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Symptomatic central nervous system infections in kidney transplant recipients: a 20-years multicenter observational study

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Abstract

Background Central nervous system (CNS) infections in kidney transplant recipients (KTRs) remain poorly characterized, with current evidence largely derived from isolated case reports over the past two decades. This multicenter study aims to systematically delineate the epidemiology, clinical profiles, and outcomes of CNS infections in a large KTR cohort.

Methods We conducted a retrospective analysis of 3,602 KTRs across three transplant centers in China (May 2004–July 2024). CNS infections were defined by: 1) neurological symptoms/signs, and 2) microbiological confirmation via cerebrospinal fluid (CSF) analysis, including metagenomic next-generation sequencing (mNGS) and routine microbiologic testing (bacterial and fungal cultures).

Results CNS infections were diagnosed in 0.53% of KTRs (19/3602), with symptom onset occurring 2–121 months post-transplantation. Etiologies included bacterial (47%, 9/19), viral (32%, 6/19), and fungal (21%, 4/19) pathogens. Notably, 79% of cases (15/19) were exclusively identified by mNGS, whereas conventional cultures failed detection. Presenting symptoms included headache (79%) and altered mental status (42%). Mortality reached 42% (8/19) within 9–22 days of diagnosis; among survivors, 73% (8/11) exhibited neurological sequelae.

Conclusions CNS infections in KTRs are rare but characterized by rapid progression and high fatality rate. While the risk of CNS infections persists throughout the post-transplant period, 1–6 months after transplantation is a higher-incidence period of CNS infections. KTRs with neurological symptoms (particularly headache and elevated CSF pressure) should undergo CSF mNGS which is critical in diagnosing such infections.

Keywords Central nervous system infections, Kidney transplant, Epidemiology, Pathogenic spectrum, Prognosis

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Introduction

With over 100,000 kidney transplant procedures performed annually worldwide, this population is projected to expand in the coming decades [1]. While immunosuppressive regimens effectively mitigate graft rejection risks in kidney transplant recipients (KTRs), they concurrently heighten vulnerability to opportunistic infections. Pulmonary, bloodstream, and urinary tract infections represent the most frequently documented infectious complications in this population [2–4]. In stark contrast, central nervous system (CNS) infections in KTRs remain critically understudied, with current evidence predominantly derived from isolated case reports over the past two decades [5–7]. Critical knowledge gaps persist regarding the epidemiology, clinical manifestations, diagnostic challenges, therapeutic management, and long-term outcomes of CNS infections within this immunocompromised cohort.

Increasing our knowledge on the current epidemiology and clinical characteristics of CNS infections in KTRs is critical for optimizing diagnostic algorithms, therapeutic interventions, and prophylactic strategies in this immunocompromised population. We performed the study to comprehensively describe the current epidemiology, clinical features, laboratory and imaging characteristics, pathogenic result, management and prognosis of CNS infections in KTRs over the past two decades.

Materials and Methods

Study design and participants

In this multicenter study, we reviewed all KTRs admitted to three transplant centers in China between May 2004 and July 2024.All patients' clinical information was recorded as Standard Electronic Health Record and stored in a central database system based on discharge codes. We extracted all relevant clinical data, including basic demographic details, transplant information, microbiological and clinical data of CNS infections. All clinical details were anonymized and informed consents were provided by patients or their legal guardians.

Data collection

We collected the data as follows: Demographic Data: Age, gender and body mass index (BMI). Transplant Data: protopathy, organ rejection, and immunosuppressive regimens. Laboratory Results: Routine blood tests, liver and renal function tests, electrolyte examinations, tacrolimus blood levels, cerebrospinal fluid (CSF) examinations, and urinalyses. Imaging Results: Brain magnetic resonance imaging (MRI). Clinical data of CNS Infections: Time of CNS infection onset after transplantation, CNS symptoms and signs at presentation, other involved sites of infection, initial diagnosis, the time of diagnosis, treatment and prognosis. Pathogenic Data: microbiological results of CSF and other samples. Metagenomic next-generation sequencing (mNGS) testing was not available until 2015 for these three centers, these samples only underwent routine microbiologic testing (bacterial and fungal smears and cultures) before 2015. The mNGS were performed using the PACEseq mNGS test, and the detection content was pathogenic microorganism next-generation sequencing (DNA + RNA). After sequencing, the low-quality, low-complexity, and shorter reads were filtered out. The remaining data were aligned to the microbial genome database (ftp://ftp.ncbi.nlm.nih.gov/genomes/). The detection range covered viruses, bacteria (including Rickettsia, Spirochetes, Chlamydia and Mycoplasma), fungi, and parasites.

Definition of CNS infection

Due to the unique immunosuppressive status of KTRs, we adopted diagnostic criteria for CNS infections as follows: 1) Presence of neurological symptoms (e.g., headache, dizziness, altered mental status, cognitive impairment, movement or sensory disorders, memory impairment, seizures); 2) Pathogens were detected in CSF via routine microbiologic testing or/and mNGS. Serum antibody testing and imaging findings were not deemed mandatory diagnostic criteria in our study because the inflammatory responses in immunosuppressed state are blunted and delayed [8, 9].

Statistical analysis

The data were analyzed with the Statistical Package for Social Sciences for Windows (version 25.0; SPSS, Chicago, Illinois). Descriptive statistics were used to summarize basic demographic data, transplant data and laboratory data. Categorical variables were represented as counts and percentages, while continuous variables were reported as means, medians, and ranges. Thirty-day survival following a CNS infection was estimated using the Kaplan–Meier method. The log-rank test was used to compare survival distribution between groups.

Results

The epidemiology

Between May, 2004 and July, 2024, a total of 3729 patients underwent kidney transplant surgery, Of these, 127 KTRs were excluded for missing data and 3602 eligible cases were summarized and analyzed. Among 1021 KTRs treated between 2004 and 2014, 236 cases (23.1%) reported neurological symptoms, but only 27 cases (11.4%) underwent CSF routine microbiologic testing; but all 27 cases returned negative results. From 2015 to 2024, 2581 KTRs were retrospectively analyzed. Six hundred eighty-four cases (26.5%)

reported neurological symptoms but only 171 cases (25%) received CSF testing (routine methods + NGS). 19 (11.1%) of 171 cases had positive results, while 152 (88.9%) cases remained negative. Thus, 19 (0.53%) KTRs were diagnosed with CNS infections in the past 20 years. Of the19 patients, 11 cases (58%) were male and the mean age was 45.26 ± 12.19 years. Other demographic and epidemiological details are presented in Table 1. The onset time of CNS infections ranged from 2 to 121 months and the median was 17 (IQR 6–41) months. 16 cases (84%) developed CNS infections within 60 months after transplantation. Compared with other time periods, 1–6 months after transplantation is a higher-incidence period of CNS infections, but such infections can still be observed in other time periods, indicating that CNS infections remain a continuous risk throughout the post-transplant continuum. The onset time varied by pathogen: 50% (3/6) of viral infections occurred within 6 months, while 89% (8/9) of bacterial infections and 75% (3/4) of fungal infections occurred within 60 and 36 months, respectively. The onset time by pathogen is shown in Fig. 1.

The transplant characteristics

The primary etiologies for transplantation included glomerulonephritis (53%, 10/19), diabetic nephropathy (16%, 3/19), and chronic interstitial nephritis (16%, 3/19). The average dialysis time before kidney transplantation was 37.53 ± 22.56 months. The predominant immunosuppressive regimens at presentation were FK506 + MMF + Pred (12/19, 63%). Four of the 19 patients (21%) had history of organ rejection before presentation. 11 patients (58%) were initially diagnosed with drug toxicity or metabolic encephalopathy prior to the confirmation of CNS infection. Among these, only four cases were deemed potentially associated with immunosuppressive drugs (tacrolimus-induced neurotoxicity or cyclosporine-related PRES). Detailed transplant data are summarized in Table 1.

The clinical features of CNS infections

The initial CNS symptoms primarily included headache (15/19, 79%), altered mental status (8/19, 42%), and dizziness (6/19, 32%). Additional symptoms included fever (11/19, 58%), cough/expectoration (9/19, 47%), and nausea (8/19, 42%). Fourteen patients (73.68%) had other involved sites of infection, including lungs (10/19, 53%), bloodstream (4/19, 21%), and skin (2/19, 11%). The average time from symptom onset to diagnosis of CNS infections was 4.37 ± 1.16 days. Details of CNS infections are presented in Table 2.

Laboratory and radiological characteristics

Laboratory test results varied by the pathogens, but blood tests showed that all 19 patients had low lymphocyte counts and proportions. In cases of bacterial infections, CSF analysis revealed elevated protein concentrations (> 400 mg/L) in 9 cases (100%), decreased glucose levels (< 2.5 mmol/L) in 8 cases (89%), and decreased chloride levels (< 120 mmol/L) in 6 cases (67%). Among the 6 viral infections, 3 (50%) had elevated CSF protein, 1 (16.67%) had elevated CSF glucose, and 2 (33.33%) displayed decreased CSF chloride. In four cases of fungal infection, 3 (75%) had elevated CSF protein, 3 (75%) had reduced CSF glucose, and 2 cases had decreased CSF chloride levels. Elevated CSF pressure (200 mmH_2O) was observed in 15 patients (79%), particularly in cases of bacterial and fungal infections.

Radiological findings were generally nonspecific and varied by pathogen. In the 6 viral infections, magnetic resonance imaging (MRI) revealed ischemic-like or demyelinating changes in 4 patients, while no abnormalities were observed in 2 cases. Meningitis or abscesses with low T1 and high T2 signals and circular enhancement were observed in the 9 bacterial infections. Occupying lesions in the cerebrum with low T1 and high T2 signals were observed in the 4 fungal CNS infections. Based on clinical manifestations and imaging characteristics, the 19 cases of central nervous system infections in this study were categorized as encephalitis ($n = 4$, 21%), meningitis ($n = 6$, 32%), and cerebral abscess ($n = 9$, 47%), Table 2.

Pathogenic result

There were 9/19 (47%) of bacterial infections, 6/19 (32%) cases of viral infections and 4/19 (21%) of fungal infections. Among the 19 CNS infections, 3 of the 9 bacterial and 1 of the 4 fungal infections were diagnosed by CSF smear and culture, while 67% (6/9) of bacterial, 75% (3/4) of fungal, and 100% (6/6) of viral CNS infections were diagnosed exclusively by mNGS. The predominant pathogens comprised Human Herpesvirus 3 (HHV-3), Klebsiella pneumoniae, and Aspergillus flavus. Notably, 50% (3/6) of viral, 78% (7/9) of bacterial, and 75% (3/4) of fungal CNS infections had concomitant infections in other organs. In 68% of CNS infections, the pathogens identified in other organ infections were consistent with those causing CNS infections. The detailed CSF pathogenic spectrum is illustrated in Table 2 and Fig. 2.

Management and outcomes of CNS infections

Due to the absence of treatment guidelines for CNS infections in the KTRs, the treatment followed the guidelines for CNS infections in general population. In

Table 1 Demography and transplant information of CNS infections

Case	Gender	Age	BMI (kg/m^2)	CNS infection onset (months)	Protopathy	Dialysis time(months)	Rejection History	Immunosuppressant at presentation	Fk506/CsA/SRL levels (ng/ml)	Renal function at presentation	Blood test (10^9/L)	Initial diagnosis at presentation
1Male		54	28.5	6	Glomerulonephritis	24	Negative	FK506 + MMF + Pred	5.4	Scr 104 μmol/L GFR 69.8 mL/min Urine Protein 206 mg/24 h	WBC 15.25 LYMPH 0.09	Cerebrovascular events
2Male		42	30.3	34	Glomerulonephritis	85	Negative	FK506 + MMF + Pred	16.9	Scr 122 μmol/L GFR62.6 mL/min Urine Protein 112 mg/24 h	WBC4.66 LYMPH 0.52	Cerebrovascular events
3 Female		47	24.7	22	Polycystic kidney	46	Negative	FK506 + MMF + Pred	8.9	Scr 122 μmol/L GFR 45.4 mL/min Urine Protein 168 mg/24 h	WBC 5.75 LYMPH 0.49	Cerebrovascular events
4 Female		60	24.4	4	Glomerulonephritis	66	Positive	FK506 + MMF + Pred	6.8	Scr 415 μmol/L GFR 9.4 mL/min Urine Protein 1012 mg/24 h	WBC 41.5 LYMPH 0.28	Cerebrovascular events
5 Male		57	23.2	121	Diabetic nephropathy	19	Negative	FK506 + MMF + Pred	10.3	Scr 103 μmol/L GFR 69.1 mL/min Urine Protein 151 mg/24 h	WBC 8.6 LYMPH 0.09	Cerebrovascular events
6 Male		35	29.8	3	Hypertensive nephropathy	32	Negative	FK506 + MMF + Pred	9.5	Scr 115 μmol/L GFR 70.6 mL/min Urine Protein 126 mg/24 h	WBC 6.5 LYMPH 0.32	Cerebrovascular events
7 Male		31	29.3	57	Chronic interstitial nephritis	76	Negative	FK506 + MMF + Pred	18.3	Scr 88 μmol/L GFR 100.4 mL/min Urine Protein 154 mg/24 h	WBC 16.9, LYMPH 0.51	Drug toxicity/ metabolic encephalopathy
8 Female		57	28.7	19	Diabetic nephropathy	38	Negative	CsA + MMF + Pred	163	Scr 409 μmol/L GFR9.8 mL/min Urine Protein 307 mg/24 h	WBC 13.3, LYMPH 0.02	Drug toxicity/ metabolic encephalopathy
9 Male		59	32.1	73	Glomerulonephritis	23	Negative	FK506 + MMF + Pred	10.4	Scr 91 μmol/L GFR 79.2 mL/min Urine Protein 263 mg/24 h	WBC 16.2, LYMPH 0.15	Drug toxicity/ metabolic encephalopathy

Table 1 (continued)

Case	Gender	Age	BMI (kg/m^2)	CNS infection onset (months)	Protopathy	Dialysis time(months)	Rejection History	Immunosuppressant at presentation	Fk506/CsA/SRL levels (ng/ml)	Renal function at presentation	Blood test (10^9/L)	Initial diagnosis at presentation
10	Female	21	20.7	32	Chronic interstitial nephritis	9	Positive	SRL + MMF + Pred	7.6	Scr 505 μmol/L GFR 9.8 mL/min Urine Protein 1229 mg/24 h	WBC 13.5 LYMPH 0.51	Drug toxicity/ metabolic encephalopathy
11	Female	28	32.8	5	Chronic interstitial nephritis	15	Negative	CsA + MMF + Pred	112	Scr95μmol/L GFR 70.2 mL/min Urine Protein 271 mg/24 h	WBC 14.4 LYMPH 0.07	CNS infections
12	Male	55	26.2	6	Glomerulonephritis	22	Positive	CsA + MMF + Pred	141.0	Scr 501 μmol/L GFR 10.4 mL/min Urine Protein 988 mg/24 h	WBC 18.7, LYMPH 0.27,	Drug toxicity/ metabolic encephalopathy
13	Male	51	25.7	10	Diabetic nephropathy	72	Negative	CsA + MMF + Pred	350.0	Scr 204 μmol/L GFR 31.6 mL/min Urine Protein 168 mg/24 h	WBC 18.6 LYMPH 0.8	Drug toxicity/ metabolic encephalopathy
14	Male	57	26.7	5	Glomerulonephritis	30	Negative	FK506 + MMF + Pred	19.5	Scr 115 μmol/L GFR 60.5 mL/min Urine Protein 285 mg/24 h	WBC 20.5 LYMPH 0.15	Drug toxicity/ metabolic encephalopathy
15	Female	43	25.1	41	Lupus nephritis	40	Negative	FK506 + MMF + Pred	18.3	Scr 115 μmol/L GFR 50.2 mL/min Urine Protein 179 mg/24 h	WBC 11.1/L LYMPH 0.02	Drug toxicity/ metabolic encephalopathy
16	Female	42	28.6	17	Glomerulonephritis	35	Positive	FK506 + MMF + Pred	10.3	Scr 305 μmol/L GFR 15.5 mL/min Urine Protein 1337 mg/24 h	WBC 11.5/L LYMPH 0.45	Drug toxicity/ metabolic encephalopathy
17	Male	55	25.1	62	Glomerulonephritis	47	Negative	FK506 + MMF	20.8	Scr 175 μmol/L GFR 36.9 mL/min Urine Protein 103 mg/24 h	WBC 10.5/L LYMPH 0.05	Drug toxicity/ metabolic encephalopathy

Table 1 (continued)

Case	Gender	Age	BMI (kg/m^2)	CNS infection onset (months)	Protopathy	Dialysis time(months)	Rejection History	Immunosuppressant at presentation	Fk506/CsA/SRL levels (ng/ml)	Renal function at presentation	Blood test ($10^9/L$)	Initial diagnosis at presentation
18	Female	37	26.8	8	Glomerulonephritis	21	Negative	SRL + MMF + Pred	8.1	Scr 101 μmol/L GFR 61.2 mL/min Urine Protein 436 mg/24 h	WBC 10.2, LYMPH 0.15	Drug toxicity/ metabolic encephalopathy
19	Male	29	26.3	5	Glomerulonephritis	13	Negative	FK506 + MMF + Pred	13.5	Scr 122 μmol/L GFR 68.6 mL/min Urine Protein 331 mg/24 h	WBC 8.7/L, LYMPH 0.27	Cerebral tumor

BMI: Body mass index, FK506: Tacrolimus, MMF: Mycophenolate mofetil, Pred: Prednison, Cs A: Cyclosporin A, SRL: Sirolimus; CNS: Central nervous system; Scr: Serum creatinine; GFR: Glomerular filtration rate; WBC: White blood cells, LYMPH: lymphocytes

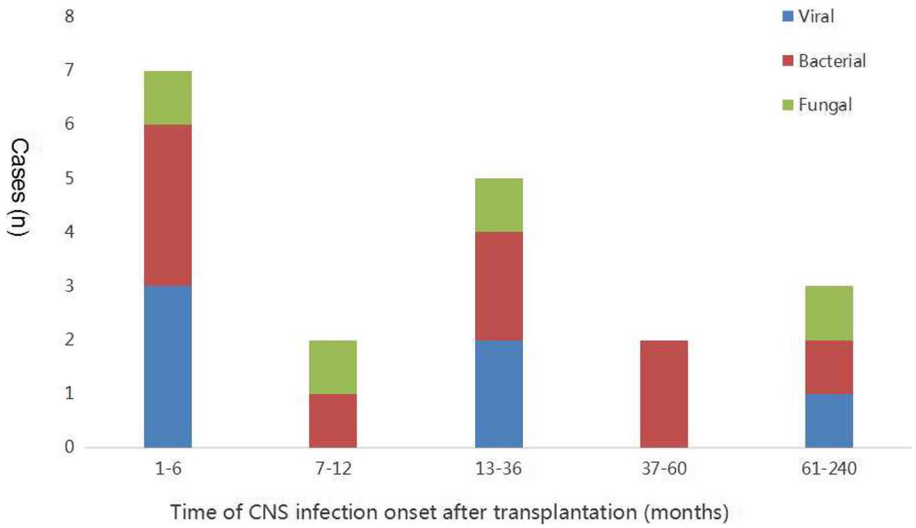

Fig. 1 Onset time of CNS infections. 1–6 months after transplantation is a higher-incidence period of CNS infections

addition to pain relief and nutritional support, the treatment approaches included discontinuation or reduction of immunosuppressive agents (19/19, 100%) and antibiotic therapy (19/19, 100%). Other main treatment measures included intracranial pressure management (13/19, 68%), human immunoglobulin (9/19, 47%) and drainage/incision surgery for brain abscesses (2/19, 11%). Among the 19 patients, 8 (42%) cases developed coma and death in 9–22 days. The average time from symptom onset to death was 15.75 ± 4.26 days. The overall 30-day mortality rate of CNS infections was 42%. Although the mortality rate of fungal infections was numerically higher (75%, 3/4) compared to viral (17%, 1/6) and bacterial infections (44%, 4/9) (Fig. 3). Of the 11 patients who survived 90 days post-CNS infection, only 3 (16%) recovered without sequelae, while 8 (42%) survivors recovered with neurologic sequelae, including hypomnesia (3/19, 16%), cognitive impairment (5/19, 26%), epilepsia (2/19, 11%), and muscle weakness (2/19, 11%) (Table 2). Besides that, two survivor's transplanted kidney ultimately lost function, necessitating the reinstitution of hemodialysis therapy.

Discussion

This multicenter cohort study, to our knowledge, is currently the largest comprehensive survey on CNS infections in KTRs. In the retrospective study, we describe the epidemiology, clinical characteristics, therapeutic management, pathogenic spectrum and clinical prognosis of CNS infections in KTRs.

Approximately 16%-53% of KTRs reported CNS abnormalities after transplantation [10–12], but most of them were diagnosed with common post-transplant CNS complications including drug toxicity, metabolic abnormalities, cerebrovascular events or brain tumor, KTRs in immunosuppressive state may not present with clinical signs and symptoms of CNS infections, even fever was absent sometimes [5, 7, 13–15]. In our study, many patients with CNS infections present with headache and dizziness, which are also common in other CNS complications. Consequently, the symptoms of CNS infections can be masked or mimicked by these conditions [13, 16, 17]. Besides that, laboratory results of blood and CSF may be also nonspecific. All patients' blood lymphocyte counts were lower than normal values. The neuroimaging showed that many viral CNS infections were similar to that of cerebral infarction, and abnormalities were observed in one-third cases of viral infections, similar results were documented in previous studies [18, 19]. Radiological examinations may not detect abnormalities in the initial stage of the disease [19], but the optimal treatment opportunity may be delayed by the time abnormalities are obvious [19].It is noteworthy that CNS infections may coexist with other CNS complications, 11 patients (58%) in our study were diagnosed with drug toxicity and metabolic abnormalities before the diagnosis of CNS infections. The coexistent etiologies complicate CNS abnormalities and delay diagnosis of CNS infections. Thus, the symptoms and confusing imaging findings contribute to the difficulty of early diagnosis of CNS infections.

In our study, 79% CNS infections were diagnosed exclusively by mNGS rather than routine microbiologic testing. Our study indicated that advanced diagnostic techniques are critical to make early diagnosis of CNS infections because pathogene load may be too low

Table 2 Clinical information of CNS infections in KTRs

Case	Clinical manifestations	Microbiological results of other involved organs	CSF analyses	CSF etiology	Diagnostic test*	Categories of CNS infection/ The time of diagnosis	Treatment	Outcome
1	Dizziness + Cognitive impairment + Hypomnesia + Fever + Cough	*Streptococcus pneumoniae* (Lung)	GLUCOSE4.15 mmol/L CSFP 163 mmH_2O CHLORIDE 124 mmol/L PRO 36.5 mg/dL	*Hantavirus*	mNGS	Meningitis 5 days	Cease immunosuppressants + Immunoglobulin + Cefoperazonev	Death
2	Dizziness	none	GLUCOSE3.2 mmol/L CSFP 211 mmH_2O CHLORIDE 128.1 mmol/L PRO 38.17 mg/dL	*Human Herpesvirus 3*	mNGS	Encephalitis 3 days	Reduce immunosuppressants + Immunoglobulin Acyclovir	Survival
3	Dizziness Headache	*Herpes simplex virus-3* (Skin)	GLUCOSE2.87 mmol/L CSFP 126mmH_2O CHLORIDE 116.2 mmol/L PRO 60.85 mg/dL	*Human Herpesvirus 3*	mNGS	Encephalitis 5 days	Reduce immunosuppressants Acyclovir	Survival with Cognitive impairment Hypomnesia
4	Headache Cognitive impairment	none	GLUCOSE3.9 mmol/L CSFP 202 mmH_2O CHLORIDE 118.6 mmol/L PRO 46.2 mg/dL	*Epstein-barr virus*	mNGS	Meningitis 5 days	Cease immunosuppressants Ganciclovir	Survival with dialysis
5	Dizziness Altered mental status Fever	none	GLUCOSE4.8 mmol/L CSFP 162 mmH_2O CHLORIDE 127.9 mmol/L PRO 27.1 mg/dL	Herpes simplex virus-1	mNGS	Encephalitis 6 days	Cease immunosuppressants Human + Immunoglobulin + Acyclovir	Survival with Cognitive impairment
6	Headache + Cognitive impairment	*Herpes simplex virus-3* (Skin)	GLUCOSE4.1 mmol/L CSFP 149 mmH_2O CHLORIDE 122.6 mmol/L PRO53.8 mg/dL	*Human Herpesvirus 3*	mNGS	Encephalitis 3 days	Cease immunosuppressants + Immunoglobulin + Acyclovir	Survival
7	Headache Altered mental status Muscle weakness Fever + vomiting	*K. pneumoniae* (Blood & liver/ Lung)	GLUCOSE1.32 mmol/L CSFP 269 mmH_2O CHLORIDE 104 mmol/L PRO 76 mg/dL	*K.pneumoniae*	mNGS	Brain Abscess 3 days	Cease immunosuppressants + Drainage of liver abscess + Mannitol Meropenem	Death
8	Dizziness Altered mental status + Fever + Nausea	Nocardia sp(Lung, shoulder)	GLUCOSE2.02 mmol/L CSFP 221 mmH_2O CHLORIDE 121 mmol/L PRO 90.3 mg/dL	*Nocardia sp*	mNGS	Brain Abscess 6 days	Cease immunosuppressants + Mannitol + Sulfamethoxazole + Linezolid	Death

Table 2 (continued)

Case	Clinical manifestations	Microbiological results of other involved organs	CSF analyses	CSF etiology	Diagnostic test*	Categories of CNS infection/ The time of diagnosis	Treatment	Outcome
9	Headache + Cognitive impairment + Muscle weakness + Fever + Cough + Nausea	none	GLUCOSE1.7 mmol/L CSFP 219 mmH_2O CHLORIDE 117 mmol/L PRO 68.9 mg/dL	*Hemolytic streptococcus*	mNGS	Meningitis 3 days	Cease immunosuppressants + Mannitol + Ceftriaxone + Vancomycin	Survival with Cognitive impairment
10	Headache + Altered mental status + Epilepsia + Fever Cough	none	GLUCOSE1.9 mmol/L CSFP 262 mmH_2O CHLORIDE 108.6 mmol/L PRO106.2 mg/dL	*K.pneumoniae*	mNGS & routine testing	Brain Abscess 4 days	Cease immunosuppressants + Immunoglobulin + Mannitol + MeropeneM	Survival with Cognitive impairment Hydrocephalus + dialysis
11	Headache + Dizziness + Muscle weakness	*Staphylococcus aureus* (Blood)	GLUCOSE1.6 mmol/L CSFP 241 mmH_2O CHLORIDE 122.3 mmol/L PRO 112.1 mg/dL	*Staphylococcus aureus*	mNGS & routine testing	Brain Abscess 2 days	Cease immunosuppressants + Mannitol Abscess Surgery	Survival with Muscle weakness Hypomnesis
12	Headache + Epilepsia + Altered mental status + Nausea	*K. pneumoniae* (Lung & Blood	GLUCOSE2.02 mmol/L CSFP 244 mmH_2O CHLORIDE 105.6 mmol/L PRO73.8 mg/dL	*K.pneumoniae*	mNGS	Brain Abscess 6 days	Cease immunosuppressants + Immunoglobulin + Abscess drainage surgery + Mannitol + Vancomycin + MeropeneM	Death
13	Headache + Altered mental status + Epilepsia + Fever + Nausea	*Corynebacterium striatum* (Lung)	GLUCOSE2.55 mmol/L CSFP 276 mmH_2O CHLORIDE 123.1 mmol/L PRO108.1 mg/dL	*Corynebacterium striatum*	mNGS	Meningitis 4 days	Cease immunosuppressants + Mannitol + MeropeneM	Survival with
14	Headache + Muscle weakness + Fever + Cough	*Streptococcus pneumoniae* (Lung)	GLUCOSE2.0 mmol/L CSFP 219 mmH_2O CHLORIDE 110.9 mmol/L PRO80.4 mg/dL	*Streptococcus pneumoniae*	mNGS & routine testing	Meningitis 5 days	Cease immunosuppressants + Immunoglobulin + Mannitol + MeropeneM	Survival with Muscle weakness
15	Headache + Muscle weakness + Fever + Nausea	*Mycobacterium tuberculosis* (Lung)	GLUCOSE2.42 mmol/L CSFP 252 mmH_2O CHLORIDE 113 mmol/L PRO 88.9 mg/dL	*Mycobacterium tuberculosis*	mNGS	Brain Abscess 5 days	Cease immunosuppressants + Mannitol + Immunoglobulin + Mannitol + Isonicotinyl Hydrazide + Rifampicin pyrazinamide	Death

Table 2 (continued)

Case	Clinical manifestations	Microbiological results of other involved organs	CSF analyses	CSF etiology	Diagnostic test*	Categories of CNS infection/ The time of diagnosis	Treatment	Outcome
16	Headache + Altered mental status + Fever Cough	*Aspergillus flavus* (Lung)	GLUCOSE1.96 mmol/L CSFP 260 mmH_2O CHLORIDE 107.2 mmol/L PRO 39.01 mg/dL	*Aspergillus flavus*	mNGS	Brain Abscess 5 days	Cease immunosuppressants + Immunoglobulin + Mannitol + Amphotericin B + Itraconazole	Death
17	Headache + Cognitive impairment + Cough	Candida albicans (Lung)	GLUCOSE2.31 mmol/L CSFP 271 mmH_2O CHLORIDE 123.9 mmol/L PRO60.5 mg/dL	*Candida albicans*	mNGS & routine testing	Meningitis 4 days	Cease immunosuppressants Mannitol + Caspofungin + Amphotericin B	Survival with Cognitive impairment Hypomnesia
18	Headache + Visual deterioration + Altered mental status + Fever + Nausea + Cough	*Aspergillus fumigatus* (Lung)	GLUCOSE2.52 mmol/L CSFP 237 mmH_2O CHLORIDE 121.5 mmol/L PRO 72.01 mg/dL	*Aspergillus fumigatus*	mNGS	Brain Abscess 5 days	Cease immunosuppressants + Mannitol + Fluconazole + Amphotericin B	Death
19	Headache + Epilepsia + Muscle weakness + Nausea + Cough	*Aspergillus flavus* ((Lung) &Urine)	GLUCOSE2.27 mmol/L CSFP 224 mmH_2O CHLORIDE 110 mmol/L PRO 78.3 mg/dL	*Aspergillus flavus*	mNGS	Brain Abscess 4 days	Cease immunosuppressants + Mannitol + Amphotericin B + Voriconazole	Death

CSF Cerebrospinal fluid, mNGS, Metagenomics Next Generation Sequencing

* Routine testing: bacterial and fungal smears and cultures

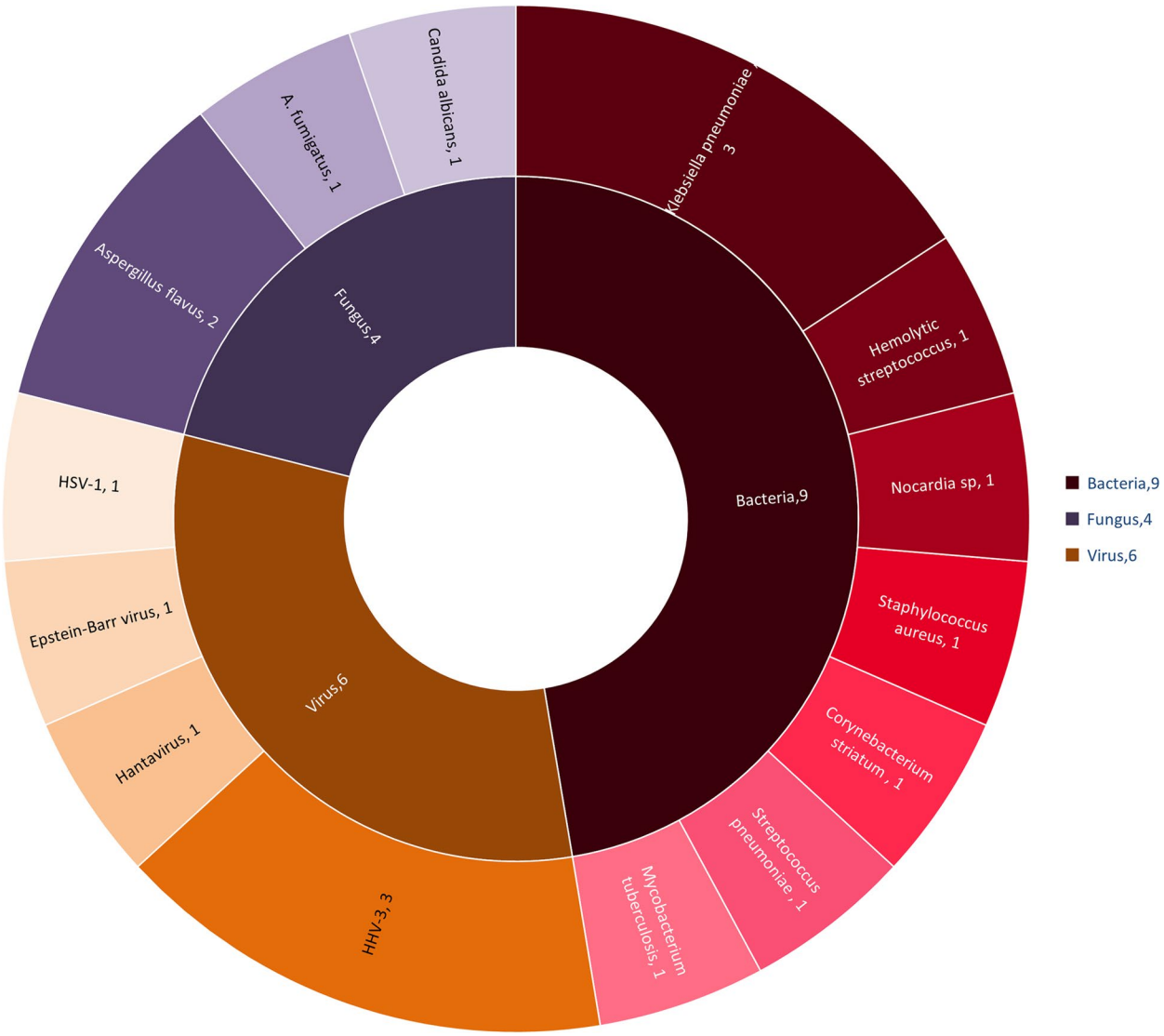

Fig. 2 Pathogenic result of CSF. Bacteria: 3 Klebsiella pneumoniae, 1 Mycobacterium tuberculosis, 1 Streptococcus pneumoniae. 1 Corynebacterium striatum, 1 Staphylococcus aureus, 1 Nocardia sp and 1Hemolytic streptococcus. Virus: 3 HHV-3, 1 HSV-1,1 Epstein-Barr virus and 1 Hantavirus. Fungus: 2 Aspergillus flavus, 1 Candida albicans and 1 Aspergillus fumigatus

to be detected by smear and culture in the initial stage of infections, while mNGS is sensitive to avoid the false negative [20, 21]. Prior studies have demonstrated that mNGS serves as a pivotal diagnostic tool in diagnosing CNS infections due to its ability to rapidly and comprehensively identify pathogens, especially in cases where traditional methods fail. One study conducted in USA found that 13 of 58 CNS infections failed to be identified by routine microbiologic testing but were identified by mNGS [22]. One study in China demonstrated that the detection rate of tuberculous meningitis was increased to 95.65% by combining mNGS and routine methods [23]. A study comprising case reports and cohort studies demonstrated that NGS is crucial for the diagnosis of pediatric CNS infections [24]. Our study indicated that conventional diagnostic approaches for CNS infections were constrained by limited access to PCR-based technologies prior to adoption of mNGS. This technological gap likely contributed to diagnostic inaccuracies, including false-negative result. Our study further underscored the critical importance of mNGS in enhancing diagnostic precision for infectious diseases.

Our study found that most of CNS infections (84.21%) occurred within 60 months after transplantation, and 1–6 months was the peak periods of onset. In the study by Nikolina et al.,69% CNS infections occurred within

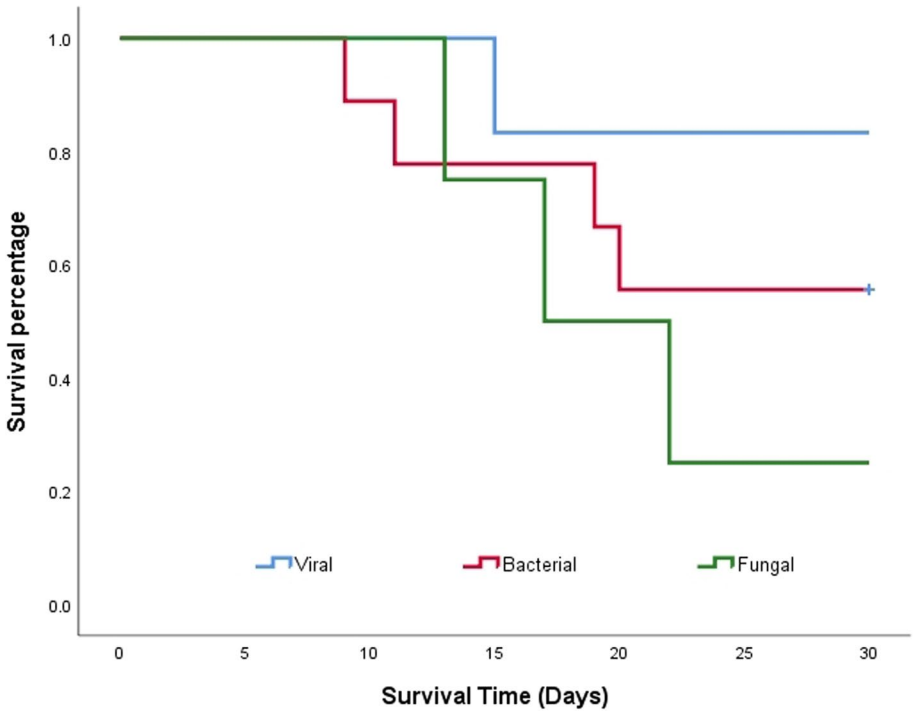

Fig. 3 Survival rate after CNS infections according to pathogen. The 30-day mortality rate was 75% (3/4) for fungal infections (green line), 17% (1/6) for viral infection (blue line), and 44% (4/9) for bacterial infections (red line)

60 months [25], while 73.17% of cases occurred within 36 months after transplantation in another study [26]. Changes of net-state of immunosuppression and epidemiological exposures seem to be the most important factors determining the onset time [2, 3].Moreover, the onset of CNS infections varies widely by pathogen type. For example, 73% of fungal infections and 44% of viral infections occurred within six months after transplant in a previous study [26]0.50% of viral infections occurred within 6 months and 75% of fungal infections occurred within 36 months in our study. The effect of immunosuppression presenting during the period from 1 to 6 months after transplantation may be the primary cause of intensive emerge of infection [2, 3].

In our study, the incidence of bacterial CNS infections were the most common CNS infections. Similar results were observed in study by Nikolina et al. [25]. But study by Lorena et al. showed that virus were the most causative pathogens, followed by fungus and bacteria [26]. One recent study by Leah found that the main pathogen causing brain abscess in transplant patients is Nocardia sp. (61.5%), followed by Aspergillus sp (25.6%) [27]. One French study reported that causes of CNS infections were almost homogeneously distributed between Fungi, Bacteria, and Viruses [7]. The different results of pathogens reported in different studies may result from climatic influences on pathogen ecology, region-specific transplant prophylaxis protocols and lifestyle-driven exposure risk. [28, 29]. It is noteworthy that the pathogen spectrum of CNS infections in KTRs is different from that of general population. Pseudomonas aeruginosa and Streptococcus pneumoniae were rare causative pathogens in general population but reported frequently in many studies including our study [15, 25, 26].

There is no consensus regarding management of CNS infections in KTRs. The primary treatment included reducing immunosuppression, which facilitate restoring the native immune response to suppress the causative pathogen. Another part of basic treatment is antibiotic therapy which could suppress the proliferation of pathogens to prevent further intracranial or systemic spread. Some scholars advocated injecting antibiotics directly into the abscess or subarachnoid space, but the effectiveness and safety should be verified by further studies [30, 31]. Even immunoglobulin is not recommended as an effective therapeutic intervention for CNS infections, it could be one part of adjunctive treatment of severe infections [32].

The mortality rate of CNS infections varied widely according to the type of pathogen, we observed that Fungal CNS infections in our study had the highest mortality of 75%, which was more than bacterial (44%) and viral infections (17%). In the study by Lorena et al. the similar mortality rates of fungal and viral infections

were 73.0% and 14.0%, respectively. The mortalities of fungal and bacterial CNS infections in kidney transplant patients were 75% and 57%, respectively [7]. Previous studies have indicated that CNS infections caused by Aspergillus are associated with a high mortality rate, approximately 80% [20, 28]. Survivors in our study recovered with different levels of neurologic sequelae, including hypomnesia, cognitive impairment, and hydrocephalus. 22.2%-45.5% of patients reported such sequelae in previous studies [7, 15, 25, 26].

There are some limitations of our study which should be mentioned. First, all data were collected retrospectively, and due to the limitations of diagnostic approaches and the incomplete implementation of etiologic testing among KTRs presenting with neurological symptoms, many CNS infection cases in this study were underdiagnosed, thus the true incidence may exceed the reported findings, necessitating further research to elucidate the actual epidemiology of CNS infections in this population. Second, we are unable to analyze the risk factors for the development of CNS infections in KTRs due to the rarity and heterogeneity of the events. Third, In the study, data collection was focused on patients who met the diagnostic criteria for CNS infections, follow-up duration was not systematically recorded for KTRs without CNS infections. Consequently, incidence per time was not reported. Additionally, the data of CNS infections in our study is only representative of China, global multicenter studies are needed to assess the burden of the disease. However, the data of the study may facilitate further strategies on diagnostic, therapeutic, and preventive approaches for the specific group of patients.

Conclusions

CNS infections represent rare but devastating complications in KTRs, marked by rapid progression and high mortality. The critical risk window extends beyond the early post-transplant phase, peaking at 1–6 months. Our findings highlight the diagnostic superiority of CSF mNGS over conventional methods in this population. We propose mandatory mNGS testing for KTRs presenting with neurological symptoms—particularly headache with elevated CSF pressure—to mitigate diagnostic delays and improve outcomes.

Abbreviations

CNS	Central nervous system
KTR	Kidney transplant recipients
mNGS	Metagenomic Next-generation sequencing
CSF	Cerebrospinal fluid
MRI	Magnetic resonance imaging
BMI	Body mass index
PRES	Posterior reversible encephalopathy syndrome

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Authors' contributions

XS-Q, HY-W conceived the study and methods. XS-Q, HY-W and JJ-D performed investigation and data collection. XS-Q, XL-Q and KC performed formal data analysis. HY-W and XL-Q supervised the investigation. XS-Q and HY-W contributed to writing the original draft. YS-S and XS-Q contributed to reviewing and editing the manuscript. XS-Q and HY-W visualized the study documents and accessed and verified all of the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Data availability

Study data can be provided upon reasonable request from corresponding author.

Declarations

Ethics approval and consent to participate

The study was conducted under the requirements of the Declaration of Helsinki and was approved by the Ethics Committee of Zhengzhou Peoples' Hospital, China (ZYCT-2405–03). The clinical details were anonymized and informed consent were provided by patients or legal guardians.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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