Neuromelioidosis: a series of seven cases in Hainan province, China

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Abstract
Melioidosis, which is caused by Burkholderia pseudomallei, is predominately a disease of tropical climates and is especially widespread in south-east Asia and northern Australia. Melioidosis affecting the central nervous system has a low incidence but a high mortality. We present seven cases of neuromelioidosis and analyze the disease characteristics and imaging features. Typical clinical features of this disease included high fever and headache. Five patients had an irregular fever with a temperature ≥ 39°C. Peripheral blood leukocytes and the neutrophil ratio were raised in all patients. On computed tomography and magnetic resonance imaging the disease mainly manifested as intracerebral single or multiple nodules, as well as ring and flake-like enhancements with rapid lesion progression. This study demonstrated the importance of imaging examination in the clinical evaluation and diagnosis of neuromelioidosis.

Keywords
Neuromelioidosis, Burkholderia, brain abscess, imaging, diagnosis

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Introduction
Melioidosis is the clinical disease that follows infection with the soil and water gram-negative aerobic bacterium Burkholderia pseudomallei. Melioidosis can involve multiple organs, and its clinical manifestations include lung and urinary tract infection, bone and soft tissue infection, severe septicaemia and neurological complications. Melioidosis is regarded as endemic in south-east Asia and northern Australia, corresponding approximately to the tropical latitudes between 20°N and 20°S.¹ The worldwide epidemiology of melioidosis has been comprehensively reviewed by Dance.²

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Melioidosis has become a global issue due to the development of tourism. 2,3 Hainan Island, China, is located in a subtropical region and is also a tourist attraction, presenting optimal conditions for the spread of melioidosis. Yang 4 conducted an epidemiological sample survey in 11 provinces of China and found that the melioidosis seroprevalence for a random sample population in the Hainan area (including Haikou, Sanya and Qionghai) accounted for 36.5% of the seroprevalence nationwide. Although melioidosis affecting the central nervous system (neuromelioidosis) only occurs in 3–5% of those with this disease, 5–7 its mortality can reach up to 25%. 7 Only a few reports of the imaging features of neuromelioidosis are available in the literature. 5,7,8 The most recent study was a retrospective analysis of the magnetic resonance imaging findings in 10 patients with neuromelioidosis. 8 The main features were the presence of rim-enhancing microabscesses along white matter tracts (including the corticospinal tracts, corpus callosum and cerebellar peduncles), thickening and enhancement of the trigeminal nerves (with spread to the trigeminal nuclei) and extra-axial disease (meningeal enhancement, extradural abscess, skull osteomyelitis and/or scalp abscess). 8 In the present study, disease characteristics and imaging features were analyzed retrospectively in patients with neuromelioidosis.

Patients and methods

Patients

Data from patients diagnosed with melioidosis by microbial detection 1 from three general hospitals in Haikou City, Hainan, China (Hainan General Hospital, Affiliated Hospital of Hainan Medical University and Haikou People’s Hospital) between February 2002 and December 2015 were analyzed retrospectively.

The culture, identification and sensitivity testing of *Burkholderia pseudomallei* had been carried out using standard procedures 9 at the microbiology laboratories of the participating hospitals. At the Hainan General Hospital, blood was cultured in flasks containing standard aerobic medium (BD Biosciences, San Jose, CA, USA), bacterial isolation was carried out on plates prepared from 5% sheep blood and Columbia agar (Guangdong Huankai Microbial Science & Technology, Guangzhou, China) and identification of the organism and drug sensitivity testing were performed using a VITEK 32 automated microbial analyzer (bioMérieux, Craponne, France). At the Affiliated Hospital of Hainan Medical University, blood was cultured in flasks containing standard aerobic medium (BD Biosciences), bacterial isolation was carried out on plates prepared from 5% sheep blood and Columbia agar (Guangdong Huankai Microbial Science & Technology), and identification of the organism and drug sensitivity testing were performed using an autoSCAN-4 automated microbial analyzer (Dade Behring, Deerfield, IL, USA). At the Haikou People’s Hospital, organism culture and isolation were achieved using culture medium and China blue–rosolic acid (Guangzhou Di King Microbial Technology, Guangzhou, China), and identification of the organism and drug sensitivity testing were performed using a VITEK 2 compact automated microbial analyzer (bioMérieux).

Clinical data for the patients were obtained from their medical records. Findings in patients confirmed as having neuromelioidosis by an integrated approach including blood culture, brain abscess fluid culture, cerebrospinal fluid routine analysis and imaging were then analyzed further.

The study protocol was approved by the institutional review board of Haikou Municipal People’s Hospital, Haikou, Hainan, China. Informed consent from the study participants was waived because of the retrospective nature of the study.
Imaging methods and evaluation

Computed tomography (CT) scanning was performed using an SCT-7000TS spiral CT scanner (Shimadzu, Kyoto, Japan), an Asteion Super 4 CT scanner (Toshiba, Tokyo, Japan), an iCT 256-slice scanner (Philips, Amsterdam, The Netherlands), Dual-Source Flash CT scanner (Siemens, Erlangen, Germany) or a HiSpeed single-row CT scanner (GE Healthcare, Chicago, IL, USA). The scan protocol used included a tube voltage of 120 kV, a tube current of 200–300 mA and a slice thickness of 8–10 mm.

Magnetic resonance imaging (MRI), with a slice thickness of 6.0–6.5 mm, was carried out using a Signa HDxt 3.0 T scanner (GE Healthcare) (repetition time [TR]/echo time [TE] values: axial or sagittal plane T1WI imaging, 1811.0/21.3 ms; axial plane T2WI imaging, 6000.0/113.6 ms; T2 flair imaging, 9002.0/167.6 ms; diffusion-weighted imaging at \( b = 1000, 7000.0/75.2 \) ms; contrast-enhanced imaging, 6.3/2.0 ms), a Signa Excite 3.0 T scanner (GE Healthcare) (TR/TE values: axial or sagittal plane T1WI imaging, 1920.9/28.3 ms; axial plane T2WI imaging, 3600.0/98.0 ms; T2 flair imaging, 9000.0/119.0 ms; diffusion-weighted imaging at \( b = 1000, 3600.0/95.0 \) ms; contrast-enhanced imaging, 500.0/8.4 ms) or a Verio 3.0 T scanner (Siemens) (TR/TE values: axial or sagittal plane T1WI imaging, 2000.0/9.0 ms; axial plane T2WI imaging, 6000.0/99.0 ms; T2 flair imaging, 8402.0/120.3 ms; contrast-enhanced imaging, 580.0/20.0, 340.0/20.0 and 320.0/20.0 for axial, coronal and sagittal views, respectively).

The images were assessed by two radiologists in consultation with each other; lesion site, range and surrounding conditions were evaluated.

Results

Clinical features

A total of 119 patients were identified as having been diagnosed with melioidosis. Of these, seven were confirmed to have neuromelioidosis, giving an incidence of 5.9%.

The patients were aged 9–66 years (mean age 47.9 years; median age 56 years) (Table 1). All patients were indigenous people from Hainan province and were of Han nationality. Typical clinical features of the disease included high fever and headache. Five of the seven patients (71%) had a fever exceeding 39.5°C, while two did not have fever. Peripheral blood leukocytes and the neutrophil ratio were raised in all patients. Five of the seven patients (71%) had diabetes mellitus (cases 2, 3, 4, 6 and 7).

Case 1 (a 31-year-old male from Ledong County) presented with a 1-week history of right-sided headache (persistent and stabbing) of unknown cause and an irregular fever of up to 39.5°C. Case 2 (a 48-year-old male from Tunchang County who did not smoke, had no history of alcohol addiction and worked as a driver) presented with fever (39.6°C) of unknown origin, paroxysmal headache and allodynia in the right occipital area that was aggravated by fever. Case 3 (a 56-year-old male from Haikou City who had smoked approximately 40 cigarettes/day for 20 years, occasionally drank alcohol and worked in agriculture) presented with a 2-month history of chest pain but no fever. Case 4 (a 65-year-old male from Lingao County who worked in agriculture) presented with a 40-day history of fever, a 14-day history of dizziness and a 5-day history of left limb weakness. Case 5 (a 9-year-old male from Dingan County) presented with a history of fever of unknown origin that had reached 40°C 4 days previously. Case 6 (a 60-year-old male from Dongfang County who worked in agriculture) had experienced head injury to the right occipital region after a fall 1 year previously and presented with a 10-day history of persistent headache of unknown cause that was particularly severe in the right temporal and occipital regions. Case 7 (a 66-year-old male from Wenchang
| Case no. | Age, years | Imaging performed | Extracerebral infection | Diagnostic approach | Outcome                  |
|---------|------------|-------------------|-------------------------|---------------------|--------------------------|
| 1       | 31         | Head CT; MRI + CE; DTI and SWI; chest X-ray; spleen US; left knee X-ray | Splenic abscess; left knee abscess | Blood culture | Nervous system damage |
| 2       | 48         | Head CT; chest CT | Lung infection          | Blood culture       | Death                    |
| 3       | 56         | Right tibia/fibula X-ray and CT; chest CT + CE; head CT, CTA and MRI + CE | Lung infection; right tibial osteomyelitis; soft tissue infection | Blood culture | Nervous system damage |
| 4       | 65         | Upper abdominal MRI + CE; head CT and MRI + CE | Thigh abscess; liver abscess | Culture of brain abscess fluid | Nervous system damage |
| 5       | 9          | Chest X-ray and CT; head CT | Lung infection; tonsillitis | Blood culture; CSF routine analysis | Improvement |
| 6       | 60         | Chest X-ray and CT; head CT | Lung infection | Blood culture | Nervous system damage |
| 7       | 66         | Chest X-ray and CT; head CT | Lung infection | Blood culture; CSF routine analysis | Family requested discharge before cure |

All patients were male. CE, contrast enhancement; CSF, cerebrospinal fluid; CT, computed tomography; CTA, computed tomography angiography; DTI, diffusion tensor imaging; MRI, magnetic resonance imaging; SWI, susceptibility weighted imaging; US, ultrasound.
County who worked in agriculture) presented with a 10-day history of irregular fever (reaching 39.7°C) and headache of unknown cause.

**Imaging**

Head CT scanning was conducted in all seven patients. The images were normal in two patients, so no further imaging was performed (cases 5 and 7). In the remaining five patients, contrast-enhanced CT scanning was performed in one patient and head MRI with contrast-enhanced MRI was undertaken in three patients (Table 1). The radiological findings are given in Table 2.

Of those with abnormal CT findings, one patient (case 2) was found to have a superior sagittal sinus thrombosis (Supplementary Figure 1a). The disease had a rapid progression. Small cysts appeared under the right occipital dura mater, there was a small amount of effusion beside the left side of the superior sagittal sinus (Supplementary Figure 1b) and left parietal lobe infarction occurred after 4 days (Supplementary Figure 1c). In addition, one patient had right occipital skull osteomyelitis with subdural small cysts (case 6). In the other three patients, the CT findings showed that a lesion located under the frontal and parietal lobe cortex that gradually involved the corona radiata, basal ganglia and brain stem as the disease progressed. The typical manifestations on MRI enhancement were multiple linear, gyrus-like and nodular enhancements in the early lesion area, with subsequent ring enhancements formed by nodule liquefaction. These enhancements finally merged together to form a large-scale enhancement. Signs were reversible after antibiotic treatment (Figures 1 and 2).

**Discussion**

The incidence of melioidosis in the present study (5.9%) is consistent with the values reported by Currie et al. (5%) and Deuble et al. (5.7%) in Australia. The risk factors for melioidosis have been widely documented and include diabetes mellitus, alcoholism, renal disease, immunosuppression and thalassaemia. Patients with these characteristics may be particularly susceptible because of a poor ability to develop a cell-mediated immune response secondary to these conditions, which are associated with poor neutrophil function. However, neuromelioidosis appears to have a different risk factor profile. Currie et al. reported that 75% of patients with neuromelioidosis were male and that those with neuromelioidosis were younger (mean age 38 years versus 47 years), and more likely to be Aboriginal (67% versus 51%) than those with any type of melioidosis. The patients in the present study had a mean age of 47.9 years and thus were slightly older than the cohort reported by Currie et al.; however, all the patients in the present study were male, which is consistent with the male preponderance reported previously. Currie et al. reported that alcoholism was present in 42% of patients with neuromelioidosis, and that alcoholism and diabetes were each present in 39% of patients with all types of melioidosis. In the present study, 71% of the patients with neuromelioidosis had diabetes, but none had a history of alcoholism, indicating that the risk factors for melioidosis may be different in China and Australia.

In the present study, two out of seven patients had a normal first head CT (29%). The rate of a positive first head CT examination for this group of patients was therefore 71%, which is higher than that reported in Australia (50%). A possible reason for this difference is that the patients in the present study may have undergone CT examination at a different disease stage to those in the previous study. In general, CT sensitivity for neuromelioidosis is relatively low. CT scanning is useful for determining the site and extent of a lesion and some of its
Table 2. Neuromelioidosis imaging manifestations.

| Case no. | Imaging date       | Imaging method | Findings                                                                 |
|----------|--------------------|----------------|--------------------------------------------------------------------------|
| 1        | 27 January 2013    | CT             | Right frontal lobe nodular lesions; relatively high-density irregularly-shaped shadow, flake-like surrounding oedema |
|          | 31 January 2013    | MRI + CE       | Large flake at right frontal lobe, temporal lobe, basal ganglia, thalamus and right side of midbrain. Main signals were long T1 and T2, with relatively few short T1 and T2 signals. Flakes of surrounding oedema showing heterogeneous enhancement. Irregularly shaped enhancements and multiple small ring-shaped enhancements, most aggregating as a flake or mass shadow. Right frontal meningeal enhancements |
| 8        | 2 February 2013     | CT + CE        | Compared with MRI on 31 January 2013, lesion and oedema extent decreased after treatment |
|          | 17 February 2013    | MRI + CE       | Compared with MRI on 31 January 2013, lesion extent obviously decreased, cyst cavity slightly increased and ring of enhancement thinned after treatment |
|          | 9 April 2013        | MRI + CE       | Compared with MRI on 17 February 2013, lesion absorbed, cyst cavity decreased, some parts changed to small nodules, and space-occupying effect disappeared after treatment |
| 2        | 7 November 2014     | CT             | Stripe-like and triangular low-density shadows in the superior sagittal sinus. Density not homogeneous for some layers |
|          | 11 November 2014    | CT             | Compared with CT on 7 November 2014, density of triangular low-density shadow in the superior sagittal sinus had become homogeneous and increased with a typical delta sign. Thin-layered crescent-like low-density shadow in the right occipital skull plate. Crescent-like low-density shadow in the left side of the superior sagittal sinus. Flake-like low-density shadow in the left parietal lobe |
| 3        | 7 February 2012     | CT             | Flake-like low-density shadow in the left frontal and parietal lobes. A few shadows of patchy density |
|          | 24 February 2012    | MRI + CE       | Compared with CT on 7 February 2012, lesion area increased after treatment. Uneven flake at the left frontal and parietal lobes. Long T1 and T2 were main signals, accompanied by few equal T1 and relatively short T2 signals. Large-scale surrounding oedema with uneven enhancement. Multiple small nodular enhancement |

(continued)
Table 2. Continued.

| Case no. | Imaging date     | Imaging method | Findings                                                                                                                                 |
|----------|------------------|----------------|------------------------------------------------------------------------------------------------------------------------------------------|
| 1        | 1 March 2012     | CTA            | Compared with MRI on 24 February 2012, nodules and patchy enhancement at left frontal and parietal lobes decreased after treatment, as had oedema extent. No cerebrovascular abnormalities |
| 4        | 3 December 2009  | CT             | Right frontal lobe nodular lesions, high-density shadow. Surrounding flake-like low-density shadow                                          |
| 4        | 4 December 2009  | MRI + CE       | Large-scale heterogeneous long T1 and long T2 signals in right frontal region and corona radiata area. Multiple linear, gyrus-like and nodular enhanced shadows with fuzzy boundaries. Flake-like long T1 and long T2 signals at bilateral mastoid |
| 15       | 15 December 2009 | MRI + CE       | Large-scale heterogeneous long T1 and long T2 signals in right side of brain stem, right frontal, temporal and parietal lobes and bilateral corona radiata area. Multiple linear, ring-shaped and flake-like enhanced shadows. Large-scale surrounding oedema. Right lateral ventricle narrowed under pressure |
| 24       | 24 December 2009 | MRI + CE       | Compared with MRI on 15 December 2009, left frontal lobe lesions increased and anterior cyst cavity of right frontal lobe lesion slightly increased |
| 13       | 13 January 2010  | MRI + CE       | Compared with MRI on 24 December 2009, lesion at right frontal, temporal and parietal lobes and bilateral corona radiata area decreased, while that at right side of the brainstem unchanged, after brain abscess drainage on multiple occasions |
| 5        | 31 October 2014  | CT             | Bilateral basal ganglia region calcification. No abnormal-density shadowing in the residual brain                                           |
| 6        | 7 September 2002 | CT             | Right occipital skull osteolytic bone absorption. Crescent-shaped low-density shadow beneath the skull plate. Soft tissue swelling under the right occipital scalp |
| 7        | 6 June 2002      | CT             | No abnormal-density shadows in the brain parenchyma                                                                                     |

CE, contrast enhancement; CT, computed tomography; CTA, computed tomography angiography; MRI, magnetic resonance imaging.
properties; for example, CT scanning revealed a subacute superior sagittal sinus thrombosis in one patient in the present study. Notable features of neuromelioidosis seen on CT scanning in the present study were nodular lesions (including small cysts), low-density regions, effusions and osteomyelitis. These findings are in general agreement with previous investigations. For example, Muthusamy et al. reported abscess formation, subdural and spinal epidural collections and osteomyelitis of the occipital bone and vertebrae, while Deuble et al. reported features such as ring-enhancing lesions, low-density areas, effusions and oedema.

However, CT is inferior to MRI for detailed evaluation of the lesion and its enhancement features (such as multiple ring enhancements corresponding to small abscesses). In the present study, the MRI features in patients with neuromelioidosis...
Magnetic resonance imaging (MRI) findings in a 65-year-old male (case 4) with neuromelioidosis and multiple brain abscesses. The patient had been diagnosed with melioidosis infection on the basis of brain abscess fluid culture, and appropriate antibiotic treatment had been started based on drug sensitivity. (a) MRI contrast-enhanced image obtained on 4 December 2009, showing cyst-like, nodular, ring-shaped and stripe-like enhancements. (b) MRI contrast-enhanced image obtained on 15 December 2009, showing a new lesion in the left frontal lobe and that lesions in the right frontal lobe had increased compared with the previous image, mainly with more cyst-like and ring-shaped enhancements. Compared with the previous image, the cyst cavity had increased and the extent of the oedema had enlarged. (c) MRI contrast-enhanced image obtained on 24 December 2009, showing that the lesions in the left frontal lobe had increased further, mainly with ring-shaped enhancements. In addition, the cyst cavity in the right frontal lobe lesion had enlarged. (d) MRI contrast-enhanced image obtained on 13 January 2010, showing that after treatment, the lesion in the bilateral frontal lobes had decreased compared with the previous image. The cyst cavity had decreased, and some parts showed small nodular enhancements.
included multiple linear, nodular and ring-shaped regions of enhancement that often merged to form larger regions of enhancement, as well as areas of oedema. A recent study by Chia-Tsong Hsu et al.\(^8\) observed rim-enhancing microabscesses in the brain parenchyma and medulla of the spinal cord, particularly along white matter tracts; in addition, meningeal enhancement, extradural and scalp abscesses and skull osteomyelitis were also found. Ring-enhancing lesions and spinal extradural collections were also reported by Deuble et al.,\(^7\) while abscess formation and collections were demonstrated by Muthusamy et al.\(^13\). It is notable that the two patients in the present study who showed no CT abnormalities were not imaged using MRI. Since CT-negative but MRI-positive results have been reported previously,\(^5,7\) it may be prudent to perform MRI examination in patients with suspected neuromelioidosis even if the CT scan is negative.

Regardless of whether CT or MRI is used, most cases of neuromelioidosis manifest during imaging as intracerebral infections complicated by multiple abscesses,\(^13–16\) in particular multiple, small, ring-enhanced lesions. This manifestation is similar to the multiple enhanced abscesses often seen with melioidosis in the lung, liver and spleen.\(^17\) Lung infection is the most common manifestation of melioidosis outside the brain\(^18\) and was seen in five patients (71%) in the present study.

Padiglione et al.\(^19\) reported that neuromelioidosis usually involved the brain stem, cerebellum and spinal cord. However, three of the five cases in the present study who had imaging-positive intracerebral manifestations had lesions in the frontal and parietal lobes that gradually involved the corona radiata, basal ganglia region and brain stem as the disease progressed. This is consistent with a previous study in which frontoparietal lesions were observed in five out of nine patients examined with neuroimaging.\(^5\)

The present study included a rare case of superior sagittal sinus thrombosis. In cerebral venous sinus thrombosis, high-density signs usually present during the acute stage (≤7 days). In this patient, there were stripe-like and triangular low-density shadows 11 days after disease onset; 4 days later, the low-density shadows had increased and had become homogeneous, and the lesion had a typical delta sign that was similar to the enhancement reported in a previous study.\(^13\) The peripheral high-density linear shadow around the low-density triangular shadow comprised the sagittal sinus wall.\(^13\) Venous sinus thrombosis in melioidosis may be related to the induction of a hypercoagulable state by acute septicaemia.\(^20\) In the present study, the patient with superior sagittal sinus thrombosis deteriorated rapidly and died, possibly because thrombolytic treatment was not initiated soon enough.

Chadwick et al.\(^16\) retrospectively analyzed five patients with neuromelioidosis and found that four had sinusitis, suggesting the two diseases had a causal relationship. However, none of the seven patients in the present study had sinusitis, although one had signs of mastoid inflammation. Thus, sinusitis might only be one of the possible routes for intracranial infection.

It is important to note that, in the present study, MRI examination in two patients (cases 1 and 4) revealed lesions in the corona radiata, basal ganglia and brain stem that were not detected by CT, indicating that MRI has an advantage in the detection of these lesions. Moreover, MRI was able to detect the morphology and number of small intracerebral cysts. In order to accurately evaluate changes in the lesions during antibiotic therapy, it is suggested that MRI scanning should be used during follow-up.

An important limitation of the present study was that MRI was carried out in only three of the seven patients. Thus, the majority of the imaging findings were based on CT scanning, which has a lower contrast
resolution than MRI, and the features of this disease on the CT images were often non-specific in nature. Nonetheless, the presence of lesions such as small cysts was a notable feature. In addition, although only three patients underwent MRI, the findings indicate that the typical presentation of neuromelioidosis was the early appearance of multiple nodular enhancements that developed into ring enhancements before eventually merging. These imaging findings suggest that single or multiple intracerebral nodules, ring and flake-like enhancements and rapid lesion progression are common features of neuromelioidosis that, together with the results of other investigations, can help establish the diagnosis.

In conclusion, the present study demonstrated the importance of imaging examinations in the clinical evaluation and diagnosis of neuromelioidosis and confirmed most of the imaging manifestations previously reported, although some differences in risk factors were found. In one rare case the disease was associated with venous sinus thrombosis, with specific imaging manifestations.

Declaration of conflicting interest
The authors declare that there is no conflict of interest.

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