Central nervous system nocardiosis diagnosed by metagenomic next-generation sequencing: A case series and literature review

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Conflict of interest
None declared

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Abstract

Background. Central nervous system (CNS) nocardiosis is a rare suppurative disease caused by the genus *Nocardia*. It is found most frequently in immunocompromised individuals.

Objectives. In this study, we retrospectively reviewed the clinical presentations, laboratory examination, therapy and outcomes of 9 patients with CNS nocardiosis diagnosed using metagenomic next-generation sequencing (mNGS) in our hospital.

Materials and methods. We reviewed 9 patients with confirmed diagnosis of CNS *Nocardia* infection from January 2017 to December 2021 in the Department of Neurology at The Third Affiliated Hospital, Sun Yat-sen University (Guangzhou, China). In addition, we searched literature related to CNS *Nocardia* infection on PubMed and included all case reports with proven CNS nocardiosis since 2016.

Results. The metagenomic next-generation sequencing (mNGS) of CSF can be used for the rapid diagnosis of nocardiosis in CNS and *N. farcinica* are the most commonly isolated species. Underlying autoimmune diseases, immunosuppressive agents including corticosteroids and organ transplantation are predisposing factors of developing CNS nocardiosis. Single or multiple hyper-enhanced ring lesions indicative of cerebral abscesses are commonly presented in brain imaging. Trimethoprim-sulfamethoxazole (TMP-SMX) is used as the primary agent for the antibacterial therapy and in combination with other antibacterial agents.

Conclusions. Our study demonstrated that mNGS of CSF can be conducted for definitive and rapid diagnosis for CNS nocardiosis.

Key words: infection, central nervous system, brain abscess, metagenomic next-generation sequencing, nocardia

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Background

Nocardiosis is a rare suppurative disease caused by gram-positive aerobic bacteria in the genus *Nocardia*. As an opportunistic infection, it is found most frequently in immunocompromised individuals, such as organ transplant recipients, patients with human immunodeficiency virus (HIV) infection, and those with hematologic malignancies.[1,2] *Nocardia* infection causes at least 6 forms of disease in humans including pulmonary, systemic, central nervous system (CNS), extra-pulmonary, cutaneous nocardiosis, and actinomycetoma.[3] The incidence of CNS nocardiosis is often secondary to lung or systemic nocardiosis,[3] and its clinical symptoms are variable, even without any external neurologic signs.[4–6] A multicentric cohort study in Japan reported 57 patients (56/317, 17.7%) had CNS nocardiosis, secondary to pulmonary nocardiosis (207/317, 65.3%).[7] *Nocardia farcinica* was found to be the most prevalent species in solid organ transplant recipients.[8] *Nocardia asteroides, N. nova* and *N. abscessus* also were the majority of invasive infection reported in the literature to date.[9,10]

Objectives

In this study, we retrospectively reviewed the clinical presentations, laboratory examination, implemented therapy, and outcomes of 9 patients with CNS nocardiosis diagnosed using metagenomic next-generation sequencing (mNGS) in our hospital.

Materials and methods

Study design

We reviewed 9 patients with confirmed diagnosis of CNS *Nocardia* infection from January 2017 to December 2021 in the Department of Neurology at The Third Affiliated Hospital, Sun Yat-sen University (Guangzhou, China). Demographic information, underlying comorbidities, clinical features, and radiological examinations were recorded. In addition, the presence of underlying disease conditions and the use of immunosuppressants comprising corticosteroids were identified. Diagnosis was made based on clinical characteristics, computer tomography (CT) or magnetic resonance imaging (MRI), as well as mNGS of the cerebrospinal fluid (CSF). Furthermore, we analyzed treatment approaches including medication and surgery.

mNGS

The general workflow of mNGS includes cerebrospinal fluid specimen collection, nucleic acid extraction, library generation, and sequencing, and aligning against published microbial genome databases. Cerebrospinal fluid DNA was extracted and purified following the standard procedures of QIAamp DNA Micro Kit (Qiagen, Hilden, Germany). Qubit 4.0 (Thermo Fisher Scientific, Waltham, USA) was used for DNA concentration and quality control. Libraries were constructed using QIAseq Ultralow Input Library Kit (Qiagen). Once qualified, the libraries were sequenced on the Nextseq 550 platform (Illumina, San Diego, USA). The raw reads generated after mNGS sequencing were filtered by removing adapters, low quality and short reads (<35 bp) to obtain clean data. Bowtie2 was used for excluding human sequences by mapping the clean data to the human reference genome (hg38). For microorganism identification, the remaining reads were then aligned against published microbial genome databases downloaded from the National Center for Biotechnology Information (fttp://ftp.ncbi.nlm.nih.gov/genomes/).

The study was conducted according to the principles expressed in the Declaration of Helsinki and approved by the Medical Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University (approval No. [2021]02-121-01). Written informed consent was obtained from all participants.

Literature review

We searched the existing English-language literature related to CNS *Nocardia* infection on PubMed. Key words included "nocardia", "nocardiosis", "central nervous system", "meningitis", "encephalitis", and "brain abscess". We included all case reports with proven CNS nocardiosis between 2016 and 2021.

Results

Underlying conditions

The clinical and microbiological features of patients were summarized in Table 1. The mean age of these CNS nocardiosis cases was 45 years, ranging from 26 to 67 years. Female patients accounted for 44% (4 of 9). Most cases (7 of 9, 77.8%) presented autoimmune diseases, including SLE (n = 4), pemphigus (n = 1), nephrotic syndrome (membranous nephropathy, n = 1), and myasthenia gravis (n = 1). Other underlying conditions consisted of renal transplantation (n = 1) and malignancy (nasopharyngeal carcinoma treated with radiotherapy; n = 1). Of these, 8 individuals were receiving immunosuppressants such as corticosteroids (1 with prednisone and 6 with methylprednisolone), mycophenolate mofetil (n = 2), cyclophosphamide (n = 1), methotrexate (n = 1), azathioprine (n = 1), and tacrolimus (n = 1). None of the patients had HIV infection, tuberculosis, cerebral vascular diseases, chronic lung disease, or hematologic malignancies.

Clinical characteristics at admission

The clinical manifestations varied in this cohort of patients. Headache was the most common symptom present in all cases. Other symptoms included fever in 7 cases and weakness in 4 cases. Two patients manifested abnormal vision: 1 with blurred vision and the other with metamorphopsia. There were 2 cases of pulmonary symptoms, of which 2 cases had cough and 1 case had expectoration. Seizure, dizziness, muscle soreness, disorientation, confusion, and diplopia were also recorded (Table 1). Patients with brain abscess (case 5, 6 and 8) presented signs of neurological deficits. Case 5 developed hemiplegia on the left side of the body, while case 6 developed abduction dysfunction of the right eye movement. Cases 5, 6 and 8 showed decreased muscle strength and abnormal muscle tone. Case 7 with meningitis showed neck rigidity and positive meningeal signs including Kernig's sign and Brudzinski's sign, but no neurological deficits were detected. For the remaining patients, no positive or specific signs were found in the neurological examination.

Laboratory test and brain imaging

On the day following admission to our hospital, all patients underwent CSF examinations. Only 3 of these patients manifested an increased intracerebral pressure (ICP). White blood cell (WBC) count and total protein were elevated in 8 and 9 patients, respectively. The levels of chloride and glucose decreased in 6 patients. The mNGS of CSF was conducted in all cases. The confidence level and specific reads were recorded in Table 1. Figure 1 shows

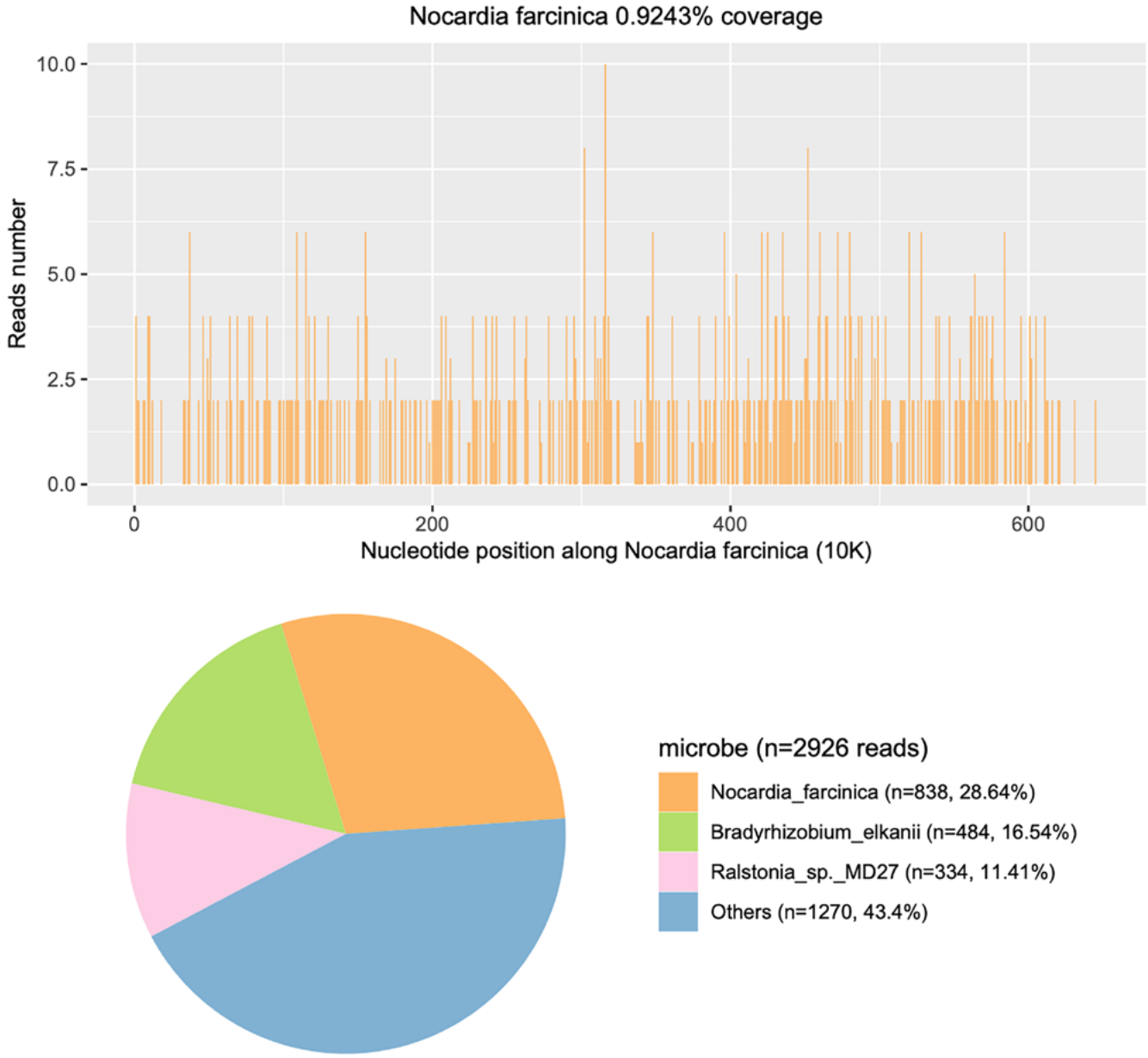

Fig. 1. Metagenomic next-generation sequencing (mNGS) results of case 6

Table 1. Nine cases of central nervous system (CNS) nocardiosis in The Third Affiliated Hospital, Sun Yat-sen University (Guangzhou, China)

Characteristic		Patient								
		1	2	3	4	5	6	7	8	9
Age/sex		26/M	47/F	44/F	28/M	56/M	26/F	67/M	55/F	53/M
Comorbidities		SLE	nasopharyngeal carcinoma	SLE	renal transplantation	pemphigus	SLE	myasthenia gravis	SLE	nephrotic syndrome (membranous nephropathy)
Immunosuppressants		prednisone, cyclophosphamide, methotrexate	none	methylprednisolone, mycophenolate mofetil	methylprednisolone, mycophenolate mofetil	methylprednisolone	methylprednisolone	azathioprine	methylprednisolone	methylprednisolone, tacrolimus
Species		*N. abscessus*	*N. farcinica*	*N. terpenica*	*N. farcinica*	*N. farcinica*	*N. farcinica*	*N. farcinica*	*N. farcinica*	*N. farcinica*
mNGS	yes/no	yes	yes	yes	yes	yes	yes	yes	yes	yes
	confidence degree	medium	none	high	high	high	high	high	high	high
	specific reads	12	none	34	29559	35	838	110	1043	71
Type of infection		meningoencephalitis, brain abscess	meningoencephalitis	meningitis	brain abscess	brain abscess	brain abscess, meningoencephalitis	meningitis	brain abscess	brain abscess
Clinical manifestations		headache, fever, blurred vision	headache, fever, weakness	fever, dizziness, headache, muscle soreness	headache, fever, seizure, metamorphopsia	fever, headache, weakness, disorientation, hemiplegia on the left side of the body, decreased muscle strength and abnormal muscle tone	cough, fever, headache, weakness, confusion, abduction dysfunction on right eye movement, decreased muscle strength and abnormal muscle tone	fever, headache, cough, expectoration, neck rigidity, Kernig's sign and Brudzinski's sign	headache, weakness, diplopia, seizure, decreased muscle strength and abnormal muscle tone	lumbosacral pain, fever, dizziness, slow response
First in-hospital CSF examination	ICP [mm H_2O]	240	150	315	170	150	160	none	200	330
	WBC counts [*10^6/L]	146	160	420	42	178	510	3680	2	2600
	chloride [mmol/L]	94.2	117.9	113.8	125.9	125	112	110.2	123.8	99.4
	glucose [mmol/L]	0.91	2.89	2.28	2.63	2.08	1.21	1.53	3.35	0.04
	total protein [mmol/L]	6.13	0.81	1.34	0.85	1.26	1.13	1.88	0.93	2.14

Table 1. Nine cases of central nervous system (CNS) nocardiosis in The Third Affiliated Hospital, Sun Yat-sen University – cont.

Characteristic		Patient								
		1	2	3	4	5	6	7	8	9
CNS imaging	CT	multiple ring-enhancing lesions in bilateral frontal and left parietal lobes	multiple ring-enhancing lesions in bilateral frontal and left temporal lobes	white matter lesion not excluded	multiple ring-enhancing lesions in left frontal and bilateral temporal occipital lobes	multiple ring-enhancing lesions in the right cerebral hemisphere, left frontal lobe, corona radiata, basal ganglia, and insula	right basal ganglia lesion	none	multiple ring-enhancing lesions in left cerebral peduncle, pons, right cerebellar hemisphere, right frontal, parietal, and occipital lobes	left basal ganglia lesion
	MRI	meningoencephalitis, multiple abscesses in bilateral frontal lobe and left posterior horn of lateral ventricle, surrounding brain edema, ventriculitis and left choroid plexus inflammation	meningoencephalitis in the left temporal lobe, right part of pons, anterior pontine cistern, cerebellopontine angle cistern and internal auditory canal	none	multiple lesions in bilateral cerebral hemisphere and cerebellum	multiple lesions with surrounding edema in the right cerebral hemisphere, left basal ganglia, insular lobe and paraventricular posterior horn	meningoencephalitis, multiple lesions in bilateral frontal, parietal lobes, corona radiata, right lateral ventricle, right basal ganglia and right para-hippocampal gyrus	meningitis, supratentorial ventricular system moderately dilated with paraventricular white matter edema (hydrocephalus)	multiple lesions with surrounding edema in right frontal lobe, parietal lobe, occipital lobe, left cerebral peduncle, pons, and right cerebellar hemisphere	multiple lesions in left radial crown-basal ganglia and posterior horn of lateral ventricle
Antibiotics		TMP-SMX, linezolid, meropenem	TMP-SMX, linezolid, moxifloxacin, ceftriaxone, vancomycin	TMP-SMX, linezolid, meropenem	TMP-SMX, linezolid, meropenem, moxifloxacin, minocycline	TMP-SMX, linezolid, meropenem, moxifloxacin	TMP-SMX, linezolid, meropenem, minocycline, amoxicillin clavulanate	TMP-SMX, linezolid, amoxicillin clavulanate, doxycycline	TMP-SMX, linezolid, meropenem, moxifloxacin, amikacin, teicoplanin	TMP-SMX, linezolid, meropenem, moxifloxacin
Surgery		EVD	none	none	none	EVD, decompressive craniectomy	none	none	EVD	none
Outcomes		death	recovery	recovery	recovery	recovery	recovery	recovery	recovery	recovery

SLE – systemic lupus erythematosus; mNGS – metagenomic next-generation sequencing; CSF – cerebrospinal fluid; CT – computed tomography; MRI – magnetic resonance imaging; ICP – intracranial pressure; WBC – white blood cells; TMP-SMX – trimethoprim-sulfamethoxazole; EVD – external ventricular drainage. In case #2, the confidence dgree and specific reads of mNGS was lost, while *N. farcinica* was detected in mNGS of CSF indeed and this patient was comfirmed as CNS nocardia infection.

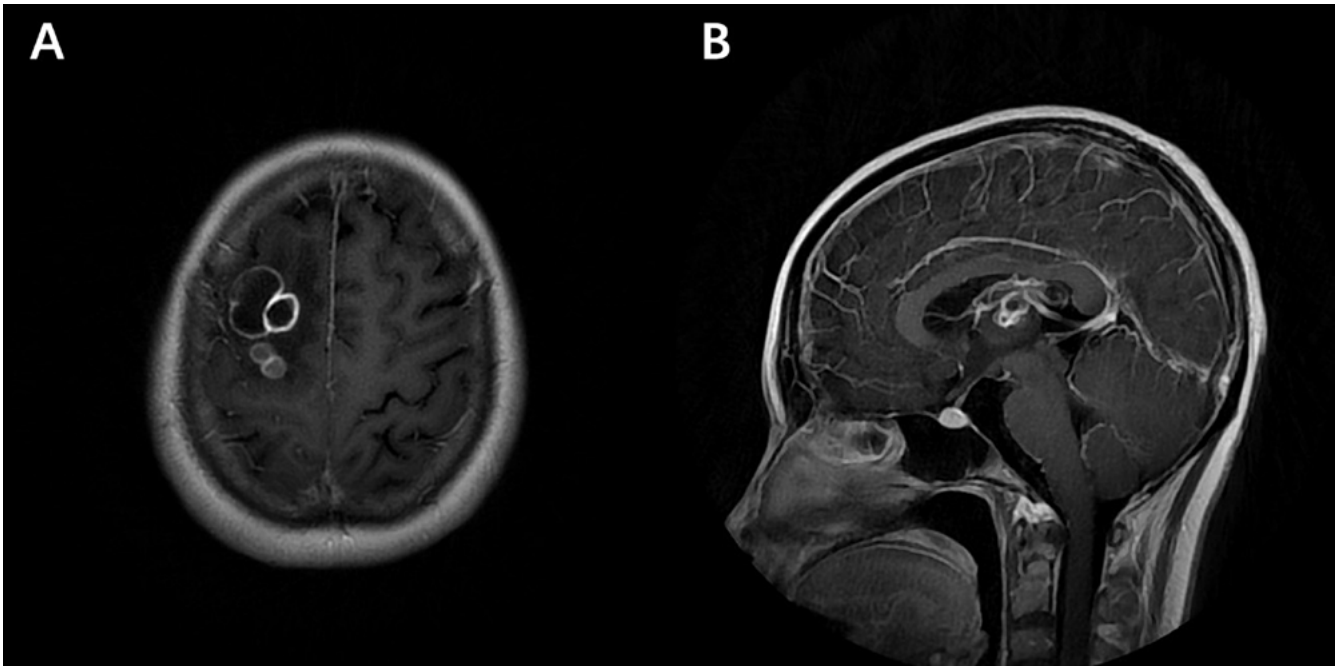

Fig. 2. Representative magnetic resonance images (MRI) images of the patients. A. The axial gadolinium-enhanced MRI image of case 8 shows multiple ring-enhancing lesions of varying sizes in the right frontal and parietal lobes; B. Sagittal T1 gadolinium-enhanced MRI image of case 6 shows ring-enhancing lesions in the right basal ganglia, with meningeal enhancement

representative mNGS results of case 6. The coverage and specific reads of *N. farcinica* detected with mNGS were 0.92% and 838, respectively. Most patients (7 of 9) were identified as *N. farcinica*-infected, and the other 2 patients had *N. abscessus* and *N. terpenica*, respectively.

The most common type of *Nocardia* infection of the CNS was brain abscess, which occurred in 6 cases according to the brain CT or MRI scan. Other types were meningoencephalitis (n = 3) and meningitis (n = 2). Brain CT scans were performed in 8 patients. Multiple ring-enhancing lesions occurred in 6 patients and single lesions in 3 patients. The frontal lobe was the most common brain region involved, occurring in 5 cases. Brain MRI was performed in 8 patients. One patient showed moderate expansion of supratentorial ventricular system with paraventricular white matter edema, suggesting hydrocephalus. Peripheral edema surrounding the lesion was seen on CT and MRI in 3 patients. Figure 2 showed representative MRI images of the patients presented.

Treatment and outcome

Both medical and surgical interventions were included in the treatment strategy. Three patients received a combination of medical and surgical treatment (patients 1, 5 and 8; Table 1) and underwent external ventricular drainage (EVD). One patient had a combined surgical procedure of EVD and decompressive craniectomy due to high ICP (patient 5). The remaining patients received antimicrobial therapy only. Both trimethoprim-sulfamethoxazole (TMP-SMX) and linezolid were prescribed in the antimicrobial therapy of all patients. In addition, 7 patients received combined therapy with meropenem, and 5 patients received moxifloxacin as part of the combined regimen. Two patients were treated with amoxicillin-clavulanate or minocycline, and 1 each with vancomycin, doxycycline, amikacin, and teicoplanin, respectively. Most patients (8/9) recovered after antimicrobial therapy with or without surgery. Only 1 patient died from a *Nocardia* complication.

Literature review

We included 57 reported cases of CNS nocardiosis published on PubMed from 2016 to 2021.[11–65] The clinical and microbiological characteristics of patients in literature review are summarized in Table 2 and the Supplementary data (https://doi.org/10.5281/zenodo.10153255). The mean age of patients was 60 years. Overall, 79.6% (43/54) of the patients were male and 20.3% (11/54) were female. A significant number of cases (14/57, 24.6%) had no comorbidities. The most common comorbid condition was diabetic mellitus, which was reported in 22.8% of the patients. Malignancy and autoimmune disease were the 2nd and 3rd most common comorbidities, reported in 21.1% and 19.3% of patients, respectively. Five patients (8.7%) received bone marrow or solid organ transplant. The most common organ transplanted was kidney (n = 3), followed by bone marrow (n = 1) and heart (n = 1). Five patients (8.7%) had a history of alcoholism. Other comorbidities included chronic lung disease (4/57, 7.0%), chronic kidney disease (3/57, 5.3%) and HIV infection (2/57, 3.5%).

Table 2. Clinical and microbiological characteristics of literature patients (n = 57)

Mean age	Gender	Comorbidities	Species	Sequencing	Type of infection	Medication	Surgery	Outcome
60	male (43/54, 79.6%) female (11/54, 20.3%)	diabetes mellitus (13/57, 22.8%) malignancy (12/57, 21.1%) autoimmune disease (11/57, 19.3%) transplant (5/57, 8.7%) alcohol abuse (5/57, 8.7%) chronic lung disease (4/57, 7.0%) chronic kidney disease (3/57, 5.3%) HIV infection (2/57, 3.5%) none (14/57, 24.6%)	*Nocardia farcinica* (20/52, 38.5%) *Nocardia cyriacigeorgica* (5/52, 9.6%) *Nocardia asiatica* (4/52, 7.7%) *Nocardia beijingensis* (4/52, 7.7%) *Nocardia paucivorans* (3/52, 5.8%) *Nocardia otitidiscaviarum* (3/52, 5.8%) *Nocardia nova* (2/52, 3.9%) *Nocardia brasiliensis* (2/52, 3.9%) *Nocardia araoensis* (2/52, 3.9%) *Nocardia abscessus* (2/52, 3.9%) *Nocardia asteroids* (1/52, 1.9%) *Nocardia kroppenstedtii* sp. *nov* (1/52, 1.9%) *Nocardia elegans/aobensis/africana complex* (1/52, 1.9%) *Nocardia mexicana* (1/52, 1.9%) *Nocardia thailandica* (1/52, 1.9%)	16S rRNA (27/57, 47.4%)	brain abscesses (46/57, 80.7%)	empiric treatment (33/56, 58.9%)	34/57, 59.6%	recovery (45/55, 81.8%)
				mNGS (3/57, 5.3%)	meningitis (5/57, 8.8%)	targeted treatment (23/56, 41.1%)	–	death (10/55, 18.2%)
				DNA sequencing (2/57, 3.5%)	disseminated infection (5/57, 8.8%)	–	–	–
				no (25/57, 43.8%)	spinal abscesses (3/57, 5.3%)	–	–	–
				–	endogenous endophthalmitis (2/57, 3.5%)	–	–	–
				–	endocarditis (1/57, 1.7%)	–	–	–
				–	ventriculitis (1/57, 1.7%)	–	–	–
				–	infectious intracranial aneurysm (1/57, 1.7%)	–	–	–
				–	–	–	–	–

HIV – human immunodeficiency virus; mNGS – metagenomic next-generation sequencing.

Of these 57 patients, 46 (80.7%) had brain abscesses on brain imaging, 5 had meningitis and 3 had spinal abscesses. Two patients with brain abscesses also had endogenous endophthalmitis. Patients with brain abscesses had endocarditis (n = 1), ventriculitis (n = 1) and infectious intracranial aneurysm (n = 1). Five patients had disseminated *Nocardia* infection in addition to CNS involvement. Other sites of infection included the lungs, skin and back. The most frequently reported species was *N. farcinica* (20/52, 38.5%), followed by *N. cyriacigeorgica* (5/52, 9.6%), *N. asiatica* (4/52, 7.7%), *N. beijingensis* (4/52, 7.7%), *N. otitidiscaviarum* (3/52, 5.8%), and *N. paucivorans* (3/52, 5.8%). Other less common species included *N. brasiliensis* (n = 2), *N. nova* (n = 2), *N. araoensis* (n = 2), *N. asteroids* (n = 1), *N. kroppenstedtii* sp. *nov.* (n = 1), *N. elegans/aobensis/africana complex* (n = 1), *N. Mexicana* (n = 1), and *N. thailandica* (n = 1). A large proportion of the patients were diagnosed using 16S rRNA sequencing (27/57, 47.4%) or mNGS (3/57, 5.3%). However, other patients were confirmed to have *Nocardia* infection using DNA sequencing, acid-fast staining and culture, etc.

In this group of patients, 41.1% (23/56) were reported to have received targeted treatment according to antimicrobial susceptibility testing and 58.9% (33/56) received antibiotics empirically. Most patients (48/56, 85.7%) underwent combined anti-microbial therapy consisting of at least 2 antibiotics. Overall, 41.1% (23/56) of the patients were administered TMP-SMX alone or with other antibiotics. A variety of other antimicrobials were used in the treatment, including ceftriaxone (17/56, 30.4%), imipenem (13/56, 23.2%), meropenem (13/56, 23.2%), linezolid (11/56, 19.6%), or amikacin (9/56, 16.1%). A large proportion of patients (34/57, 59.6%) underwent surgical intervention with combination antimicrobial therapy.

Results were reported for 55 patients. Overall, 45 patients (81.8%) recovered completely or with complications, and 10 patients (18.2%) died.

Discussion

To date, only limited case reports described using mNGS to diagnose CNS nocardiosis. In this study, we retrospectively reported 9 cases of CNS *Nocardia* infection confirmed with mNGS, and analyzed the clinical and microbiological features, treatment strategies, and outcomes. To the best of our knowledge, this is the largest case series of CNS nocardiosis diagnosed using mNGS.

It is of great importance to isolate and culture *Nocardia* spp. for microbiological diagnosis and use of sensitive antimicrobial agents. Nevertheless, *Nocardia* spp. grow relatively slowly, which makes them difficult to culture in the laboratory. In recent years, sequencing technologies including 16S rRNA sequencing and mNGS were developed for definitive and rapid diagnosis of clinical infectious diseases.[28] The mNGS allows direct detection of the microbial community in the natural state, without isolation and culture, and therefore could be applied to diagnosing bacterial infection caused by those more difficult to culture, such as *Nocardia* spp.[45,66] In the literature review, nearly half of patients underwent 16S rRNA sequencing, but only 3 patients used mNGS for diagnosis.

Predisposing factors for the development of CNS nocardiosis include age, gender and immunosuppressive status.[67,68] The mean age of CNS nocardiosis patients in our hospital and in the literature was 45 and 60 years, respectively. The higher incidence of CNS nocardiosis in the elderly may be result of immunosenescence, which refers to the decline of the immune system associated with aging and may lead to excessive accumulation of pro-inflammatory cytokines and inflammaging.[69,70] However, the mean age of our case series was much younger than the literature review and previous studies, which may be due to the presence of comorbidities and immunosuppressive conditions in our cohort.

It is well known that systemic *Nocardia* infection occurs mainly in immunocompromised patients. Accordingly, most of the patients (8/9, 88.9%) in our study had received immunosuppressive agents, with 7 patients receiving corticosteroid treatment (prednisone and methylprednisolone). In a previous study, high-dose and long-term corticosteroid treatment was considered a risk factor for the development of nocardiosis.[71,72]

It is noteworthy that 7 patients in our group had autoimmune diseases, with systemic lupus erythematosus (SLE) being the most common (n = 4). Cell-mediated immunodeficiency was implied as one of the major risk factors for the development of *Nocardia* infection.[73] In our case series, patients with autoimmune diseases were using steroids and other immunosuppressive agents such as mycophenolate mofetil, azathioprine and methotrexate, which inhibit cell-mediated immunity.

The incidence of *Nocardia* infection in organ transplant patients has been reported to range from <1% to 3.5%.[74–76] In our case series and literature review, we found that kidney transplant recipients ranked the 1st place, accounting for 66.6% (4/6) of the transplant patients. However, in a matched case-control study comprising of 5,126 organ transplant recipients, the highest rate (3.5%) of *Nocardia* infection was found in lung transplant recipients, followed heart (2.5%), intestine (1.3%), kidney (0.2%), and liver (0.1%) transplants.[74] Risk factors for post-transplant patients developing this disease include the use of high-dose corticosteroids, anti-lymphocyte globulin, higher levels of calcineurin inhibitors, and previous cytomegalovirus disease.[8,77]

As seen in our case series, most patients presented with fever and headache, typical of those with CNS infection. Neurological complaints including weakness, seizures, dizziness, disorientation, and confusion were also present in this case series. However, in a Queensland (Australia) case series of 20 cases, few patients presented with classic infectious symptoms.[78] Clinical presentation varies from patient to patient and there are no specific symptoms to guide clinicians in making the diagnosis. Patients with CNS nocardiosis may have single or multiple hyperenhancing ring lesions suggestive of cerebral abscesses on CT or MRI. The frontal lobe was the most common site of infection according to our study and a recent report,[68] due to inhalation or direct spread from paranasal sinuses.[79]

Brain abscess and/or meningitis caused by other opportunistic infectious pathogens such as *Klebsiella pneumoniae*[80] and *Escherichia coli*[81] should be considered in differential diagnosis of CNS nocardiosis. Central nervous system nocardiosis masquerading brain metastasis is not uncommon and has been reported.[47,82] For example, in a case report by Voide et al.,[83] a patient initially diagnosed with non-small cell lung cancer presented delirium during chemotherapy treatment, and subsequently underwent CT and MRI. The brain lesions were initially interpreted as CNS metastasis, but later stereotactic biopsy and Ziehl–Neelsen staining of lesion showed *N. farcinica* infection. In addition, CNS nocardiosis should be differentiated from ischemic stroke. Lavalard et al.[84] reported an immunocompromised female initially treated as cerebral stroke but later confirmed to have CNS *Nocardia* infection. Despite treatment with cotrimoxazole and rifampicin, she did not improve and died 3 months after treatment concluded.

Nocardia farcinica was the most common species found in both our patients and patients in the literature. This is consistent with previous reports that *N. farcinica* was the most commonly isolated species in patients.[68,85] Compared with other species, *N. farcinica* is more virulent and more likely to cause CNS nocardiosis or disseminated disease.[78,86] However, *N. abscessus* and *N. asteroids* are quite rare in both our case series and literature patients, whereas these 2 species were common in previously published studies.[78,85] To date, the current study reports the 2nd case of CNS nocardiosis infected with *N. terpenica*. The first reported patient with CNS *N. terpenica* infection was from Nanchang, China.[87]

Due to its low rate of resistance and good penetration into the CNS,[88] TMP-SMX is considered as the fundamental treatment in CNS *Nocardia* infection. All patients in our cohort and the majority of patients in the literature were taking TMP-SMX. In the literature, patients receiving antibiotic regimens that included eTMP-SMX had higher survival rates and lower relapse rates.[78,89] Although there

are no definitive clinical guidelines, it is recommended that patients with CNS nocardia infection should receive TMP-SMX at a dose of 25–50 mg/kg per day for at least 12 months to prevent relapse.[71]

In addition to TMP-SMX, other effective antimicrobials against *Nocardia* spp. include linezolid, meropenem, moxifloxacin, imipenem, and ceftriaxone in our series or in patients from the literature. Although targeted antimicrobial treatment based on antimicrobial susceptibility testing is widely recognized as the optimal therapy, patients in our hospital or in a large proportion of case reports receive only empirical treatment. However, mNGS cannot detect the resistance of *Nocardia* spp. Because CNS nocardiosis is rare in the world, there is a lack of definitive and effective antibiotic regimens, and larger, multicenter randomized controlled trial is needed to determine the optimal treatment for this disease.

As is shown in our case series, $^1/_3$ of the patients in our study and 59.6% (34/57) of the literature patients underwent neurosurgery including EVD and decompressive craniectomy. In the previous studies, patients treated with a combination therapy of medicine and surgery had higher survival rates than those who received antibiotics only.[68,78,86] However, the prognosis of patients with CNS nocardiosis relies on multiple factors such as age, immune status of patients, time from disease onset to diagnosis, different *Nocardia* spp., antimicrobial regimens, and the duration of treatment, among others. Therefore, the favorable prognosis of surgery may be due to the bias of selecting patients with better status for surgery.

Limitations

This study has several limitations. Our case series is a single center study and only 9 patients were included. In a recent study involving 24 patients with *Nocardial* brain abscess, lung and skin were the most common primary infectious sources (37.5% and 12.5%, respectively).[68] Unfortunately, the primary infectious sites of this case series were not recorded in our electronic medical records. Therefore, we were unable to identify the primary source of the CNS *Nocardia* infection. In addition, all patients in our cohort were treated empirically, as no antimicrobial susceptibility testing was performed.

Conclusions

Our study demonstrated that CSF mNGS can be conducted for definitive and rapid diagnosis of CNS nocardiosis. Elderly and immunocompromised individuals, especially those receiving immunosuppressive drugs, have a higher incidence of CNS *nocardia* infection. Antimicrobial therapy including TMP-SMX in combination with neurosurgery may reduce mortality and recurrence rates.

Supplementary data

The Supplementary materials are available at https://doi.org/10.5281/zenodo.10153255. The package includes the following files:

Supplementary Table 1. Clinical and microbiological characteristics of literature patients.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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