INTERNAL MEDICINE JOURNAL

RACP Specialists. Together

doi:10.1111/imj.70017

ORIGINAL ARTICLE

Central nervous system tuberculosis in Western Sydney: a 10-year retrospective cohort study

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Key words
tuberculosis, tuberculous meningitis, tuberculoma, central nervous system, Western Sydney, Australia.

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Received 28 May 2024; accepted 6 January 2025.

Abstract

Background: Central nervous system tuberculosis (CNS-TB) is a rare complication of tuberculosis. There is a lack of data surrounding investigation and management of this in Australia.

Aim: To review CNS-TB cases in Western Sydney, Australia, and understand the epidemiology, investigation, diagnosis, management and outcomes in a low-prevalence setting.

Methods: Retrospective cohort study of all CNS-TB patients managed in Western Sydney from 2013 to 2022. Demographics, risk factors, clinical presentation, investigations and management were reviewed. Clinical outcomes like hospital length-of-stay, adverse drug reactions, paradoxical reactions, functional disability and treatment outcomes, including cure, treatment failure, loss to follow-up and death, were also measured.

Results: Thirty-nine CNS-TB cases were identified, with 16 (41%) confirmed by nucleic acid amplification test or culture of CNS specimens and 23 (59%) diagnosed presumptively without CNS microbiological confirmation. The median age was 32 years. Thirty-seven (95%) were overseas-born; 27 (69%) had no comorbidities. Presenting symptoms included fever (82%), headache (64%) and weight loss (51%). Twenty-five (64%) used fluoroquinolones and nine (23%) used high-dose rifampicin. Steroids were used in all patients. Six (15%) were prescribed aspirin for primary stroke prevention. Twenty-eight (73%) completed treatment, with one requiring re-treatment for presumed treatment failure. Six (15%) were lost to follow-up, and five (13%) died during their treatment course. Twenty-one (54%) experienced an adverse drug reaction.

Conclusion: Tuberculosis is an ongoing public health issue in Australia, with CNS-TB being its most devastating form, and all clinicians to be aware of this rare complication. The efficacy of newer treatment options requires further study.

Introduction

Tuberculosis (TB) is one of the most common infectious diseases, affecting an estimated 10.6 million people globally in 2022. The disease burden is geographically concentrated, with eight countries accounting for over two-thirds of all cases.[1] Central nervous system (CNS) TB constitutes around 1% of diagnosed TB cases[2] and manifests as either tuberculous meningitis or tuberculomas, with mortality rates approaching 20% in human immunodeficiency virus (HIV)-negative individuals and up to 50% in HIV-positive individuals.[3] Large case series of CNS-TB are available from high-prevalence countries.[4] However, data from low-prevalence settings is lacking. A single case series involving 22 CNS-TB cases in Australia[5] was published 30 years ago, predating the widespread availability of rapid molecular testing methods,[6] and the incorporation of high-dose dexamethasone into standard treatment practices.[7] Standard

Funding: None.
Conflict of interest: None.

TB treatment includes the use of rifampicin and isoniazid for at least 6 months together with pyrazinamide and ethambutol for the first 2 months in those with fully susceptible TB.[8] Managing CNS-TB poses additional challenges due to reduced CNS absorption of drugs like ethambutol and rifampicin.[9] Despite increasing evidence supporting the inclusion of fluroquinolones[10] for the treatment of CNS-TB due to improved CNS penetration, there is currently no consensus on the optimal treatment regimen for CNS-TB, other than the addition of dexamethasone and extending the standard therapy duration to 12 months.[11]

The Western Sydney Local Health District (WSLHD) is a large health precinct in New South Wales (NSW), Australia, comprising four hospitals and serving over 1.1 million people, with 46.8% of residents born overseas.[12] WSLHD had the highest rate of TB notifications in NSW, with 16.9 cases per 100 000 population in 2021.[13] Extrapulmonary cases accounted for over one-third of TB notifications in NSW, with 4% involving the CNS.[12]

We conducted a retrospective review spanning 10 years (2013–2022) to assess and describe the demographics, risk factors, clinical presentation, diagnosis, management and clinical outcomes of adults with CNS-TB diagnosed and managed in WSLHD.

Methods

Study population

Adult patients aged 16 years or older who were diagnosed and treated for CNS-TB within WSLHD, between 1 January 2013 and 31 December 2022, were included in the study.

Cases were identified by reviewing relevant clinical codes based on the International Classification of Diseases, 10th Revision (ICD-10) for previously admitted patients with CNS-TB across all WSLHD hospitals. Additionally, positive *Mycobacterium tuberculosis* microbiology results for cerebrospinal fluid (CSF) and CNS tissue through nucleic acid amplification test (NAAT) and/or culture were extracted from the microbiology laboratory database. These were then correlated with hospital clinical notes, community TB service and infectious diseases clinics.

The inclusion criteria were: (i) the diagnosis of CNS-TB based on a positive CSF or CNS tissue acid-fast bacilli (AFB) stain, mycobacterial culture or *M. tuberculosis* NAAT, or (ii) presumptive diagnosis of CNS-TB, based on demographics, clinical findings and investigations; and (iii) diagnosis of CNS-TB was made within the study period.

The date of diagnosis was defined as the earliest of the following: (i) day of commencement of empirical treatment for CNS-TB; (ii) day of microbiological confirmation if not already on treatment; or (iii) day that CNS-TB was considered the most probable diagnosis if the patient was already on TB treatment.

Cases were excluded if they were presumptively diagnosed with CNS-TB but later found to have an alternate cause for their clinical syndrome.

Data collection

Patient demographics, clinical symptoms on presentation, social and medical risk factors, investigations, treatment regimen and duration and clinical outcomes were collected from medical records.

Clinical treatment outcomes, classified according to the World Health Organisation (WHO) 2021 update, included cure, treatment complete, treatment failure, lost to follow-up and death.[14] As repeat sampling is rarely performed to confirm cure in CNS-TB, treatment completion was considered a successful treatment outcome for this study. Other clinical outcomes reviewed included hospital length of stay, hospital re-admission, adverse drug reactions (ADR), paradoxical-immune reconstitution inflammatory syndrome (IRIS) reactions, functional disability at the time of hospital discharge and treatment completion and TB-related mortality and all-cause mortality at 3 months and 12 months. The Modified Rankin Scale defined functional disability.[15]

Ethical approval

This study was approved by the WSLHD Human Research Ethics Committee (2023/ETH00483).

Results

Fifty-one cases of CNS-TB were identified through initial screening. Twelve were excluded (Fig. 1), leaving 39 cases of CNS-TB for inclusion in the final analysis.

Of the 39 cases, 16 (41%) were microbiologically confirmed either on CSF ($n = 14$) or brain tissue ($n = 2$) with positive AFB stain, culture or NAAT. AFBs were seen in one CSF specimen and both tissue specimens; all three were both NAAT and culture-positive. Table 1 depicts a summary of these results. The remaining 23 (59%) cases were presumptive diagnoses based on available investigations: 13 had *M. tuberculosis* detected at other sites and 10 were microbiologically negative. The majority ($n = 11$, 85%) of presumptive diagnoses with *M. tuberculosis* detected at other sites had visible brain

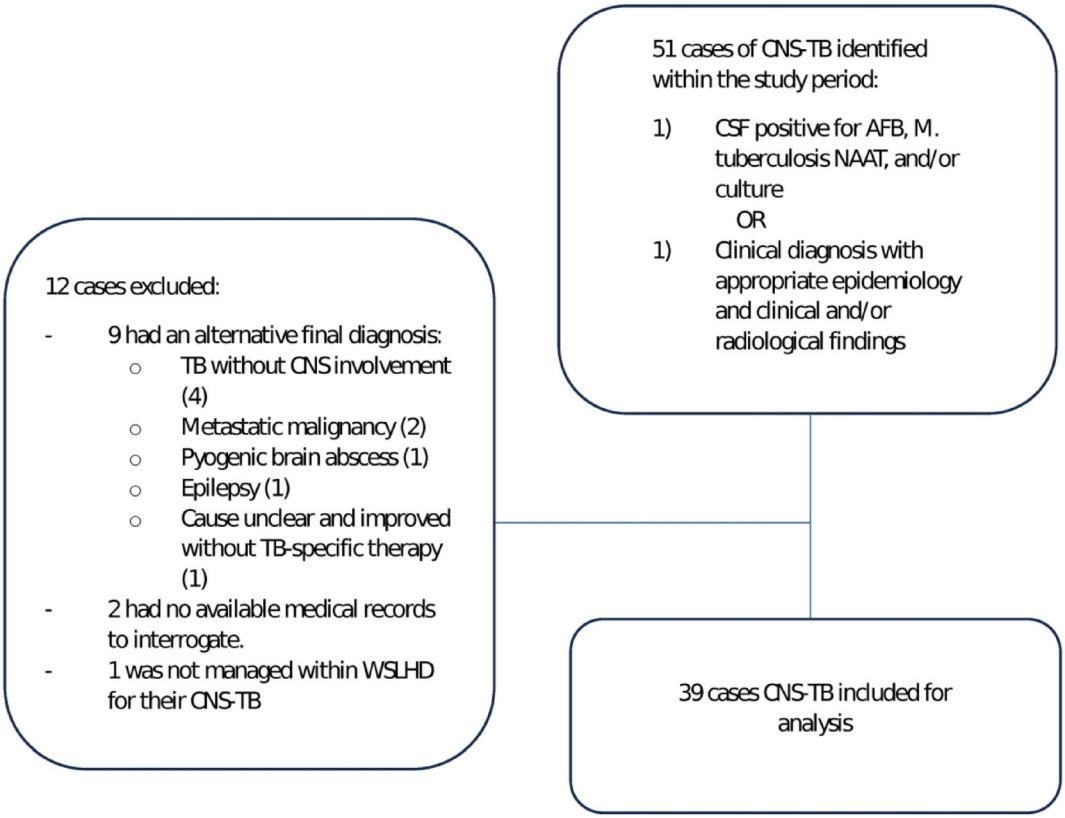

Figure 1 Patient inclusion for the study. AFB, acid fast bacilli; CNS-TB, central nervous system tuberculosis; CSF, cerebrospinal fluid; NAAT, nucleic acid amplication test; WSLHD, Western Sydney Local Health District.

lesions on imaging suggestive of tuberculomas. However, seven (54%) either had no detectable pleocytosis in CSF ($n = 3$) or had no CSF collected ($n = 4$). Conversely, most microbiologically negative cases ($n = 8$, 80%) had no visible brain lesions on imaging, but all had CSF collected with a detectable pleocytosis.

Table 1 Diagnostics and susceptibilities of central nervous system tuberculosis specimens in Western Sydney between 2013 and 2022

Patient	Specimen	AFB	NAAT	Culture	Hain line probe assay test	Cepheid Xpert MTB/RIF	Culture sensitivities	Resistance genes
1	CSF	−	−	+	Performed	NP	Fully susceptible	Nil detected
2	CSF	−	+	+	NP	NP	Fully susceptible	NP
3	CSF	−	+	+	NP	NP	Fully susceptible	NP
4	CSF	−	+	−	NP	NP	NP	NP
5	Tissue	+	−	+	NP	NP	Fully susceptible	NP
6	CSF	−	+	−	Performed	NP	NP	Inhibin subunit alpha
7	CSF	−	+	−	NP	NP	NP	NP
8	CSF	+	+	+	Invalid result	NP	Fully susceptible	NP
9	CSF	−	−	+	NP	NP	Fully susceptible	NP
10	CSF	−	−	+	NP	NP	Fully susceptible	NP
11	CSF	−	+	+	Performed	NP	Fully susceptible	Nil detected
12	Tissue	+	+	+	Performed	NP	Fully susceptible	Nil detected
13	CSF	−	+	+	Invalid result	Performed on culture	Fully susceptible	Nil detected
14	CSF	−	−	+	Performed	Performed on culture	Fully susceptible	Nil detected
15	CSF	−	+	−	NP	Performed on CSF (unvalidated)	NP	Nil detected
16	CSF	−	+	+	Performed	Performed on culture	Fully susceptible	Nil detected

AFB, acid-fast bacilli; CSF, cerebrospinal fluid; NAAT, nucleic acid amplification test; NP, not performed.

Patient demographics and risk factors

Demographic features are presented in Table 2. Twenty-one patients were female (54%). The median age of diagnosis was 32 years (17–83). Thirty-seven patients (95%) were born overseas, with median duration in Australia before CNS-TB diagnosis being 2 years. India was the most common country of origin ($n = 19$, 49%), followed by Nepal ($n = 9$, 23%). Two patients (5%) were born in Australia; both reported previously visiting a current or previous TB high incidence country with no other identified risk factors. Other risk factors included known TB contacts ($n = 13$, 33%), smoking ($n = 5$, 13%) and healthcare work ($n = 4$, 10%).

Twenty-seven (69%) patients did not have any comorbidities. Six (15%) patients had diabetes mellitus and two (5.1%) had chronic kidney disease. Four patients (10%) had established immunodeficiency; two from haematological malignancy, one from chemotherapy and one from immunosuppressive medications. Two (5%) patients were newly diagnosed with HIV following their CNS-TB diagnosis; CD4 count was 1/μL and 224/μL.

Clinical presentation and investigations

Table 3 summarises clinical features and investigation results. The most common symptoms were fever ($n = 32$, 82%), headache ($n = 25$, 64%) and weight loss ($n = 20$, 51%). Focal neurological signs were seen in 16 (41%) patients, including cranial nerve deficits ($n = 10$, 26%) and peripheral limb deficits ($n = 6$, 15%). Four patients ($n = 4$, 10%) presented with an established stroke. Median number of days from admission to CNS-TB diagnosis was 3 days (0–45).

Interferon-gamma release assay (IGRA) testing was performed in 23 (59%) cases; 17 were immunocompetent and six were immunocompromised. In the immunocompetent patients, 12 (71%) were positive, four (23%) negative and one (6%) was indeterminate. Of the six immunocompromised patients, including the two HIV patients, four were negative and two had an invalid result.

The median time to first lumbar puncture (LP) was 1 day (0–33). The median opening pressure was 18 cmH_2O (5–35). The median CSF protein and glucose were 1.4 mmol/L (0.1–9.2) and 2.3 g/L (0.2–5.2) respectively. The median leukocyte count in CSF was 124×10^6 cells/L (0–3818), with mononuclear cell predominance. Fourteen patients had *M. tuberculosis* detected in CSF; either by NAAT alone ($n = 5$) or culture alone ($n = 4$), or both ($n = 5$); only one specimen had detectable AFB, and was both NAAT and culture positive. An in-house NAAT assay that targeted the *IS6110* and internal transcribed spacer gene sequences was used for all samples. The mean volume of CSF collected was 5.3 mL; slightly higher in those with negative microbiology (5.4 mL) compared to those with positive culture and/or NAAT (5.1 mL). Twenty (51%) patients had confirmed active pulmonary TB on either culture or NAAT of respiratory specimens.

Eight positive CSF specimens by either NAAT or culture had a Hain GenoType Line Probe Assay test

Table 2 Characteristics of 39 patients diagnosed with central nervous system tuberculosis (CNS-TB) in Western Sydney, Australia in 2013–2022

Total number (*n*)		39
Age, median (range)		32 (17–83)
Gender, *n* (%)	Male	18 (46%)
	Female	21 (54%)
Body mass index, median (range)		22.0 (15.9–36.6)
Country of origin, *n* (%)	India	19 (49%)
	Nepal	9 (23%)
	Australia	2 (5%)
	Sri Lanka	2 (5%)
	Afghanistan	1 (3%)
	China	1 (3%)
	Kenya	1 (3%)
	Malaysia	1 (3%)
	Myanmar	1 (3%)
	Philippines	1 (3%)
	Vietnam	1 (3%)
Total years in Australia prior to diagnosis if overseas-born, median (range)		2 (0–65)
Risk factors, *n* (%)	Previous travel to current or previous TB high incidence country	39 (100%)
	Reported TB exposure	13 (33%)
	Active smoker	5 (13%)
	Healthcare worker	4 (10%)
	Alcohol abuse	1 (3%)
Comorbidities, *n* (%)	Diabetes mellitus	6 (15%)
	Immunodeficiency/ suppression (excluding HIV)	4 (10%)
	Chronic kidney disease	2 (5%)
	HIV	2 (5%)
	Chronic respiratory disease	0 (0%)
Microbiological diagnosis, *n* (%)†	Positive	16 (41%)
	Negative	23 (59%)
Primary pathology, *n* (%)	Meningitis	20 (51%)
	Tuberculoma	19 (49%)
Other sites of tuberculosis, *n* (%)	Pulmonary	23 (59%)
	Non-CNS extrapulmonary TB	13 (33%)
Days until CNS-TB diagnosis from admission, median (range)		3 (0–45)

†Includes acid-fast bacilli smear, culture or nucleic acid amplification test on cerebrospinal fluid or cerebral tissue.

CNS, central nervous system; HIV, human immunodeficiency virus; TB, tuberculosis.

Table 3 Clinical and investigation findings on Western Sydney central nervous system tuberculosis patients between 2013 and 2022

Clinical features				
Duration (days) of symptoms prior to presentation, median (range)				10 (2–90)
Signs/Symptoms, *n* (%)	Fever			32 (82%)
	Headache			25 (64%)
	Weight loss			20 (51%)
	Confusion or reduced consciousness			17 (44%)
	Focal neurology			16 (41%)
	Cough			13 (33%)
	Neck stiffness			8 (21%)
	Photophobia			6 (15%)
	Seizures			2 (5%)
Investigations				
Initial bloods, median (range)	Haemoglobin (g/L)			122 (80–164)
	Total white cell count ($\times 10^9$/L)			8.2 (3.4–132.2)
	C-reactive protein (mg/L)			28 (2–229)
	Sodium (mmol/L)			134 (108–142)
Cerebrospinal fluid profile	Opening pressure on initial lumbar puncture in cmH_2O, median (range)			18 (5 to >34)
	Biochemistry, median, (range)	Protein (g/L)		1.4 (0.11–9.18)
		Glucose (mmol/L)		2.3 (0.2–5.2)
	Cell count, median (range)	Total leukocytes ($\times 10^6$/L)		124 (0–3818)
		Polymorphs ($\times 10^6$/L)		7 (0–195)
		Mononuclear cells ($\times 10^6$/L)		67.5 (0–3742)
Microbiology	CSF	Unique patients with at least one specimen collected		34 (87%)
		Positive results (% total CSF specimens)	Overall	14 (41%)
			Acid fast bacilli stain	1 (3%)
			Culture	10 (26%)
			NAAT	10 (26%)
	Tissue (CNS)	Unique patients with at least one specimen collected		2 (5%)
		Positive results (% total tissue specimens)	Culture	2
			NAAT	1
	Respiratory	Unique patients with at least one specimen collected		39 (100%)
		Positive results (% total respiratory specimens)	Overall	20 (51%)
			Acid fast bacilli stain	4 (10%)
			Culture	15 (39%)
			NAAT	13 (33%)
	Other specimens positive on NAAT or culture (not CNS or respiratory)			13 (33%)
Radiology				
Computed tomography brain	Performed (%)			33 (85%)
	Abnormality detected in first available scan (%)			13 (39%)
	Signs	Discrete lesion		9
		Basal/Leptomeningeal enhancement		0
		Hydrocephalus		2
		Infarction		2
Magnetic resonance imaging brain	Performed (%)			38 (97%)
	Abnormality detected in first available scan (%)			30 (79%)
	Signs	Discrete lesion		17
		Basal/Leptomeningeal enhancement		14
		Hydrocephalus		2
		Infarction		3

CNS, central nervous system; CSF, cerebrospinal fluid; NAAT, nucleic acid amplification test.

attempted; six were successful, and two were invalid. Only one patient had detectable drug resistance with an *inhA* gene mutation detected consistent with low-level isoniazid resistance. All cultured specimens were found to be fully susceptible to standard TB therapy. From 2021, Cepheid Xpert MTB/RIF assay was used directly on cultured specimens to detect genotypic rifampicin resistance, all tested negative in this study. One additional unvalidated attempt was made directly on CSF, but was also negative.

CNS imaging was performed for all patients; either computed tomography (CT) alone ($n = 1$, 3%) or magnetic resonance imaging (MRI) alone ($n = 6$, 15%), or both ($n = 32$, 82%). Abnormalities were detected in 39% and 79% of first available CT and MRI scans, respectively. Initial imaging findings included discrete lesions suggestive of tuberculomas (44%), basal/leptomeningeal enhancement (36%), infarction (10%) and hydrocephalus (5%). Figure 2 depicts examples of these findings. Clinical presentation and risk factors were similar between those presenting with or without tuberculomas, aside from weight loss, where tuberculoma patients were more likely to have weight loss than meningitis patients (68% vs 40%).

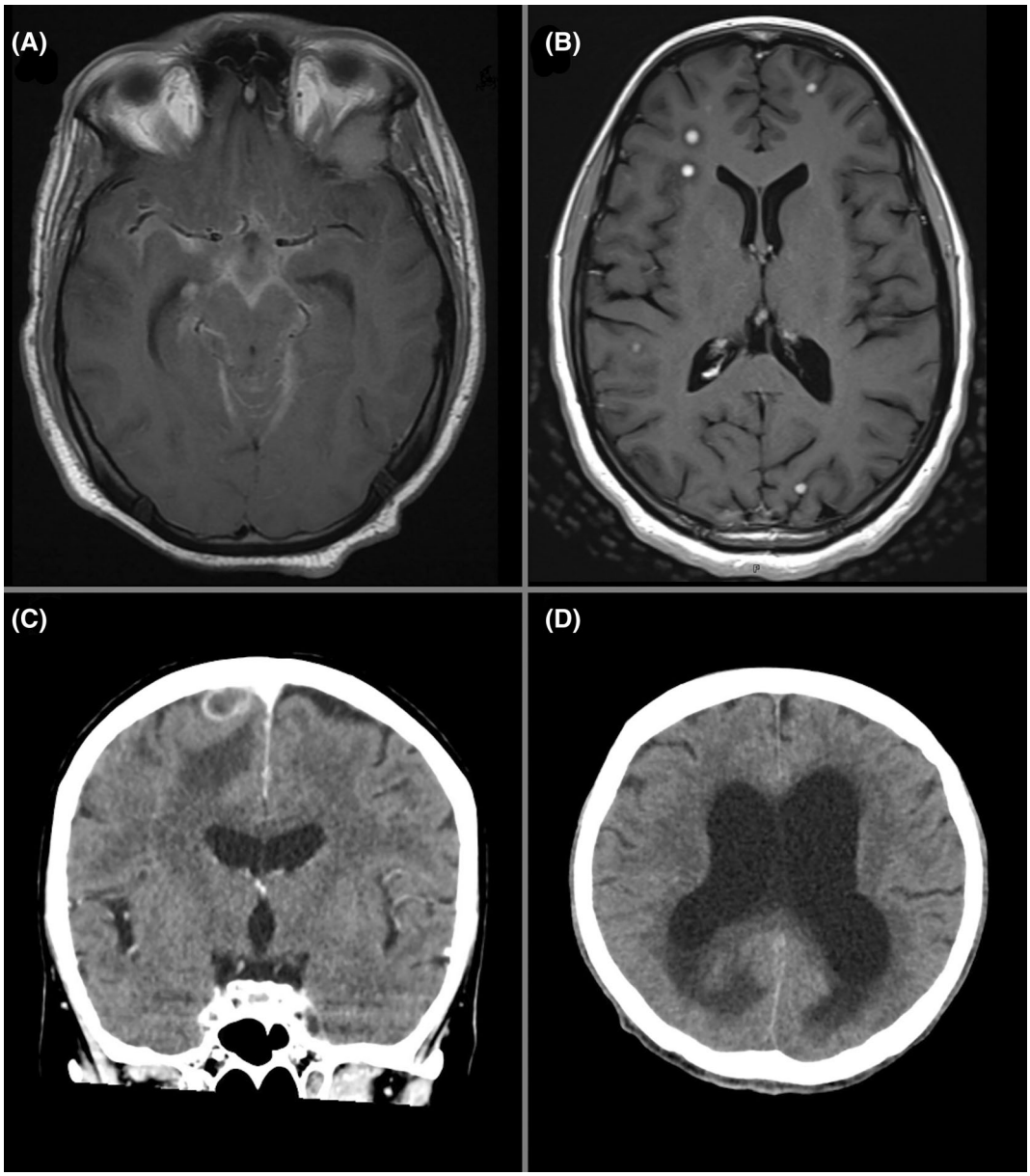

Figure 2 Different radiological manifestations of central nervous system tuberculosis. (A) A T1-weighted contrast magnetic resonance imaging (MRI) brain scan depicting severe leptomeningeal enhancement of the basal cisterns. (B) A T1-weighted contrast MRI with numerous enhancing nodules with mild oedema, suggestive of multiple small tuberculomas. (C) A contrast-enhanced computed tomography (CT) brain scan depicting a 1.5 × 1.7 × 1 cm ring-enhancing lesion in the posterior right frontal lobe with vasogenic oedema, concerning for a single tuberculoma. (D) A non-contrast CT showing moderate–severe hydrocephalus.

Management

For the intensive phase of treatment, 36 (92%) regimens included a rifamycin-based agent together with isoniazid and pyrazinamide. Rifampicin was used in the majority of cases, with three patients receiving rifabutin instead due to concerns about rifampicin drug interactions. High-dose rifampicin, defined as 900 mg or more, was used in nine (23%) patients. Twenty-five (64%) regimens included a fluoroquinolone. Of the fluoroquinolones, moxifloxacin ($n = 18$) was prescribed more commonly than levofloxacin ($n = 7$).

Twenty-eight (72%) patients completed the intended treatment regimen – the median duration of intensive and complete treatment was 67 and 364 days, respectively. Table 4 summarises the treatment regimens and duration for those who completed the intended therapy. For patients without available drug susceptibilities ($n = 21$), fluoroquinolone-based regimens were favoured ($n = 16$, 76%) over non-fluoroquinolone-based combinations ($n = 5$, 24%); the median duration of intensive and complete treatment was the same. Duration of fluoroquinolone use varied in those who completed treatment; five (25%) ceased within

Table 4 Management of central nervous system tuberculosis patients in Western Sydney, Australia 2013–2022

Primary treatment regimen			
Treatment regimens utilised, including those who did not complete treatment[1]	HRZE†		14 (36%)
	HRZE + FQ†		13 (33%)
	HRZ + FQ†		9 (23%)
	Other (all included FQ and excluded rifamycin)		3 (8%)
Antimicrobial usage and duration in patients who completed intended treatment			
Total number of patients who completed intended treatment, *n* (%)			28 (72%)
Rifamycin	Usage		28 (100%)
	Agent (% of total usage)	Rifampicin	27 (96%)
		Rifabutin	1 (4%)
	Duration in days, median (range)		365 (72–551)
	High dose rifampicin usage (over 600 mg/day)		9 (32%)
Isoniazid	Usage		27 (96%)
	Duration in days, median (range)		365 (250–551)
Pyrazinamide	Usage		28 (100%)
	Duration in days, median (range)		70 (6–378)
Ethambutol	Usage		21 (75%)
	Duration in days, median (range)		59 (1–370)
Fluoroquinolone	Usage		19 (68%)
	Agent (% of total usage)	Moxifloxacin	13 (68%)
		Levofloxacin	6 (32%)
	Duration in days, median (range)		178 (29–537)
Second-line drug usage (*n*)	Linezolid		2
	Amikacin		2
	Capreomycin		1
Overall median treatment duration (days)	Intensive phase with four or more antimicrobials, median (range)		67 (32–378)
	Total, median (range)		364 (250–551)
Adjunctive corticosteroids			
Usage, *n* (%)			39 (100%)
Initial formulation	Dexamethasone		24 (62%)
	Prednisone		12 (31%)
	Methylprednisolone		2 (5%)
	Hydrocortisone		1 (3%)
Initial dose (mean)	Equivalent dexamethasone dose (mg/24 h)		20.0
	Equivalent weight-based dexamethasone dose (mg/kg/24 h)		0.30
Duration in days in patients who completed intended treatment, median (range)			68 (4–1007)
Other adjunctive treatments			
Immunomodulator usage for paradoxical tuberculosis-related IRIS, *n* (%)			4 (14%)
Aspirin commenced for central nervous system tuberculosis-related stroke prevention, *n* (%)			6 (21%)
Surgical intervention, *n* (%)			4 (14%)

†H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol; FQ: fluoroquinolone.

IRIS, immune reconstitution inflammatory syndrome.

the 2-month intensive phase, whereas 15 (75%) were utilised for longer. Drug levels were measured for four patients (10%), but no dose changes were observed.

Corticosteroids were used in all patients, with dexamethasone being the most utilised agent ($n = 24$, 62%). The median duration of corticosteroids in those who completed treatment was 68 days (4–1007). For patients that did not have a documented paradoxical-IRIS or other indication, this range was shorter (4–268 days). Aspirin was commenced for primary stroke prevention in CNS-TB for six patients (15%) and secondary prevention in three patients who presented with stroke. Neurosurgical intervention was performed in six patients (15%); most commonly external ventricular drainage ($n = 4$).

Clinical outcomes

All measured outcomes have been summarised in Table 5. For initial hospitalisation, the median length of stay was 18 days (range 3–127). Twenty-one patients (54%) required re-admission to hospital within 1 year. Of these, 14 (36%) were TB-related, including four medication reactions. There was at least one documented ADR in 21 patients (54%); the most common being drug-induced liver injury ($n = 10$, 26%), nausea ($n = 6$, 15%) and rash ($n = 5$, 13%). Of the 25 patients who were managed with a fluoroquinolone-based regimen, the majority ($n = 17$, 68%) had a reported ADR, with liver injury the most common ($n = 10$, 40%). Of the nine patients who were given high-dose rifampicin, seven (78%) reported an ADR, also most commonly liver injury ($n = 4$).

Ten (26%) patients developed paradoxical-IRIS. In these patients, median length of stay was extended to 25 days. The median time from TB treatment initiation to the development of paradoxical-IRIS was 47 days (8–171). Eight (80%) were managed with either restarting steroids or steroid-dose increase. Four (40%) patients required further immunosuppression with either methotrexate ($n = 1$) and/or infliximab ($n = 4$).

Twenty-eight (73%) patients completed their treatment course, six (15%) were lost to follow-up in WSLHD, and five (13%) died before completing therapy. Of the 28 patients who completed treatment, 27 were considered to have achieved a successful treatment outcome. One patient was considered to have failed treatment, with disease relapse diagnosed overseas without microbiological confirmation; therapy was restarted overseas and continued upon return to Australia. Of the six patients who were lost to follow-up, five had returned to their home country before treatment completion and could not be contacted, and

Table 5 Clinical outcomes of central nervous system tuberculosis patients in Western Sydney, Australia 2013–2022

Hospitalisation			39 (100%)
Length of stay for primary admission, median (range)			18 (3–127)
Re-admission to hospital within 1 year, *n* (%)	For TB disease-related reasons		10 (26%)
	For TB medication-related reasons		4 (10%)
	For any reason		21 (54%)
Adverse drug reactions, *n* (%)	Overall		21 (54%)
	Drug induced liver injury		10 (26%)
	Nausea/vomiting		6 (15%)
	Rash		5 (13%)
	Behavioural change		3 (8%)
	Alopecia		2 (5%)
	Uveitis		1 (3%)
	Eosinophilia		1 (3%)
Development of paradoxical TB-related IRIS			10 (26%)
Treatment outcomes	Successful treatment outcome		27 (69%)
	Lost to follow-up before completing treatment		6 (15%)
	Treatment failure		1 (3%)
	Death (TB-related)	Total	2 (5%)
		3 months	2 (5%)
		12 months	2 (5%)
	Death (all-cause)	Total	5 (13%)
		3 months	2 (5%)
		12 months	5 (13%)
Functional outcome based on Modified Rankin Score, median (range)	At hospital discharge		1 (0–6)
	At treatment completion		0 (0–5)

IRIS, immune reconstitution inflammatory syndrome; TB, tuberculosis.

one had moved to another Australian city with planned follow-up, but outcomes could not be confirmed.

Of the five deaths, two were considered directly due to CNS-TB, and both died within 14 days of admission from CNS-related complications; one co-infected and newly diagnosed with HIV. Three patients died from other causes: two due to disseminated cytomegalovirus disease in haematological malignancy and one due to lymphoma complications. Functional outcome was measured using the Modified Rankin Scale; the median scores at hospital discharge and at treatment completion were 1 and 0 respectively. Health and safety outcomes at 24 months were not available for all patients, and thus not measured.

Of the 10 patients who were treated presumptively as CNS-TB without microbiological confirmation of pulmonary or extrapulmonary TB disease, similar clinical outcomes were seen when compared to the entire study cohort, with one death (10%) not thought to be TB-related, and five patients reporting ADRs (50%).

Discussion

In this retrospective study of 39 individuals treated for CNS-TB in Western Sydney, Australia, we observed a high treatment success rate, low mortality and evolving diagnostic and management approaches.

The all-cause mortality in our cohort was 13%, considerably lower than the reported global mortality of 20%–50%.[3] Reasons for this could include earlier access to healthcare and wider availability of health resources in metropolitan Australia. About half of the patients experienced at least one ADR; similar to a recent prospective study that reported ADRs in 47.9% of patients on TB medications.[16]

Routine corticosteroid use became widespread following evidence showing its significant mortality benefit in CNS-TB,[7] and all patients in our study received steroids. About one-quarter of our patients developed paradoxical-IRIS. The significance of this is difficult to evaluate, as reported rates vary significantly, from 2% to 23% for HIV-negative individuals with pulmonary or extrapulmonary TB, and up to 54.2% in HIV-positive CNS-TB patients.[17] The median time to paradoxical-IRIS reaction in our cohort was 47 days, previous literature has demonstrated a similar timeframe of 56 days.[18] The most commonly reported focal neurological deficit was cranial nerve palsy, consistent with the known pathophysiological process of CNS-TB,[19] with a recent review finding an incidence of 33.3%.[20]

There were almost equal numbers of female and male patients, consistent with recent data that demonstrated a similar incidence of TB meningitis between the two sexes.[21] The most recent NSW Health TB report showed significant multi-ethnic incidence of TB, with the predominant country of birth being India at 20%.[13] Almost half of CNS-TB cases in our study were born in India; likely reflective of the higher proportion of Indian migrants in WSLHD compared to other parts of NSW.[22] Two-thirds of patients did not have any previously known medical comorbidities; this was not unexpected given the relatively low median age at diagnosis of 32 years. Two patients were newly diagnosed with HIV, reinforcing the importance of HIV screening in extrapulmonary TB.

Less than half of patients demonstrated positive microbiology for *M. tuberculosis* on either CSF or tissue biopsy for definitive diagnosis. Only one CSF specimen demonstrated visible AFB on staining; previous reviews have outlined sensitivities of AFB staining to be as low as 10%, thought to be due to the paucibacillary nature of CNS-TB infections.[23] Culture yield depends on CSF volume[24]; unfortunately our case numbers were too low to discern a significant difference in CSF volume between those with definitive and presumed diagnoses. NAAT is a relatively newer diagnostic tool, and the optimal methods to increase sensitivity such as sample centrifugation are still being investigated.[25]

IGRA has generally been considered ineffective as a screening tool for CNS-TB.[26] The six immunocompromised patients who had IGRA performed either had a negative or invalid result, which was not unexpected given the reliance of the test on effective lymphocytes, and supporting the notion that negative IGRA does not rule out active TB.[27] However, IGRA was positive in over 70% of patients in our study without immunocompromise. The sensitivity of IGRA is improved in immunocompetent patients, and our study suggests it may be a useful adjunct to diagnosis even in the presence of active CNS disease.

In vitro data support fluoroquinolones due to their CNS penetration,[28] but inadequate clinical data is available for consensus recommendation of fluoroquinolones in treating CNS-TB.[29] Almost two-thirds of our cohort were managed with a fluoroquinolone-based regimen. The most recent WHO guidelines suggest levofloxacin over moxifloxacin due to less drug interactions including rifampicin.[30] While most patients were prescribed moxifloxacin, this was likely due to moxifloxacin being more readily available than levofloxacin in NSW during the study period. Understanding the limitations of our low case numbers, mortality was similar in those who received fluoroquinolones ($n = 3$, 12%) and those who did not ($n = 2$, 14%), and there was no clear outcome difference between those patients who received fluoroquinolones for 8 weeks compared to those who

received it for longer. All nine patients prescribed high-dose rifampicin survived; while this may offer better CNS penetration,[31] it has not been previously shown to have any significant mortality benefit.[31] Unlike previous studies,[32] patients in our cohort who received fluoroquinolones or high-dose rifampicin regimens had higher rates of adverse effects, primarily drug-induced liver injury.

Stroke is reported to occur in almost 30% of CNS-TB patients, with proposed mechanisms including thrombosis, arteritis, arterial compression by basal inflammation, and vasospasm.[33] A recent meta-analysis showed that aspirin use in CNS-TB for stroke prevention led to a significant reduction in stroke development, but had no overall mortality benefit.[34] In our study, stroke occurred in none of the six patients started on aspirin for primary prevention. Of the patients who presented with stroke and were commenced on aspirin for secondary prevention, one had antiplatelet agents briefly withheld in preparation for a procedure, and subsequently developed further strokes.

Limitations

Due to the small cohort size, our study was underpowered and limited our ability to report statistical significance. Randomised control trials with larger patient cohorts would be required to investigate the role of recent treatment trends like fluoroquinolone use.

Conclusion

Tuberculosis is a global health issue, with CNS-TB being one of the most concerning complications. Even in well-resourced healthcare settings like Australia, CNS-TB occurs and causes significant morbidity and mortality albeit much lower mortality than has been reported elsewhere. Due to Australia's identity as a multicultural country with growing levels of migration, all practising clinicians must recognise TB as a potential cause of CNS disease, particularly in patients born, or who have lived, in high TB incidence countries. Larger scale studies are required to review the effectiveness of newer treatment additions such as fluoroquinolones, high-dose rifampicin, or aspirin for stroke prophylaxis, and to further define the optimal treatment regimen and duration for CNS-TB infection.

Acknowledgements

We would like to acknowledge all the treating clinicians in WSLHD who were involved in the care of these patients. Open access publishing facilitated by Western Sydney University, as part of the Wiley - Western Sydney University agreement via the Council of Australian University Librarians.

Data availability statement

The de-identified data we analysed are not publicly available, but requests to the corresponding author for the data will be considered on a case-by-case basis.

References

1 World Health Organization. *Global Tuberculosis Report 2023*. Geneva: WHO; 2023.
2 Dian S, Ganiem AR, van Laarhoven A. Central nervous system tuberculosis. *Curr Opin Neurol* 2021; **34**: 396–402.
3 Seid G, Alemu A, Dagne B, Gamtesa DF. Microbiological diagnosis and mortality of tuberculosis meningitis: systematic review and meta-analysis. *PLoS One* 2023; **18**: e0279203.
4 Boonyagars L, Sangketchon C, Pholtawornkulchai K. Presentation, clinical characteristics, and treatment outcomes among tuberculous meningitis patients with and without HIV infection at Vajira Hospital, Thailand: a retrospective cohort study. *J Int Assoc Provid AIDS Care* 2021; **20**: 23259582211045551.
5 Watson JD, Shnier RC, Seale JP. Central nervous system tuberculosis in Australia: a report of 22 cases. *Med J Aust* 1993; **158**: 408–13.
6 Stevens WS, Scott L, Noble L, Gous N, Dheda K. Impact of the GeneXpert MTB/RIF technology on tuberculosis control. *Microbiol Spectr* 2017; **5**: 1–21.
7 Thwaites GE, Nguyen DB, Nguyen HD, Hoang TQ, Do TT, Nguyen TC *et al*. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *N Engl J Med* 2004; **351**: 1741–51.
8 Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A *et al*. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. *Clin Infect Dis* 2016; **63**: e147–95.
9 Panjasawatwong N, Wattanakul T, Hoglund RM, Bang ND, Pouplin T, Nosoongnoen W *et al*. Population pharmacokinetic properties of antituberculosis drugs in Vietnamese children with tuberculous meningitis. *Antimicrob Agents Chemother* 2020; **65**: 1–21.
10 Smith AGC, Gujabidze M, Avaliani T, Blumberg HM, Collins JM, Sabanadze S *et al*. Clinical outcomes among patients with tuberculous meningitis receiving intensified treatment regimens. *Int J Tuberc Lung Dis* 2021; **25**: 632–9.
11 Thwaites G, Fisher M, Hemingway C, Scott G, Solomon T, Innes J *et al*. British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. *J Infect* 2009; **59**: 167–87.
12 Western Sydney Local Health District. *Hospitalisation and Death Rates by Sex, WSLHD Compared to the Rest of NSW*. Sydney: WSLHD; 2021 (updated 2021 August; cited 2024 Feb). Available from URL: https://www.wslhd.health.nsw.gov.au/SocialHealthAtlas/Pages/BriefProfileWSLHD.html?64.

13 NSW TB Program. *Tuberculosis in New South Wales – Surveillance Report 2021*. Sydney: NSW Health; 2023.
14 Linh NN, Viney K, Gegia M, Falzon D, Glaziou P, Floyd K *et al*. World Health Organization treatment outcome definitions for tuberculosis: 2021 update. *Eur Respir J* 2021; **58**: 2100804.
15 Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. *Stroke* 2007; **38**: 1091–6.
16 Djochie RDA, Anto BP, Opare-Addo MNA. Determinants of adverse reactions to first-line antitubercular medicines: a prospective cohort study. *J Pharm Policy Pract* 2023; **16**: 70.
17 Lanzafame M, Vento S. Tuberculosis-immune reconstitution inflammatory syndrome. *J Clin Tuberc Other Mycobact Dis* 2016; **3**: 6–9.
18 Cheng VC, Yam WC, Woo PC, Lau SK, Hung IF, Wong SP *et al*. Risk factors for development of paradoxical response during antituberculosis therapy in HIV-negative patients. *Eur J Clin Microbiol Infect Dis* 2003; **22**: 597–602.
19 Davis AG, Rohlwink UK, Proust A, Figaji AA, Wilkinson RJ. The pathogenesis of tuberculous meningitis. *J Leukoc Biol* 2019; **105**: 267–80.
20 Wen A, Cao WF, Liu SM, Zhou YL, Xiang ZB, Hu F *et al*. Incidence and risk factors of cranial nerve palsy in patients with tuberculous meningitis: a retrospective evaluation. *Infect Drug Resist* 2023; **16**: 829–41.
21 Humayun M, Chirenda J, Ye W, Mukeredzi I, Mujuru HA, Yang Z. Effect of gender on clinical presentation of tuberculosis (TB) and age-specific risk of TB, and TB-human immunodeficiency virus coinfection. *Open Forum Infect Dis* 2022; **9**: ofac512.
22 NSW Government. *Western Sydney District Data Profile*. Sydney: NSW Government; 2023.
23 Foppiano Palacios C, Saleeb PG. Challenges in the diagnosis of tuberculous meningitis. *J Clin Tuberc Other Mycobact Dis* 2020; **20**: 100164.
24 Thwaites GE, Chau TT, Farrar JJ. Improving the bacteriological diagnosis of tuberculous meningitis. *J Clin Microbiol* 2004; **42**: 378–9.
25 Bahr NC, Tugume L, Rajasingham R, Kiggundu R, Williams DA, Morawski B *et al*. Improved diagnostic sensitivity for tuberculous meningitis with Xpert® MTB/RIF of centrifuged CSF. *Int J Tuberc Lung Dis* 2015; **19**: 1209–15.
26 Lan Y, Chen W, Yan Q, Liu W. Interferon-gamma release assays for tuberculous meningitis diagnosis: a meta-analysis. *Arch Med Sci* 2021; **17**: 1241–50.
27 Yamasue M, Komiya K, Usagawa Y, Umeki K, Nureki SI, Ando M *et al*. Factors associated with false negative interferon-gamma release assay results in patients with tuberculosis: a systematic review with meta-analysis. *Sci Rep* 2020; **10**: 1607.
28 Donald PR. Cerebrospinal fluid concentrations of antituberculosis agents in adults and children. *Tuberculosis* 2010; **90**: 279–92.
29 Rizvi I, Malhotra HS, Garg RK, Kumar N, Uniyal R, Pandey S. Fluoroquinolones in the management of tuberculous meningitis: systematic review and meta-analysis. *J Infect* 2018; **77**: 261–75.
30 World Health Organization. *WHO Treatment Guidelines for Isoniazid-Resistant Tuberculosis: Supplement to the WHO Treatment Guidelines for Drug-Resistant Tuberculosis*. Geneva: World Health Organization; 2018 (cited 2024 Feb). Available from URL: https://www.ncbi.nlm.nih.gov/books/NBK531412/.
31 Mezochow A, Thakur KT, Zentner I, Subbian S, Kagan L, Vinnard C. Attainment of target rifampicin concentrations in cerebrospinal fluid during treatment of tuberculous meningitis. *Int J Infect Dis* 2019; **84**: 15–21.
32 Heemskerk AD, Bang ND, Mai NT, Chau TT, Phu NH, Loc PP *et al*. Intensified antituberculosis therapy in adults with tuberculous meningitis. *N Engl J Med* 2016; **374**: 124–34.
33 Sy MCC, Espiritu AI, Pascual JLR. Global frequency and clinical features of stroke in patients with tuberculous meningitis: a systematic review. *JAMA Netw Open* 2022; **5**: e2229282.
34 Rohilla R, Shafiq N, Malhotra S. Efficacy and safety of aspirin as an adjunctive therapy in tubercular meningitis: a systematic review and meta-analysis. *EClinicalMedicine* 2021; **34**: 100819.