and immunity to melioidosis. *Acta Trop 74:* 201–210.
5. Chadwick D, Ang B, Sitoh Y, Lee C, 2002. Cerebral melioidosis in Singapore: a review of five cases. *Trans R Soc Trop Med Hyg 96:* 72–76.
6. Suputtamongkol Y, Chaowagul W, Chetchotisakd P, Lertpatanasuwun N, Intaranongpai S, Ruchutrakool T, Budhsarawong D, Mootsikapun P, Wuthiekanun V, Teerawatasook N, 1999. Risk factors for melioidosis and bacteremic melioidosis. *Clin Infect Dis 29:* 408–413.

7. Rajkovic I, Williams R, 2005. Abnormalities of neutrophil phagocytosis, intracellular killing and metabolic activity in alcoholic cirrhosis and hepatitis. *Hepatology 6:* 252–262.
8. Matzner Y, Goldfarb A, Abrahamov A, Drexler R, Friedberg A, Rachmilewitz EA, 2008. Impaired neutrophil chemotaxis in patients with thalassaemia major. *Br J Haematol 85:* 153–158.
9. Gallacher S, Thomson G, Fraser W, Fisher B, Gemmell C, MacCuish A, 2009. Neutrophil bactericidal function in diabetes mellitus: evidence for association with blood glucose control. *Diabet Med 12:* 916–920.
10. Hirabayashi Y, Kobayashi T, Nishikawa A, Okazaki H, Aoki T, Takaya J, Kobayashi Y, 1988. Oxidative metabolism and phagocytosis of polymorphonuclear leukocytes in patients with chronic renal failure. *Nephron 49:* 305–312.
11. Currie BJ, Fisher DA, Howard DM, Burrow JNC, 2000. Neurological melioidosis. *Acta Trop 74:* 145–151.
12. Kumar GS, Raj PM, Chacko G, Lalitha MK, Chacko AG, Rajshekhar V, 2008. Cranial melioidosis presenting as a mass lesion or osteomyelitis. *J Neurosurg 108:* 243–247.
13. Kalita J, Misra U, 2000. Comparison of CT scan and MRI findings in the diagnosis of Japanese encephalitis. *J Neurol Sci 174:* 3–8.
14. Woods ML, Currie BJ, Howard DM, Tierney A, Watson A, Anstey NM, Philpott J, Asche V, Withnall K, 1992. Neurological melioidosis: seven cases from the Northern Territory of Australia. *Clin Infect Dis 15:* 163.
15. Koszyca B, Currie B, Blumbergs PC, 2004. The neuropathology of melioidosis: two cases and a review of the literature. *Clin Neuropathol 23:* 195–203.
16. Cheng AC, O'Brien M, Freeman K, Lum G, Currie BJ, 2006. Indirect hemagglutination assay in patients with melioidosis in northern Australia. *Am J Trop Med Hyg 74:* 330–334.
17. Kandasamy Y, Norton R, 2008. Paediatric melioidosis in north Queensland, Australia. *J Paediatr Child Health 44:* 706–708.