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Case report

Metagenomic next-generation sequencing assistance in identifying *Mycobacterium avium* meningoencephalitis: A case report and literature review

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ABSTRACT

Nontuberculous mycobacteria associated intracranial infection is a rare disease that mainly occurs in HIV-infected patients. The disease has a poor prognosis. The authors report a case of nontuberculous mycobacterial meningoencephalitis in a non-AIDS patient, but long history of poorly controlled type 2 diabetes mellitus. A 55-year-old, right-handed, male patient presented with an 8-day history of fever, episodes of severe headache with signs of meningeal irritation. MRI showed hyperintensities/contrast enhancement in the visual pathways, basal ganglia sellar region and leptomeninges. No etiological diagnosis was reached until metagenomic next-generation sequencing (mNGS) was used, showing the presence of *Mycobacterium avium*. The patient was cured with aggressive antimycobacterial therapy. The authors discuss the clinical manifestations and drug therapy of nontuberculous mycobacteria-related intracranial infections by reviewing relevant literature. As meningoencephalitis by *Mycobacterium avium* has a high mortality an early diagnosis and appropriate therapeutic interventions are warranted. For this reason, the use of mNGS can be helpful to avoid therapeutic delay.

Non-tuberculous mycobacteria (NTM) is a general term used to refer to mycobacterial species other than *Mycobacterium (M.) tuberculosis* complex and *M. leprae* [1]; *M. avium* complex (MAC) is the most common NTM causing lung infections. MAC consists in 12 species, among which, 3 main species can cause disease in humans: *M. avium*, *M. intracellulare*, and *M. chimaera* [2]. These pathogens can be found in surfaces or tap water, milk, food, soil, domestic or wild animals as well as the human body surface or diverse body

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secretions without causing disease; however, immunosuppression is a major predisposing factor to NTM infection [3]. NTM diseases mainly involve lungs, lymphatic system and skin, occasionally a disseminated presentation may be observed affecting the central nervous system (CNS). NTM infections involving CNS mainly occur in immunocompromised patients with acquired immunodeficiency syndrome (AIDS). In non-AIDS patients, NTM-related intracranial infections are particularly rare, but they might be fatal and should be rapidly identified. However, conventional microbial culture methods used for diagnosing NTM infections present challenges due to their long culture time and low positive culture rate [4,5]. In recent years, CSF metagenomic next-generation sequencing (mNGS) has emerged as an increasingly important diagnostic tool, particularly for encephalitis, meningitis, and brain abscesses with unknown etiology [6]. The mNGS based on a second-generation sequencing technology is capable to detect the DNA of all microorganisms in the samples by sequencing and comparing with the microbial database in order to identify suspected pathogenic microorganisms [6]. The detection process includes: nucleic acid extraction, library construction, sequencing, data analysis, and analysis report. A large prospective study demonstrated that mNGS has a detection rate of 57.0% for definite NTM infections of the CNS [7]. Herein, we report a case of *M. avium* meningoencephalitis in a non-AIDS patient diagnosed by mNGS, where other methods failed to provide an etiological diagnosis for the neurological manifestations. We also reviewed relevant literature on MAC infections of the nervous system.

1. Case presentation

A 55-year-old, right-handed, male patient was admitted to the hospital on August 25, 2022, due to an 8-day history of repeated episodes of severe headache accompanied by vomiting. The patient also complained of blurred vision and episodes of increased body temperature up-to 38.0 °C, occurring mainly during the afternoon. Physical examination on admission revealed drowsiness, mental confusion, pupils were round and equal on both sides, menace reflex showed inconsistent blinking and banded cloth did not elicited optokinetic nystagmus suggesting decreased vision in both eyes. The rest of cranial nerves were intact. Muscle strength was slightly decreased in all extremities (Medical Research Council, grade 4), deep tendon reflexes were normal, Babinski sign was absent bilaterally. There was prominent neck's resistance and a positive Kernig sign. Lack of cooperation by the patient precluded examination of the sensory system. A head CT scan on admission showed small ischemic lesions in the bilateral basal ganglia. Lumbar puncture examination was performed showing increased white blood cells (WBCs) 733 $\times$ 10^6/L, glucose 3.71 mmol/L and protein 1.78 g/L. A

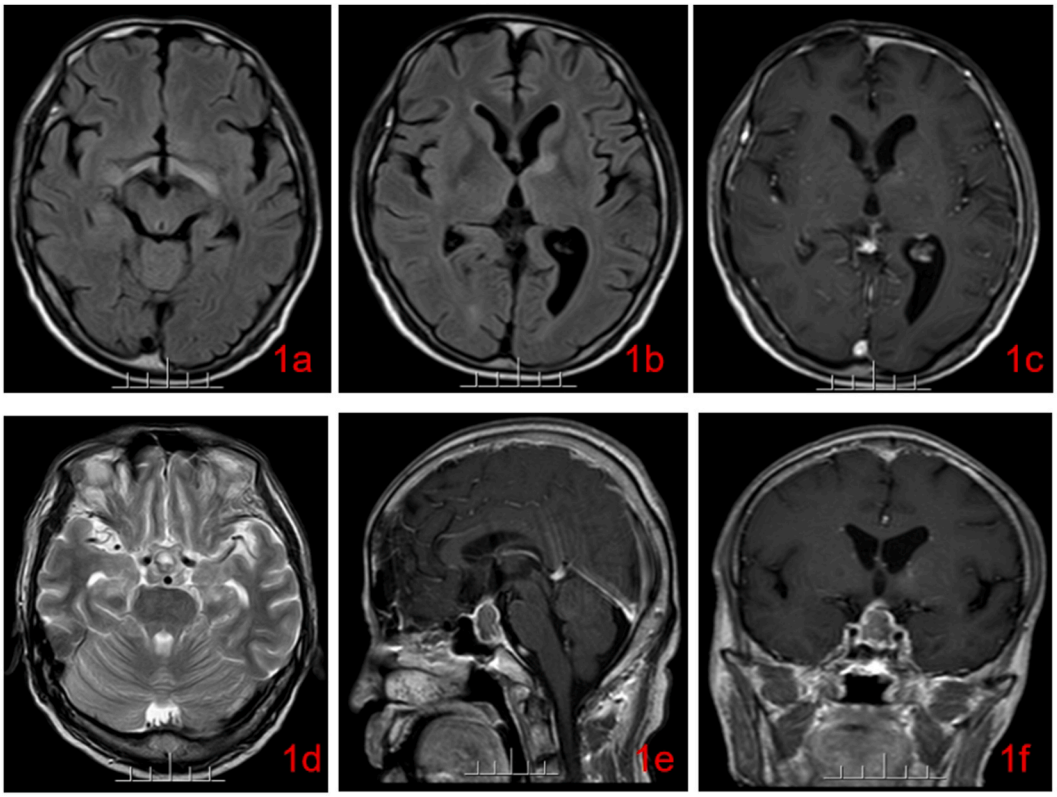

Fig. 1. Brain magnetic resonance imaging (MRI) before treatment. Axial T2/fluid attenuated inversion recovery (FLAIR) showing hyperintensity of the optic tract, a low signal intensity inner and a high signal intensity outer of the left basal ganglia (1a, 1b). Enhanced axial T1W demonstrating multi-punctate and linear enhancements in the left basal ganglia and leptomeninges (1c). Axial T2W showing a circular asymmetry density in the sella turcica and suprasellar region (1d). Enhanced sagittal T1W and enhanced coronal T1W demonstrating a ring-like enhancement in the sella turcica and suprasellar region (1e, 1f).

diagnosis of probable CNS infection was established and the patient was started with empiric therapy consistent with acyclovir and ceftriaxone. The fever was relieved, but the headache aggravated in frequency and severity; gait difficulty and lethargy eventually developed. The patient endorsed a history of diabetes mellitus type 2 lasting over 10 years with poor glycemic control owing to irregular consumption of antiglycemic drugs.

Laboratory tests on admission showed mild hyponatremia (sodium, 131 mmol/L) with low level of plasmatic cortisol: 9.9. ug/L (62–194 μg/L) and a random blood glucose of 3.1 mmol/L. Bacterial and fungal CSF cultures were negative. Ink-, acid-fast staining, tuberculosis spot test and cryptococcus capsular antigen tests were all negative. We performed mNGS in CSF, which came positive for *M. avium*. The brain magnetic resonance imaging (MRI) revealed extensive hyperintensities in the pre- and postchiasmatic optic tracts and the left basal ganglia. There was intrasellar ring-like contrast enhancement extending to the suprasellar region along with diffuse pia-matter enhancement. A possible pituitary infection with necrosis extending to the meninges was considered (Fig. 1a–f). Combined with the patient's medical history and auxiliary examination, the diagnosis of MAC meningoencephalitis complicated with hypopituitarism in the context of uncontrolled type-2 diabetes mellitus was established.

We started treatment with intravenous hydrocortisone and a sliding scale insulin regimen. The patient was put on high dose of oral isoniazid 600 mg/d, besides rifampicin 450 mg/d + azithromycin 300 mg/d + moxifloxacin 400 mg/d. After 5 days, the patient had no headache attacks, the vision improved remarkably, and the CSF parameters were significantly improved, opening pressure: 100 mmH_2O, WBCs 22 × 10^6/L, lymphocytes 78%, glucose 5.1 mmol/L, chloride 120.5 mmol/L, protein 1.04 g/L, considering that the combination of azithromycin with moxifloxacin may induce serious cardiac toxicity, azithromycin was discontinued, however, no side effects of antimycobacterial agents were reported by the patient. After 10 days, a new brain MRI showed a significant reduction of hyperintensities in the optic chiasm, left basal ganglia and the original intrasellar, suprasellar and pia matter enhancement significantly decreased (Fig. 2a–f). After 14 days of hospitalization, the patient's clinical symptoms were completely relieved, and he was discharged with oral isoniazid, rifampicin, and moxifloxacin. The patient returned to the hospital for reexamination 1 month later, he still endorsed episodes of mild headache without blurred vision or muscle weakness. The CSF analytics further improved, showing a lower opening pressure (80 mmH_2O), WBCs 2 × 10^6/L, glucose 7.7 mmol/L, chloride 122.2 mmol/L, protein 0.62g/L. The brain MRI showed a further reduction in sella turcica and suprasellar region lesions (Fig. 3a–f). The patient was instructed to continue anti-MAC treatment, so far, he has been followed-up for 9 months and his condition was stable without discomfort.

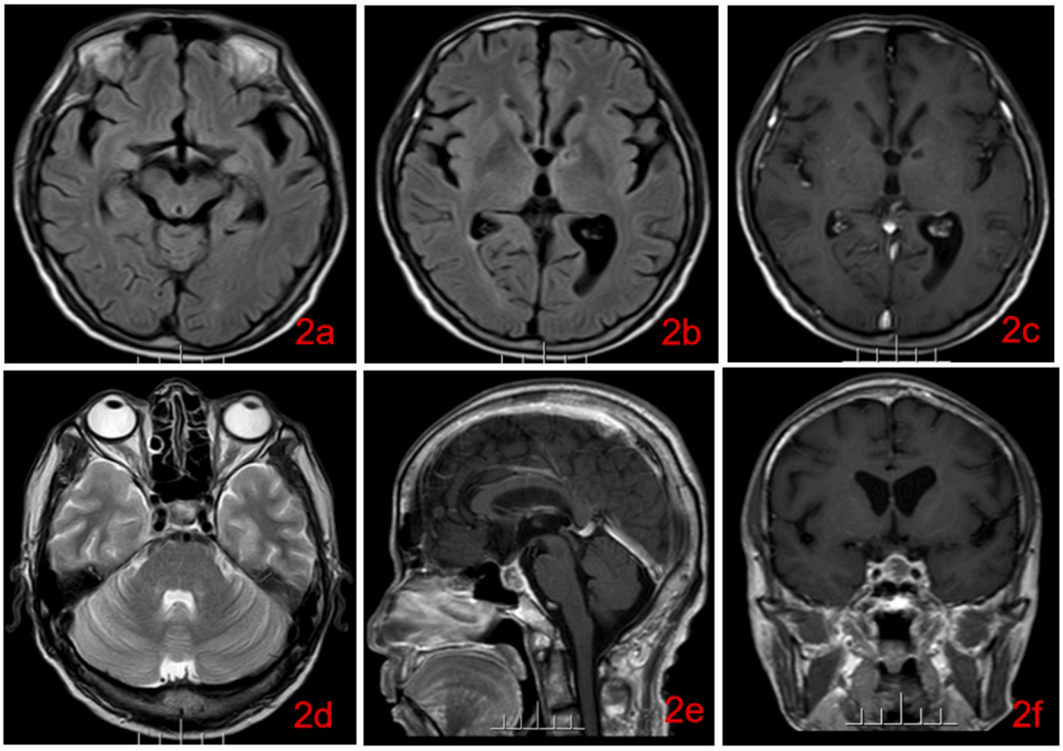

Fig. 2. MRI 10 days following treatment initiation, axial T2/FLAIR showing hyperintensity of the optic tract, a low signal intensity inner and a high signal intensity outer of the left basal ganglia (2a, 2b). Enhanced axial T1W demonstrating multi-punctate and linear enhancements in the left basal ganglia and leptomeninges (2c). Axial T2W showing a circular asymmetry density in the sella turcica and suprasellar region (2d). Enhanced sagittal T1W and enhanced coronal T1W demonstrating a ring-like enhancement in the sella turcica and suprasellar region (2e, 2f). The imaging changes (2a-2f) indicate a significant reduction in the observed inflammatory changes as compared to the baseline study.

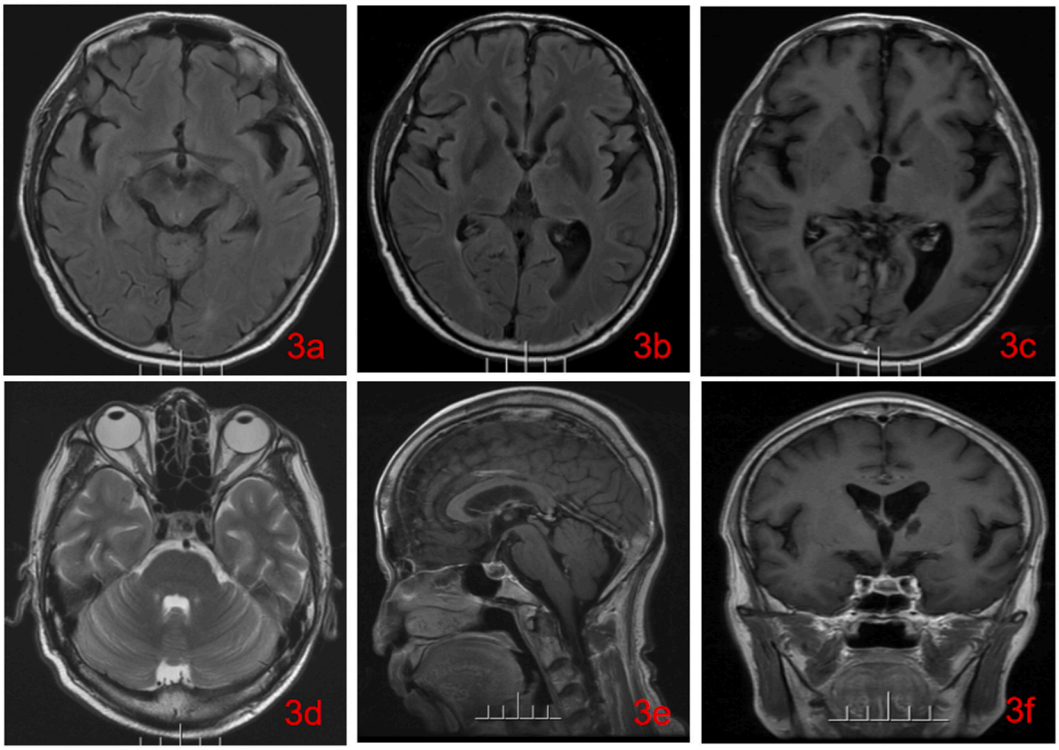

Fig. 3. MRI 1 month following treatment initiation, axial T2/FLAIR showing hyperintensity of the optic tract, a low signal intensity inner and a high signal intensity outer of the left basal ganglia (3a, 3b). Enhanced axial T1W demonstrating no longer contrast enhancement in the left basal ganglia and leptomeninges (3c). Axial T2W showing a circular asymmetry density in the sella turcica and suprasellar region (3d). Enhanced sagittal T1W and enhanced coronal T1W demonstrating a ring-like enhancement in the sella turcica and suprasellar region (3e, 3f). All imaging changes (3a-3f) demonstrate additional improvement compared to the previous study.

2. Literature review

The English-language literature search was done with the use of "central nervous system infection", "meningitis", "encephalitis", "meningoencephalitis" and "non-tuberculous mycobacteria" as search terms, through PubMed and Web of Science databases, Chinese-language literature was also reviewed through Wanfang Medical Network and CNKI database. There were 22 articles found that are related to infection caused by MAC, among them, there were 19 in English literature and 3 in Chinese literature, including 43 patients, and a total of 44 patients after adding our case. The clinical data of 44 patients are summarized and details are show in Table 1. The proportion of males (54.5%) was greater than that of females (34.1%), the clinical manifestations were mainly fever (56.8%), headache (54.5%) and altered level of consciousness (6.8%); Leukemia is an important underlying disease of MAC infection in 3 cases (6.8%), but AIDS was the main underlying disease in 27 cases (61.4%), diabetes mellitus was reported only in our case (2.3%). Imaging findings mainly manifested as meningitis, brain abscess and meningoencephalitis. The primary way to detect pathogens is through culture, accounting for 61.4% of all cases, while both PCR (11.4%) and mNGS (4.5%) are indispensable tools in the discovery of MAC. The overall prognosis was unfavorable, with a mortality rate of 54.5%. Cases of CNS infections secondary to MAC are shown in Table 2.

3. Discussion

4.1. General features and risk factors

MAC species are distributed worldwide. Besides lung disease, they can cause extrapulmonary disseminated infection, which mainly occurs in severely immunocompromised patients, such as those suffering advanced HIV-infection, hematologic malignancies, or in individuals who have received immunosuppressive therapy. Despite increasing reports of extrapulmonary NTM infection, CNS infections remain quite rare in both HIV-positive and HIV-negative patients. Flor and colleagues [9] reported 52 patients with NTM disease of the CNS in 1996, the frequency of immunosuppression was 54% (28 cases), among which, AIDS was the most common underlying condition observed in 24 patients. Whereas, Tabatabaei and colleagues [30] studied 12 cases with NTM (*M. kansasii*) disease of the CNS, from which, only 2 cases occurred in HIV-negative patients. Whereas, tumor, and diabetes mellitus were the main risk factors in non-AIDS patients. However, a proportion of patients have no identifiable risk factors, this group represented 25% of cases in our review.

Table 1
Summary of demographic, clinical and neuroimaging features in 44 patients.

Feature	Number of examples	Frequency (%)
Gender		
Male	24	54.5%
Female	15	34.1%
Unknown	5	11.4%
Clinical manifestations		
Fever	25	56.8%
Headache	24	54.5%
Change of consciousness	3	6.8%
Underlying medical conditions		
AIDS	27	61.4%
Leukemia	3	6.8%
Diabetes	1	2.3%
None	11	25.0%
Others	2	4.5%
Imaging		
Meningitis	12	27.3%
Meningoencephalitis	5	11.4%
Brain abscess	4	9.1%
Encephalitis	1	2.3%
pathogen detection method		
Culture	27	61.4%
PCR	4	9.1%
Culture + PCR	1	2.3%
mNGS	2	4.5%
Prognosis		
Survive	19	43.2%
Death	24	54.5%
Unknown outcome	1	2.3%

The pathogen species isolated seem to vary depending on the underlying disease. In non-immunosuppressed patients, it seems tumor are considered the most common predisposing factors for MAC infection. In our case, MAC infection was probably related to uncontrolled diabetes mellitus. Diabetic patients are susceptible to various types of infection, including active tuberculosis [31] which is associated to altered $CD4^{-}$and CD8-lymphocite mediated responses, likely contributing to altered immune cellular responses to *M. tuberculosis* infection [32,33]. Although the association between diabetes mellitus and MAC disease remains unclear, it can be expected to have negative effects [34], our study shows that diabetes mellitus underlies CNS NTM disease in 2.3% of cases.

4.2. Diagnosis and role of mNGS

Early diagnosis is difficult in patients with extrapulmonary MAC infection, particularly owing to its slow-growing in culture media; however, it has been reported that through mNGS the detection time varies from 6 hours to 7 days (average: 48 hours) [35,36], which is usually faster compared to traditional NTM culture. NTM can be divided into rapid growth type and slow growth type according to the growth rate. Rapid-growing NTM such as *M. abcessus*, *M. fortuitum*, and *M. chelonea* usually form colonies less than 1 week after initial isolation on culture media. On the other hand, slow-growing NTM which include MAC and *M. kansasii* usually take over 1 week to form identifiable colonies, delaying treatment initiation. Compared with traditional culture, mNGS has the advantages of a rapid detection of a large number of pathogens, particularly in culture-negative cases [37]. In a cohort study of patients with tuberculous meningitis, mNGS was confirmed to improve the detection rate of such pathogen [38]. Another study found that in newly diagnosed patients with suspected CNS infection, mNGS had a 90% sensitivity compared with culture, and its detection rate increased by about 25% [39]. For patients with chronic CNS infectious diseases of unknown etiology, such as chronic meningitis, the detection of mNGS in CSF is preferred.

The CSF analytics in patients with NTM infections are non-specific, showing great similarity with meningitis by *M. tuberculosis* and may overlap with bacterial meningitis in some instances, making the diagnosis difficult (Table 2). CSF cytology is characterized by increased WBC count, usually less than 500×10^6/L, and rarely $>1000 \times 106$/L with predominant lymphocytes, in some instances, multinucleated cells may predominate, CSF protein is usually high, between 0.5 and 3 g/L, but it can be > 3 g/L in severely affected patients, CSF glucose and chloride may be normal or reduced.

4.3. Treatment and drug resistance

The patient we presented was diagnosed with NTM infection through mNGS, but the CSF cultures were consistently negative, consequently, the absence of drug sensitivity data made targeted treatment challenging. We had to resort to empirical rather than targeted treatment. Unfortunately, there are no relevant treatment guidelines for CNS NTM infections, and treatment is mainly based on general principles of NTM disease therapy and previous case reports. The Guidelines for the Diagnosis and Treatment of

Table 2
Summary of previous cases in the literature (MAC CNS infections).

Cases	Age	Gender	Clinical manifestations	Underlying medical conditions	Diagnostic imaging	Cerebrospinal fluid	pathogen detection method	Treatment options	Drug sensitivity	Course	Prognosis
1 [8]	25	Male	Fever, headache, impaired consciousness	None	Meningitis	WBCs, 96/mm^3 (lymphocyte-dominated); GLU, 28 mg/dL	PCR	STM (intrathecal injection for 8 days); INH + EH + CYS + STM + OFX	NA	2 months	Survived
2 [9]	26	Female	Hemiplegia	AIDS	Meningoencephalitis	WBCs, 4/mm^3; PRO, 115 mg/dL; GLU, 36 mg/dL	NA	INH + RIF + ETH + CLR + OFX + AMK	NA	NA	Died
3 [9]	36	Male	Fever, coma, hemiplegia	AIDS	Brain abscess	Normal	Culture	INH + RIF + ETH	NA	NA	Died
4 [10]	46	Female	Chills, fever	leukemia	NA	Normal	mNGS	MFX (4 months), CLR (4 months), LZD	NA	11 months	Survived
5 [11]	45	Female	Headache, aphasia, hemiplegia	AIDS	Brain abscess	WBCs, 18 × 10^6/L; PRO, 1171 mg/mL; GLU, 2.05 mmol/L	Culture	RFB + MFX + AZM	NA	4 weeks	Survived
6 [12]	31	Female	Fever, confusion, stiff neck	None	Meningitis	WBCs, 45.3 × 10^6/L; PRO, 2.76 g/L; GLU, 3.1 mmol/L	Culture	CIP + AMK + ETH + AM + CFZ	R: INH, STM, RIF, ETH, PZA, ETO, CM, AMK, CIP, AM; S: CYS, CFZ	NA	Died
7 [13]	40	Male	Headache, swelling of the left eyelid, blurred vision, diplopia	None	Brain abscess	NA	Culture	CLR + ETH + RIF	NA	12 months	Survived
8 [14]	42	Male	Headaches, altered mentation, dizziness, vomiting	AIDS	Normal	WBCs, 283 mm^{-3}; PRO, 80mg/d ， GLU, CSF/serum 42/103mg/dL	PCR	CLR + CIP + RFB + PZA + INH, altered to CLR monotherapy on day 18	NA	8 months	Survived
9 [15]	23	Male	Fever	AIDS	Meningoencephalitis	WBCs, 6/mL; PRO, 141 mg/dL; GLU, 32 mg/dL	Culture	LFX + CLR + ETH + RFB	NA	4 weeks	Survived
10 [16]	52	Male	Dizziness, headache, gait disturbance, frequent falls	None	Brain abscess	NA	PCR	NA	NA	NA	NA
11 [17]	58	Male	Fever	AIDS	NA	Total leukocyte count (mm^{-3}), 20; PRO (mg/dL), 53; GLU (mg/dL), 32	Culture + PCR	NA	NA	1 day	Died
12 [17]	38	Male	Headache	AIDS	NA	Total leukocyte count (mm^{-3}), 110; PRO (mg/dl), 600; GLU (mg/dL), 63	PCR	None	NA	0 day	Died
13 [18]	63	Male	Headaches, word-finding difficulties	Sarcoidosis	NA	NA	Brain biopsy	ETH + CLR	NA	11 months	Survived
14 [19]	28	Male	Anorexia, dysphagia, weight loss, fever, headache	AIDS	Encephalitis	No visible leukocyte, normal PRO, reduced GLU (24 mg/dL), increased CSF lactate dehydrogenase (40 mg/dL)	Culture*	AmB+5-FC ，FCZ*; AZM+ +ETH + RFB	AmB, 5-FC*; INH + RIF	12 months	Survived
15 [20]	29	Female	NA	None	Meningitis	NA	NA	NA	NA	NA	Survived
16 [21]	5	Female	NA	None	Meningitis	Increased cells and protein, low glucose	Culture	NA	NA	NA	Died
17 [21]	14	Male	NA	None	Meningitis	Cloudy; WBCs, 3000/mm3	Culture	PEN + SSZ	NA	2 weeks	Survived

(*continued on next page*)

Table 2 (*continued*)

Cases	Age	Gender	Clinical manifestations	Underlying medical conditions	Diagnostic imaging	Cerebrospinal fluid	pathogen detection method	Treatment options	Drug sensitivity	Course	Prognosis
18 [22]	46	Female	Headaches, diplopia, decreased visual acuity	None	Meningitis	WBCs, 83/mm^3 (100% lymphocytes); PRO, 38 mg/dL; GLU, 32 mg/dL	Culture*	AmB+5-FC; INH + RIF added	R: INH, PAS, RIF, ETH, STM, CYS	1 year	Survived
19 [23]	1	Female	NA	None	Meningitis	NA	NA	NA	NA	NA	Died
20 [23]	8	Male	NA	Chronic otitis media	Otitis, cervical adenitis; no meningitis	NA	NA	NA	NA	NA	Survived
21 [24]	30	Male	Fever	AIDS	encephalopathy	NA	Culture	NA	NA	NA	Died
22 [25]	NA	NA	NA	Leukemia	Meningitis	NA	NA	NA	NA	NA	Died
23 [26]	40	Female	Fever	None	Meningitis	WBCs, 471mm^3 (13% PMNs, 84% lymphocytes); PRO, 234 mg/dL; GLU, 41 mg/dL	NA	PEN + CLR + INH + RIF	NA	2 days	Survived
24 [26]	58	Male	NA	Leukemia	NA	NA	NA	NA	NA	NA	Died
25,26 [27]	NA	NA	NA	AIDS	Meningoencephalitis	WBCs, 13/mm^3 and 15/mm3; PRO levels increased	NA	NA	NA	NA	Died
27,28 [28]	NA	NA	NA	AIDS	Meningitis	NA	NA	NA	NA	NA	Died
29-43 [29]	33 ± 4†	9 Male, 6 Female	Weight loss, fever, seizures, confusion, headaches,and vomiting‡	AIDS	NA	Lymphocytes, 71%; PRO, 41 mg/dL± 18 mg/dL†; GLU, 54 mg/dL±23 mg/dL†	Culture	NA	NA	NA	In-hospital mortality, 67%
44 (PR)	55	Male	Headache, fever	Diabetes	Meningoencephalitis	WBCs, 88 × 10^6/L; GLU, 2.1 mmol/L; CL, 112.7 mmol/L; PRO, 1.31 g/L	mNGS	INH + RIF + AZM + MFX	NA	7 weeks	Survived

Note: AM = Ansamycin; AmB = amphotericin B; AMK = amikacin; AZM = azithromycin; CFZ = clofacimine; CIP = ciprofloxacin; CM = capreomycin; CYS = Cycloserine; GLU: glucose; LFX = levofloxacin; CLR = clarithromycin; ETH = ethambutol; ETO = ethionamide; FCZ = fluconazole INH = isoniazid; LZD = linezolid; MAC = *Mycobacterium avium* complex; MEM = meropenem; MFX = moxifloxacin; NA = not available; OFX = ofloxacin; PAS = *para*-aminosalicylic acid; PEN = penicillin; PR = present report; PRO: protein; PZA = pyrazinamide; R = drug resistance; RFB = rifabutin; RIF = rifampicin; S = sensitive; STM = streptomycin; SSZ = sulfizoxazole; WBCs: white blood cell count; † Mean ± SD; ‡ Fifteen patients had weight loss, eight had fever, two had seizures, four had confusion, and five had headaches and vomiting; * MAC and Cryptococcus neoformans co-infection.

Nontuberculous Mycobacterial Disease (2020 Edition) [1] states that combined anti-mycobacterial drug is the method of choice, but drug resistance should be considered depending on the species.

Drug resistance of NTM varies among species. For example, fast-growing NTM such as *M. abcessus*, *M. chelonea* and *M. fortuitum* are naturally resistant to isoniazid. Rifampicin has robust activity against *M. kansasii* and *M. gordonae*, but has a weak antibacterial activity against MAC; whereas *M. scrofulaceum* seems resistant to rifampicin. Moxifloxacin had strong effect on slow growing NTM such as MAC, *M. kansasii*, *M. gordonae* and *M. xenopi*; however, the antibacterial activity against fast-growing NTM such as *M. abcessus* and *M. chelonea* is weak, and it has certain antibacterial activity against *M. fortuitum* [1]. However, the correlation between susceptibility test results and clinical efficacy has not been fully established. MAC is generally sensitive to macrolides, clofazimine, and aminoglycoside antibiotics, and it has mixed sensitivities to rifampicin, rifabutin, ethambutol, fluoroquinolones, and linezolid [37]. Except for macrolides and amikacin from which susceptibility testing is recommended, the correlation between clinical outcome and *in vitro* susceptibility test results for the rest of antimicrobials remains unclear, and routine *in vitro* susceptibility testing for ethambutol, rifabutin, clofazimine, rifampicin, moxifloxacin, and ciprofloxacin, is not recommended for MAC infections. For MAC, the minimal inhibitory concentration (MIC) of macrolides and amikacin is clinically relevant to *in vivo* reactions, the MIC of azithromycin against MAC is 2∼128 μg/mL^{1}; in the vast majority of patients who have not previously received treatment for MAC, their infection generally respond properly to macrolides. When MAC shows resistances to macrolides, they must be rapidly replaced by other drugs. For CNS infections, a multidrug therapeutic regimen similar to NTM lung disease is commonly used. However, azithromycin, clarithromycin, and amikacin have poor access to the CNS owing to low blood-brain barrier (BBB) permeability, making treatment more difficult. Moreover, adverse drug reactions, such as liver and kidney damage, cardiac and hematologic toxicity should also be considered, in our case, the early use of a fluoroquinolone combined with a macrolide increased the risk of Q-T interval prolongation; therefore, azithromycin was discontinued after 5 days, retaining moxifloxacin. In addition, the combination of fluoroquinolones and macrolides has been reported to increase the risk factor for drug-resistance of the latter group [40]. Komachi et al. [8] reported a case of *M. intracellulare* meningitis in immunocompetent patients, using streptomycin, amikacin, ethambutol, cycloserine, etc. The response was poor; however, after adding fluoroquinolone (ofloxacin) the patient's condition improved. Central nervous system infections usually need prolonged treatment to reduce the risk of recurrence.

4.4. Mortality

CNS infections by NTM are severe and have poor prognosis. A mortality rate of 72.8% has been reported in patients with AIDS. Whereas in non- AIDS patients, the mortality rate although significantly lower (32.4%), remains very high [6,39]. Several conditions may be related to low survival, including immunosuppression, delayed diagnosis and treatment, drug-resistance, failure of antimycobacterial drugs to cross the BBB or patient fragility due to high comorbidity [6,39].

Our study has limitations, for example, we were not able to assess MAC sensitivity to antimycobacterial drugs, as we did not use specific culture media for such bacteria, highlighting the role of mNGS when a specific cause is not suspected. Sensitivity was not further searched as the patient showed a rapid and robust clinical improvement with the provided antimycobacterial regimen. We recognize that our initial approach to treat this patient was conservative and owing to the high mortality related a more aggressive therapeutic approach is usually warranted. However, it should be noted that we used high doses of INH in our patient, increasing the risk of side effects such a numbness, clumsiness, vomiting, fatigue or dark urine, they were not reported by our patient and he had a robust clinical response.

5. Conclusions

Infections of the CNS by MAC are uncommon, difficult to diagnose and have a very high mortality rate. They frequently occur in immunocompromised, mostly HIV-positive patients, but are also observed in other conditions causing impaired immune responses such as poorly controlled diabetes mellitus. In those cases, CSF analyzed with second-generation mNGS can be useful for infections that are difficult to diagnose by culture or other techniques. Rapid detection of MAC and other NTM can lead to early treatment that may increase survival.

Ethics statement

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements. Participant' legal guardian/next of kin was consent to participate in this study. Informed consent was obtained from the guardian for the publication of all images, clinical data and other data included in the manuscript.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors on reasonable request.

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CRediT authorship contribution statement

Changsheng Wang: Writing – original draft. **Mengqiu Pan:** Resources. **Qinjian Lin:** Formal analysis. **Mohammad Mofatteh:** Writing – review & editing. **Yimin Chen:** Writing – review & editing. **José Fidel Baizabal-Carvallo:** Writing – review & editing. **Fanghua Su:** Methodology. **Zhanhang Wang:** Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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