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ORIGINAL ARTICLE

The burden and epidemiology of community-acquired central nervous system infections: a multinational study

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Abstract Risk assessment of central nervous system (CNS) infection patients is of key importance in predicting likely pathogens. However, data are lacking on the epidemiology globally. We performed a multicenter study to understand the burden of community-acquired CNS (CA-CNS) infections between 2012 and 2014. A total of 2583 patients with CA-CNS infections were included from 37 referral centers in 20 countries. Of these, 477 (18.5%) patients survived with sequelae and 227 (8.8%) died, and 1879 (72.7%) patients were discharged with complete cure. The most frequent infecting

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pathogens in this study were *Streptococcus pneumoniae* (n = 206, 8%) and *Mycobacterium tuberculosis* (n = 152, 5.9%). Varicella zoster virus and *Listeria* were other common pathogens in the elderly. Although staphylococci and *Listeria* resulted in frequent infections in immunocompromised patients, cryptococci were leading pathogens in human immunodeficiency virus (HIV)-positive individuals. Among the patients with any proven etiology, 96 (8.9%) patients presented with clinical features of a chronic CNS disease. Neurosyphilis, neurobrucellosis, neuroborreliosis, and CNS tuberculosis had a predilection to present chronic courses. *Listeria monocytogenes*, *Staphylococcus aureus*,

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M. tuberculosis, and *S. pneumoniae* were the most fatal forms, while sequelae were significantly higher for herpes simplex virus type 1 ($p < 0.05$ for all). Tackling the high burden of CNS infections globally can only be achieved with effective pneumococcal immunization and strategies to eliminate tuberculosis, and more must be done to improve diagnostic capacity.

Introduction

The central nervous system (CNS) can be infected with numerous infectious agents, which result in significant morbidity and mortality, despite the effectiveness of available antimicrobials [1–5]. In large international cohorts, the case–fatality rates for adults with pneumococcal, tuberculous, and herpetic CNS infections are 14, 17, and 10%, respectively, despite treatment [6–8]. Thus, risk assessment in this subgroup of patients is of key importance in predicting the likely pathogen leading to rational treatment. Although there are considerable data on the epidemiology of these CNS infectious syndromes, data are lacking to facilitate our understanding of the cumulative epidemiology of community-acquired CNS (CA-CNS) infections. We, therefore, performed a multicenter study to provide an insight into CA-CNS infections and to better understand the burden of infection in community settings, and to explore risk assessment data for the management of these infections.

Materials and methods

Study design

We designed a multicenter, retrospective, cross-sectional study performed in the infectious diseases and neurology departments of participating referral hospitals. The study was led by the Infectious Diseases International Research Initiative (ID-IRI). We approached >50 survey sites in >25 countries to participate in this study. Data were collected retrospectively during the period from 1st May 2012 to 1st May 2014 and included all CA-CNS infection patients over the age of 15 years hospitalized at the survey sites. All epidemiological, clinical, laboratory, therapeutic, and outcome data were collected using a standardized questionnaire (Excel 2010). The participant centers submitted their individual datasets via email to the lead hospital for analysis. Patient confidentiality was considered and the study was approved ethically by the institutional review board of Fatih Sultan Mehmet Education and Research Hospital in Istanbul.

Definitions

The diagnoses were made according to the clinical suspicion of the examining clinicians based on compatible clinical presentations of the patients with CA-CNS infections, and in accordance with standard definitions [2–5, 9]. The CA-CNS infections were defined as infections affecting the CNS, and were acquired in daily life. These infectious disorders were not associated to infections in the healthcare settings.

Chronic CA-CNS infection	Patients with symptoms for more than four weeks at the time of diagnosis were included in this category [10].
Elderly classification	Patients over the age of 64 years were classified as elderly [11].
Primary immunosuppression	Congenital immunodeficiency diseases are classified in this category [12].
Secondary immunosuppression	Immunodeficiency conditions depending on underlying immune diseases or due to immunosuppressive treatments are defined as secondary [12].
Probable immunosuppression	Patients with probable immunosuppressive conditions like human immunodeficiency virus (HIV; immune status unknown), diabetes mellitus, malignity, pregnancy, and others were included in this group. Patients were included in this group when they did not have detailed data in our database in determining the level of immunosuppression.
Adverse clinical outcome	Either death or sequelae were defined as adverse clinical outcomes.
Data sources and measurements	The microbiological diagnoses of patients compatible with CNS infections were made according to the microbiological techniques below and are presented in detail in Table 1:

a) Neurosyphilis: CSF VDRL, serum VDRL/RPR, fluorescent treponemal antibody absorption (FTA-ABS), *T. pallidum* particle agglutination (TPPA)/*T. pallidum* hemagglutination test (TPHA), *T. pallidum* microhemagglutination (MHA-TP) [13].
b) Neuroborreliosis: Molecular testing and serology [14].
c) Neurobrucellosis: Non-specific CSF culture, blood culture, CSF Rose Bengal test, CSF

Table 1 The efficacy of the microbiological methods used in the diagnosis of community-acquired central nervous system (CA-CNS) infections

Bacteria/fungus	Tested	Positive	Positivity (%)	Overall (%)	Bacteria/fungus	Tested	Positive	Positivity (%)	Overall (%)
T. pallidum					*Fusobacterium* spp.				
CSF VDRL	179	17	9.49	0.65	Culture (CSF)	1414	1	0.07	0.04
Serum VDRL/RPR	346	6	1.73	0.2	Molecular	222	1	0.45	0.04
CSF FTA-ABS	10	1	10	0.04	Subtotal cases		2		0.08
Serum FTA-ABS	35	5	14.28	0.19	*Borrelia* spp.				
Subtotal cases		24		0.93	Molecular	128	13	10.1	0.5
Brucella spp.					Serology	508	25	4.92	0.97
Culture (CSF)	1414	3	0.21	0.1	Subtotal cases		38		1.47
Culture (blood)	1565	1	0.06	0.04	*Enterococcus* spp.				
CSF Rose Bengal	90	6	6.67	0.2	Culture (CSF)	1414	4	0.28	0.15
CSF Wright aggl. test	81	8	9.87	0.3	Culture (blood)	1565	2	0.13	0.07
Serum Rose Bengal	188	11	5.85	0.4	Subtotal cases		5		0.19
Serum Wright aggl. test	207	13	6.28	0.5	*Micrococcus* spp. (blood)	1565	1	0.06	0.04
CSF molecular	1	0	0	0	*Gemella* spp. (CSF)	1414	1	0.07	0.04
Serology	508	1	0.19	0.04	*Peptococcus* spp.				
Subtotal cases		14		0.54	Culture (CSF)	1414	1	0.07	0.04
M. tuberculosis					Culture (blood)	1565	1	0.06	0.04
Culture (CSF)	528	38	7.19	1.5	Subtotal cases		1		0.04
ARB	566	33	5.83	1.3	*Peptostreptococcus* spp.				
PCR	57	10	17.54	0.4	Culture (CSF)	1414	2	0.14	0.08
Anti-TB treatment		107		4	Culture (blood)	1565	1	0.06	0.04
Subtotal cases		152		5.88	Subtotal cases		3		0.12
S. pneumoniae					*Lactobacillus* spp. (CSF)	1414	1	0.07	0.04
Culture (CSF)	1414	148	10.46	5.7	Corynebacteria (CSF)	1414	1	0.07	0.04
Culture (blood)	1565	85	5.43	3.3	*Actinomyces* spp. (CSF)	1414	5	0.35	0.19
Molecular	222	31	13.96	1.2	*Escherichia coli*				
Serology	300	40	13.3	1.5	Culture (CSF)	1414	6	0.42	0.23
Subtotal cases		206		7.97	Culture (blood)	1565	5	0.32	0.19
Streptococcus spp. (other)					Subtotal cases		9		0.35
Culture (CSF)	1414	36	2.54	1.4	*Enterobacter* spp.				
Culture (blood)	1565	20	1.27	0.8	Culture (CSF)	1414	2	0.14	0.08
Molecular	222	16	7.20	0.6	Culture (blood)	1565	1	0.06	0.04
Subtotal cases		55		2.13	Subtotal cases		3		0.12
Staphylococcus spp.					*Proteus* spp. (CSF)	1414	2	0.14	0.08
Culture (CSF)	1414	27	1.90	1	*Morganella* spp. (CSF)	1414	3	0.21	0.12
Culture (blood)	1565	47	3	1.8	*Campylobacter* spp. (CSF)	1414	1	0.07	0.04
Molecular	222	3	1.35	0.1	*Aggregatibacter* spp.				
Subtotal cases		71		2.75	Culture (CSF)	1414	2	0.14	0.08
Listeria spp.					Culture (blood)	1565	1	0.06	0.04
Culture (CSF)	1414	22	1.55	0.9	Subtotal cases		3		0.12
Culture (blood)	1565	12	0.76	0.46	*Pseudomonas* spp.				
Molecular	222	3	1.35	0.1	Culture (CSF)	1414	4	0.28	0.15
Subtotal cases		27		1.04	Culture (blood)	1565	4	0.25	0.15
Nocardia spp.					Subtotal cases		7		0.27
Culture (CSF)	1414	1	0.07	0.04	*Acinetobacter* spp.				
Culture (blood)	1565	2	0.13	0.08	Culture (CSF)	1414	4	0.28	0.15
Molecular	205	1	0.48	0.04	Culture (blood)	1565	1	0.06	0.04
Subtotal cases		4		0.15	Subtotal cases		4		0.15
Klebsiella spp.					*Moraxella* spp. (CSF)	1414	2	0.14	0.08
Culture (CSF)	1414	6	0.42	0.2	*Sphingomonas* spp. (CSF)	1414	2	0.14	0.08
Culture (blood)	1565	2	0.13	0.08	*Prevotella* spp.(CSF)	1414	2	0.14	0.08
Molecular	222	1	0.45	0.04	*Bacteroides* spp. (blood)	1565	1	0.06	0.04
Subtotal cases		7		0.27	*Saccharomyces cerevisiae* (mol.)	222	1	0.45	0.04
Haemophilus spp.					*Xanthomonas* spp. (mol.)	222	1	0.45	0.04
Culture (CSF)	1414	7	0.49	0.3	*Aerococcus urinae* (mol.)	222	1	0.45	0.04
Culture (blood)	1565	1	0.06	0.04	*Cryptococcus* spp.				
Molecular	222	2	0.90	0.08	Culture (fungal)	509	19	3.73	0.74
Serology	300	2	0.67	0.08	Culture (CSF)	1414	8	0.56	0.31
Subtotal cases		10		0.39	Culture (blood)	1565	7	0.44	0.27
Capnocytophaga spp.					CSF antigen	207	25	12.1	0.96
Culture (CSF)	1414	2	0.14	0.08	Molecular	14	2	14.3	0.08
Culture (blood)	1565	2	0.13	0.08	Subtotal cases		27		1.04

Table 1 (continued)

Bacteria/fungus	Tested	Positive	Positivity (%)	Overall (%)	Bacteria/fungus	Tested	Positive	Positivity (%)	Overall (%)
Molecular	222	1	0.45	0.04	*Candida* spp.				
Subtotal cases		3		0.12	Culture (fungal)	509	2	0.39	0.08
Neisseria spp.					Culture (CSF)	1414	1	0.07	0.08
Culture (CSF)	1414	22	1.55	0.9	Culture (blood)	1565	3	0.19	0.01
Culture (blood)	1565	8	0.51	0.3	Serology	508	1	0.19	0.04
Molecular	222	17	7.65	0.7	Subtotal cases		5		0.19
Serology	300	11	3.67	0.4					
Subtotal cases		45		1.74					

Viruses/parasites	Method	Tested	Positive	Positivity (%)	Overall (%)
HSV-1 (CSF)	Molecular	811	46	5.6	1.8
	Serology	508	2	0.3	0.08
HSV-2 (CSF)	Molecular	791	34	4.3	1.3
HSV-1/2 (CSF)	Serology	508	1	0.2	0.04
HSV (serum)	Molecular	4	1	25	0.04
	Subtotal		74		2.8
EBV (CSF)	Molecular	231	16	6.9	0.62
CMV (CSF)	Molecular	261	2	0.8	0.08
CMV (serum)	Molecular	5	2	40	0.08
	Subtotal		5		0.2
VZV (CSF)	Molecular	548	88	16	3.4
	Serology	508	4	0.8	0.15
	Subtotal		91		3.5
SFTV (CSF)	Molecular	4	1	25	0.04
WNV (CSF)	Molecular	78	8	10	0.3
	Serology	508	13	2.6	0.5
	Subtotal		35		1.35
TBEV	Serology	508	92	18	3.6
Parechovirus (CSF)	Molecular	7	1	14	0.04
Mumps virus (CSF)	Molecular	23	6	26	0.23
Adenovirus (CSF)	Molecular	37	1	2.7	0.04
	Serology	508	1	0.2	0.04
	Serum molecular	7	3	42	0.12
	Subtotal		4		0.15
Enterovirus (CSF)	Molecular	347	88	25	3.4
	Serology	508	1	0.2	0.04
	Serum molecular	9	3	33	0.12
	Subtotal		92		3.6
Measles virus	Serology	508	1	0.2	0.04
HHV6 (CSF)	Molecular	92	3	3.3	0.12
HIV (CSF)	Molecular	24	12	50	0.46
JCV (CSF)	Molecular	22	5	23	0.2
RSV (CSF)	Molecular	5	1	20	0.04
PIV (CSF)	Molecular	5	1	20	0.04
	Serology	508	1	0.2	0.04
	Subtotal		2		0.08
Toxoplasma spp. (CSF)	Molecular	44	4	9	0.15
	Serology	508	1	0.2	0.04
	Serum molecular	3	3	100	0.12
	Subtotal		8		0.3

SFTV Sandfly fever Toscana virus; *WNV* West Nile virus; *TBEV* tick-borne encephalitis virus; *PIV* parainfluenza virus

Wright agglutination test, serum Rose Bengal test, serum Wright agglutination test, CSF-PCR [15].

d) CNS tuberculosis: CSF culture for tuberculosis, acid fast staining of CSF, molecular testing (MTB PCR), and response to anti-tuberculosis treatment in probable cases [16].

e) Other bacterial infections: Non-specific CSF culture, blood culture, and molecular testing [1, 17].

f) Cryptococcal CNS disease: Fungal CSF culture, non-specific CSF culture, blood culture, CSF cryptococcal antigen testing, and molecular testing [17].
g) Candidal CNS disease: Fungal CSF culture, non-specific CSF culture, blood culture, and serological testing [18].
h) Viral CNS infections: Molecular testing and serology [3, 5].
i) CNS toxoplasmosis: Molecular testing and serology [5].

The detection of pathogens was directly related to the technical capacity of the participating centers and the diagnostic approaches of the examining clinicians. HIV parameters (e.g., CD4+ T-cell counts and HIV-RNA levels) indicating severity of illness were not in our database. Hence, HIV-positives are included in a separate block.

Statistical methods

Chi-square, Pearson's chi-square, continuity correction of Pearson, and Fisher's exact test were used to analyze the data. We used a cut-off *p*-value of $p < 0.05$ to indicate significance for all tests. Continuous variables were analyzed by using histograms and the Kolmogorov–Smirnov test for normality. After this separation, a Mann–Whitney *U*-test was used for variables that were not distributed normally.

Results

A total of 2583 patients with CA-CNS infections were included from 37 referral centers in Albania, Bosnia and Herzegovina, Croatia, Czech Republic, Denmark, Egypt, France, Hungary, Hong Kong, Iran, Italy, Kazakhstan, Kosovo, Pakistan, Portugal, Romania, Serbia, Syria, Texas/USA, and Turkey. Table 1 highlights the microbiological techniques and their positivity rates used in the diagnosis.

Infectious syndromes

There were 2603 infectious CNS syndromes identified in 2583 cases. Patients were classified as meningitis ($n = 1292$, 50%), encephalitis ($n = 208$, 8%), meningoencephalitis ($n = 888$, 34.4%), and meningoencephalomyelitis ($n = 1$, 0.04%). There were 144 (5.6%) patients with suppurative intracranial infections. These were brain abscesses ($n = 97$), subdural empyemas ($n = 14$), epidural abscesses ($n = 31$), other abscesses ($n = 2$), other syndromes ($n = 69$), and arachnoiditis ($n = 2$). The distribution of infectious CNS syndromes is presented in Table 2.

Microbiological data

In this study, a CNS pathogen was disclosed in 1079 (41.8%) patients. However, no infecting pathogen was detected in 1504 (58.2%) patients. The diagnoses were established with either direct or indirect methods, or with the combination of different methods, as indicated in Table 1. We identified *Streptococcus pneumoniae* ($n = 206$, 8%) and *Mycobacterium tuberculosis* ($n = 152$, 5.9%) as the frequent causative agents. The distribution of infecting pathogens according to the ultimate diagnosis and immunosuppressive states are presented in Tables 3 and 4, respectively. Common pathogens in CA-CNS infections are presented in Fig. 1.

In 77 out of 2583 (3%) patients, multiple etiological agents were detected. In 75 cases, two causative agents were identified and in two patients, three agents were recorded. When these patients were categorized according to clinical presentations, there were 43 cases of meningitis, in which 87 different organisms were identified [*S. pneumoniae* ($n = 20$), *T. pallidum* ($n = 10$), enteroviruses ($n = 9$), cryptococci ($n = 7$), EBV ($n = 5$), streptococci other than pneumococci ($n = 4$), *N. meningitidis* ($n = 3$), VZV ($n = 3$), WNV ($n = 3$), coagulase-negative staphylococci ($n = 2$), *Borrelia* spp. ($n = 2$), HHV-6 ($n = 1$), CMV ($n = 1$), *Brucella* spp. ($n = 1$), *Listeria* spp. ($n = 1$)]. In 26 patients with meningoencephalitis, 53 agents were recorded as multiple pathogens [TBEV ($n = 16$), *Borrelia* spp. ($n = 13$), VZV ($n = 10$), *M. tuberculosis* ($n = 3$), HSV ($n = 3$), enteroviruses ($n = 3$), EBV($n = 2$), *S. pneumoniae* ($n = 1$), coagulase-negative staphylococci ($n = 1$), *Cryptococcus* ($n = 1$)]. In five patients with encephalitis, ten agents [HSV-1 ($n = 4$), *S. aureus* ($n = 1$), *S. pneumoniae* ($n = 1$), VZV ($n = 1$), WNV ($n = 1$), EBV ($n = 1$), enterovirus ($n = 1$)] were identified. Finally, in three patients with brain abscesses, six pathogens were disclosed [streptococci other than pneumococci ($n = 2$), *Neisseria* spp. ($n = 2$), CMV ($n = 1$), EBV ($n = 1$)].

Age distribution

The mean age of the cases was 47.63 (SD ± 19.8) years. 446 (17.3%) patients were elderly, with a mean age of 74.58 (SD ± 7.02) years. Among the patients with any identified pathogen, the numbers of patients over 65 years and less than 65 years of age were 250 (23.2%) and 829 (80.9%), respectively. Although *S. pneumoniae* [59/250–147/829 ($p = 0.039$)], *Listeria* spp. [13/250–14/829 ($p = 0.004$)], and VZV [41/250–50/829 ($p < 0.001$)] caused significantly more infections in the elderly, *M. tuberculosis* [23/250–129/829 ($p = 0.011$)], enteroviruses [2/250–89/829 ($p < 0.001$)], and

Table 2 The presentation of the patients according to etiological agents

	No.	Meningitis	Encephalitis	Meningoencephalitis	Brain abscess	Subdural empyema	Epidural abscess	Other abscesses	Other syndromes	Arachnoiditis	Chronic infections			Age (years)		
											Agents (*n*, %)		Patients* (%)	<65	>65	*p*-Value
T. pallidum	24	22	1	0	1	0	0	0	0	0	24	100	18	22	2	0.134
Brucella spp.	14	12	0	1	0	0	1	0	0	0	6	42.8	4.5	13	1	0.210
M. tuberculosis	152	84	4	59	1	0	2	0	3	1	37	24.3	28	129	23	**0.011**
S. pneumoniae	206	136	4	65	1	2	0	0	0	0	0			147	59	**0.039**
Streptococcus spp. (other)	55	22	0	14	16	3	4	0	0	0	0			45	10	0.0462
S. aureus	48	28	1	4	3	2	9	2	1	0	1	2.1	0.7	32	16	0.125
Co-NS	23	11	1	7	3	0	1	0	1	0	2	8.7	1.5	19	4	0.999
Listeria spp.	27	20	1	6	0	0	0	0	0	0	0			14	13	**0.004**
Nocardia spp.	4	0	0	0	4	0	0	0	0	0	1	25	0.7	0	4	
Klebsiella spp.	7	4	0	0	3	0	0	0	0	0	1	14.3	0.7	7	0	
Haemophilus spp.	10	8	0	1	1	0	0	0	0	0	0			9	1	
Capnocytophaga spp.	3	2	0	1	0	0	0	0	0	0	0			1	2	
Neisseria spp.	45	35	0	8	2	0	0	0	0	0	0			38	7	0.279
Fusobacterium spp.	2	1	0	0	2	0	0	0	0	0	0			2	0	
Borrelia spp.	38	19	0	19	0	0	0	0	1	0	10	26.3	7.5	27	11	0.507
Enterococcus spp.	5	3	0	2	1	0	0	0	1	0	0			2	3	
Micrococcus spp.	1	1	0	0	0	0	0	0	0	0	0			1	0	
Gemella spp.	1	0	0	0	1	0	0	0	0	0	0			1	0	
Peptococcus spp.	1	0	0	1	0	0	1	0	0	0	0			1	0	
Peptostreptococcus spp.	3	0	0	1	1	1	1	0	0	0	0			3	0	
Lactobacillus spp.	1	0	0	0	1	0	0	0	0	0	0			1	0	
Corynebacteria	1	1	0	0	0	0	0	0	0	0	0			1	0	
Actinomyces spp.	5	0	0	0	4	0	1	0	0	0	0			4	1	
Escherichia coli	9	6	0	0	0	0	3	0	0	0	0			1	8	
Enterobacter spp.	3	2	0	1	0	0	0	0	0	0	0			2	1	
Proteus spp.	2	1	0	0	1	0	0	0	0	0	0			2	0	
Morganella spp.	3	0	0	1	0	0	2	0	0	0	0			1	2	
Campylobacter spp.	1	0	0	0	0	0	1	0	0	0	0			0	1	
Aggregatibacter spp.	3	0	0	0	3	0	0	0	0	0	0			1	2	
Pseudomonas spp.	7	3	0	1	2	0	0	0	1	0	0			4	3	
Acinetobacter spp.	4	1	0	3	0	0	0	0	0	0	0			4	0	
Moraxella spp.	2	0	0	1	0	0	1	0	0	0	0			2	0	
Sphingomonas spp.	2	2	0	0	0	0	0	0	0	0	0			2	0	
Prevotella spp.	2	0	0	0	2	0	0	0	0	0	0			2	0	
Bacteroides spp.	1	0	0	0	0	0	1	0	0	0	0			1	1	
Xanthomonas spp.	1	0	0	1	0	0	0	0	0	0	0			1	0	
Aerococcus spp. *urinae*	1	0	0	0	1	0	0	0	0	0	0			1	0	
Cryptococcus spp.	27	23	0	4	0	0	0	0	0	0	3	11.1	2.2	21	6	0.999
Candida spp.	5	4	0	1	0	0	0	0	0	0	1	20	0.7	5	0	

Table 2 (continued)

	No.	Meningitis	Encephalitis	Meningoencephalitis	Brain abscess	Subdural empyema	Epidural abscess	Other abscesses	Other syndromes	Arachnoiditis	Chronic infections			Age (years)		
											Agents (*n*, %)		Patients* (%)	<65	>65	*p*-Value
Saccharomyces cerevisiae	1	0	0	0	0	1	0	0	0	0	0			1	0	
HSV-1	48	7	21	19	0	0	0	0	0	0	1	2.1	0.7	31	17	0.060
HSV-2	34	17	6	10	0	0	0	0	1	0	1	2.9	0.7	26	8	1.000
HSV-1/2	1	1	0	0	0	0	0	0	0	0	0			1	1	
EBV	16	9	3	3	10	0	0	0	0	0	3	18.8	2.2	12	4	0.772
CMV	5	3	0	0	2	0	0	0	0	0	1	20	0.7	3	2	
VZV	91	17	11	61	0	0	0	0	2	0	0			50	41	**0.000**
SFTV	1	0	0	1	0	0	0	0	0	0	0			1	0	
WNV	36	19	5	11	10	0	0	0	0	0	3	8.3	2.2	28	8	0.999
Parechovirus	1	0	1	0	0	0	0	0	0	0	0			1	0	
Mumps virus	6	1	0	5	0	0	0	0	0	0	0			6	0	
Measles virus	1	0	0	1	0	0	0	0	0	0	10	100	0.7	1	1	
Adenovirus	4	3	0	0	0	0	0	0	0	0	0			4	0	
PIV	2	1	0	1	0	0	0	0	0	0	0			2	0	
Enterovirus	91	74	3	15	0	0	0	0	0	0	1	1.1	0.7	89	2	**0.000**
HHV6	3	2	1	0	0	0	0	0	0	0	0			3	0	
HIV	12	2	4	5	10	0	0	0	0	0	6	50	4.5	10	2	0.693
JCV	5	0	4	1	0	0	0	0	0	0	2	40	1.5	5	0	
RSV	1	1	0	0	0	0	0	0	0	0	0			1	0	
TBEV	92	1	4	84	0	0	0	0	3	0	0			79	13	**0.043**
Toxoplasma spp.	8	0	0	1	7	0	0	0	0	0	4	50	3	6	2	
Specified	1079	546	64	388	48	7	23	2	15	1	96	8.9	73	829	250	
Unspecified	1504	746	144	500	49	7	8	0	54	1	36	2.4	27	1288	216	
Total patients	2583	1292	208	888	97	14	31	2	69	2	132	5.1	0	2117	466	

Co-NS Coagulase-negative staphylococci; *HSV* herpes simplex virus; *EBV* Epstein–Barr virus; *CMV* cytomegalovirus; *SFTV* sandfly fever Toscana virus; *WNV* West Nile virus; *PIV* parainfluenza virus; *HHV* human herpesvirus; *HIV* human immunodeficiency virus; *JCV* JC virus; *RSV* respiratory syncytial virus; *TBEV* tick-borne encephalitis virus

*Percentage for chronic CNS disease

Table 3 The distribution of infecting pathogens according to the ultimate diagnosis

	FR	HU	RO	CZ	DK	HR	BA	KS	SB	AL	IT	PT	TR	SY	IR	KZ	PK	HK	EG	TX	Total	%		Culture(+)	
																								No.	%
Total	194	188	146	301	192	66	162	87	50	81	53	60	302	80	74	124	114	75	165	69	2583	100		458	100
S. pneumoniae	25	7	29	6	26	3	4	1	21	2	11	8	34	0	1	14	0	0	0	13	205	8		178	38.9
S. anginosus	0	0	0	4	10	0	0	0	0	0	0	2	0	0	0	0	0	4	0	0	20	2		17	9.3
S. sanguinis	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1			1	
S. bovis	1	0	1	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	4			4	
S. mitis	2	1	0	0	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8			4	
S. salivarius	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	2			1	
S. pyogenes	1	2	0	0	0	0	0	0	2	0	1	0	0	0	0	0	0	1	0	0	7			7	
S. viridans	0	1	0	0	1	0	0	1	0	1	0	0	0	0	0	0	0	0	0	1	5			5	
Untyped	0	0	0	1	3	0	0	0	0	0	0	1	2	0	0	0	0	0	0	0	8			4	
S. aureus	1	7	3	5	5	0	2	0	1	1	5	2	4	0	2	1	1	5	0	3	48		1.9	48	10.5
Co-NS	0	0	1	2	3	0	0	2	1	3	2	3	1	0	1	1	0	3	0	0	23		0.9	23	5.0
Enterococcus spp.	1	0	2	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	5	*		5	1.1
Micrococcus luteus	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	*		1	*
Gemella spp.	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	*		1	*
Peptococcus spp.	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	*		1	*
Peptostreptococci spp.	0	0	0	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	*		3	*
L. monocytogenes	3	5	0	0	2	1	2	0	2	0	1	3	6	0	0	0	0	2	0	0	27		1	25	5.4
Lactobacillus spp.	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	*		1	*
Corynebacteria	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	*		1	*
Actinomyces spp.	0	0	1	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	*		4	*
Nocardia spp.	1	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	4	*		3	*
E. coli	0	0	1	1	0	0	0	1	0	0	0	2	2	0	0	0	1	0	0	1	9		1	9	5.4
Klebsiella spp.	1	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	4	0	0	7			7	
Enterobacter spp.	1	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	3			3	
P. mirabilis	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	2			2	
M. morganii	0	1	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	3			3	
Campylobacter spp.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1			1	
H. influenzae	0	0	1	0	0	1	0	0	0	0	3	1	1	0	0	0	0	0	0	0	7	*		7	1.5
Haemophilus spp.	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	2	*		2	*
Brucella spp.	0	0	0	0	0	0	0	0	0	2	0	0	7	2	2	0	0	0	0	0	13		0.5	3	*
Capnocytophaga spp.	2	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	*		2	*
Aggregatibacter spp.	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	3	*		3	*
N. meningitidis	3	17	0	2	8	2	1	0	0	1	0	1	6	0	0	0	0	0	1	0	42		1.6	26	5.6
Kingella kingae	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	*		1	*
Eikenella corrodens	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	*		2	*
Pseudomonas spp.	0	1	0	0	1	0	1	0	1	0	0	2	0	0	0	0	1	0	0	0	7		0.6	7	3.3
Acinetobacter spp.	0	1	0	0	0	0	1	0	1	1	0	0	0	0	0	0	0	0	0	0	4			4	
Moraxella spp.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	2			2	
Sphingomonas spp.	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2			2	
Prevotella spp.	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	*		2	*
B. fragilis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	*		1	*
Xanthomonas spp.	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	*		0	0
Aerococcus urinae	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	*		0	0
Fusobacterium spp.	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	*		1	*
M. tuberculosis	3	2	38	0	3	0	14	17	1	6	0	3	25	9	2	0	21	5	0	3	152		5.8	5	1.1
Cryptococcus spp.	4	0	4	0	0	0	0	0	0	0	4	6	1	0	1	0	0	5	0	2	27		1	20	4.3
Candida spp.	0	1	0	1	0	0	0	0	0	0	0	0	1	0	1	0	1	0	0	0	5	*		4	*
Saccharomyces cerevisiae	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	*		0	0
HSV-1	12	3	0	4	9	0	0	0	0	0	4	0	7	3	1	0	1	1	0	3	48		1.8		
HSV-2	10	2	0	4	12	0	0	0	0	0	0	2	1	1	1	0	0	0	0	1	34		1.3		
HSV-1/2	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	*			
EBV	4	2	0	1	1	0	0	0	0	0	3	0	4	0	0	0	0	0	0	1	16		0.6		
CMV	0	4	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	5	*			
VZV	13	1	0	54	11	3	0	0	0	0	2	1	2	0	0	0	0	2	0	2	91		3.5		
SFTV	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	*			
WNV	0	5	0	0	0	2	1	7	0	0	0	0	0	0	0	0	0	18	0	3	36		1.4		
Parechovirus	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	*			

Table 3 (continued)

	FR	HU	RO	CZ	DK	HR	BA	KS	SB	AL	IT	PT	TR	SY	IR	KZ	PK	HK	EG	TX	Total	%	Culture(+)	
																							No.	%
Mumps virus	0	1	0	4	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	*		
Measles virus	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	*		
Adenovirus	0	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	*		
PIV	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	*		
Enterovirus	20	4	0	12	22	8	0	0	0	0	1	8	16	0	0	0	0	0	0	0	91		3.5	
HHV-6	2	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	3	*		
HIV	8	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	9		0.5	
JCV	4	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	5	*		
RSV	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	*		
TBEV	0	14	0	75	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	92		3.5	
Toxoplasma spp.	4	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0	0	0	0	8	*		

Co-NS Coagulase-negative staphylococci; *SFTV* sandfly fever Toscana virus; *WNV* West Nile virus; *TBEV* tick-borne encephalitis virus; *PIV* parainfluenza virus; *FR* France; *HU* Hungary; *RO* Romania; *CZ* Czech Republic; *DK* Denmark; *HR* Croatia; *BA* Bosnia and Herzegovina; *KS* Kosovo; *SB* Serbia; *AL* Albania; *IT* Italy; *PT* Portugal; *TR* Turkey; *SY* Syria; *IR* Iran; *KZ* Kazakhstan; *PK* Pakistan; *HK* Hong Kong; *EG* Egypt; *TX* Texas

*The percentage was not specified for <0.005

TBEV [13/250–79/829 (p = 0.032)] affected adults significantly more than the elderly (Table 2).

Chronicity

96 (8.9%) out of 1079 patients with any identified pathogen presented with clinical features of chronic meningitis. *Treponema pallidum* (24/96–0/983; $p < 0.001$), *Brucella* spp. (6/96–8/983; $p = 0.001$), *M. tuberculosis* (37/96–115/983; $p < 0.001$), and *Borrelia* spp. (10/96–28/983; $p = 0.001$) were more likely to be causing chronic infections, while streptococci other than pneumococci (0/96–55/983; $p = 0.012$), *Neisseria meningitidis* (0/96; 45/983; $p = 0.046$), VZV (0/96–91/983: $p = 0.003$), enteroviruses (1/96–90/983; $p = 0.011$), and TBEV (0/96–92/983; $p < 0.001$) frequently presented non-chronic patterns. *Streptococcus pneumoniae* (0/96–206/983; $p < 0.001$) always presented with acute patterns (Table 2).

Immunosuppressive states

There were 741 immunosuppressive conditions in 603 (23.3%) out of 2583 patients. Of these, there were 170 (6.6%) confirmed (primary and secondary) immunosuppressive patients and 571 (22.1%) probable immunosuppressive conditions in 508 cases. The distribution was as follows:

1. Primary immunosuppression: One hyper IgM syndrome (type 1), two hypogammaglobulinemia, one mucocutaneous candidiasis, one IgA deficiency.
2. Secondary immunosuppression: Acute lymphocytic leukemia, bone marrow transplantation, amyloidosis, acute myelocytic leukemia, autoimmune hemolytic anemia, leukemia, myelofibrosis, pyoderma gangrenosum, multiple myelomas, and myelodysplastic syndrome were seen in one patient. Two monoclonal gammopathies, two chronic lymphocytic leukemias, two large cell lymphomas, three cirrhosis, six solid organ transplantations, seven splenectomies, 31 with chemotherapy, and 121 systemic corticosteroid use were other conditions.
3. Probable immunosuppression: 263 diabetes mellitus, 116 malignities, 84 HIV infections, 27 pregnancies, 15 alcoholics, ten chronic liver diseases, six Addison's disease, six end-stage renal disease, seven systemic lupus erythematosus, three rheumatoid arthritis, three intravenous drug users, two ulcerative colitis, and two psoriasis. Hypersplenism, acute renal failure, Behçet's disease, positive anti-GM/GSF antibody, brain tumor, congenital leukodystrophy, disseminated sclerosis, Down syndrome, generalized herpetic infection, genital herpes, Crohn's disease, non-Hodgkin lymphoma, panhypopituitarism, scleroderma, and ankylosing spondylitis were seen in one patient.

When the patients with a etiologically proven agent was considered (n = 1179), *S. aureus* was more frequent in diabetics (11/121, 9.1%) compared to non-diabetics (37/958, 3.9%) (p = 0.017). Coagulase-negative staphylococci were more common in patients with secondary immunosuppression (6/95, 6.3%) than the others (18/984, 1.8%) (p = 0.015) and in patients with concurrent malignancies (n = 4/61, 6.6%) compared to those without concurrent malignancies (n = 20/1018, 2%) (p = 0.042). *Listeria monocytogenes* was more common in secondary immunosuppression (9/95, 9.5%) than those without (18/984, 1.8%) (p = 0.015) and in malignancy patients (n = 5/61, 8.2%) compared to those without malignity (22/1018, 2.2%) (p = 0.015). Finally, cryptococci was the most frequent in etiologically proven CNS infection patients with HIV infection (n = 13/50, 26%) compared to HIV-negative patients (n = 14/1029, 1.4%) ($p < 0.001$).

Table 4 The distribution of ultimate microbiological diagnoses according to the immunosuppression status of the patients

		Probable immunosuppressive conditions						Confirmed immunosuppressive conditions		
	No.	Mal	DM	HIV	Pg	Other	Subtotal	Primary	Secondary	Subtotal
T. pallidum	24	0	0	0	0	0	0	0	0	0
Brucella spp.	14	1	0	0	0	0	1	0	0	0
M. tuberculosis	152	6	18	9	2	6	41	1	10	11
S. pneumoniae	206	14	27	3	3	7	54	1	25	26
Streptococcus spp. (other)	55	1	6	1	1	6	15	0	3	3
S. aureus	48	2	11	0	0	4	17	0	5	5
Co-NS	23	4	4	0	0	1	5	0	6	6
Listeria spp.	27	5	4	0	0	3	12	0	9	9
Nocardia spp.	4	0	0	0	0	0	0	0	2	2
Klebsiella spp.	7	2	1	0	0	0	3	0	0	0
Haemophilus spp.	10	0	1	0	0	0	1	0	1	1
Capnocytophaga spp.	3	1	0	0	0	0	1	0	1	1
Neisseria spp.[a]	45	1	3	0	1	0	5	0	4	4
Fusobacterium spp.	2	0	0	0	0	0	0	0	0	0
Borrelia spp.	38	2	3	0	0	0	5	0	2	2
Enterococcus spp.	5	0	0	0	0	0	0	0	1	1
Micrococcus spp.	1	0	0	0	0	0	0	0	0	0
Gemella spp.	1	0	0	0	0	1	1	0	0	0
Peptococcus spp.	1	0	0	0	0	0	0	0	0	0
Peptostreptococcus spp.	3	0	1	0	0	0	1	0	0	0
Lactobacillus spp.	1	0	1	0	0	0	1	0	0	0
Corynebacteria	1	1	0	0	0	0	1	0	0	0
Actinomyces spp.	5	0	2	0	0	0	2	0	0	0
Escherichia coli	9	2	3	0	0	0	5	0	0	0
Enterobacter spp.	3	1	0	0	0	0	1	0	0	0
Proteus spp.	2	0	0	0	0	0	0	0	0	0
Morganella spp.	3	0	2	0	0	0	2	0	0	0
Campylobacter spp.	1	0	1	0	0	0	1	0	0	0
Aggregatibacter spp.	3	0	0	0	0	0	0	0	0	0
Pseudomonas spp.	7	0	1	0	0	0	1	0	0	0
Acinetobacter spp.	4	1	1	0	0	0	2	0	0	0
Moraxella spp.	2	1	0	0	0	0	1	0	0	0
Sphingomonas spp.	2	2	0	0	0	0	2	0	4	4
Prevotella spp.	2	0	1	0	0	0	1	0	0	0
Bacteroides spp.	1	0	0	0	0	0	0	0	1	1
Xanthomonas spp.	1	0	0	0	0	0	0	0	1	1
Aerococcus urinae	1	0	0	0	0	0	0	0	0	0
Cryptococcus spp.	27	2	1	13	0	1	17	1	5	6
Candida spp.	5	0	2	0	0	1	3	1	0	1
Saccharomyces cerevisiae	1	0	0	0	0	0	0	0	0	0
HSV-1	48	1	6	1	1	1	9	0	3	3
HSV-2	34	3	3	0	0	0	6	0	5	5
HSV-1/2	1	0	0	0	0	0	0	0	0	0
EBV	16	2	3	3	0	0	8	0	3	3
CMV	5	0	0	1	0	0	1	0	1	1
VZV	91	7	12	1	2	2	24	1	10	11
SFTV	1	0	0	0	0	0	0	0	0	0

Table 4 (continued)

		Probable immunosuppressive conditions						Confirmed immunosuppressive conditions		
	No.	Mal	DM	HIV	Pg	Other	Subtotal	Primary	Secondary	Subtotal
WNV	36	0	7	1	0	0	8	0	0	0
Parechovirus	1	0	0	0	0	0	0	0	0	0
Mumps virus	6	0	0	0	0	0	0	0	0	0
Measles virus	1	0	0	0	0	0	0	0	0	0
Adenovirus	4	0	0	0	0	0	0	0	0	0
PIV	2	0	0	1	0	0	1	0	0	0
Enterovirus	91	1	4	0	0	1	6	0	3	3
HHV-6	3	1	0	0	0	0	1	0	1	1
HIV	12	0	1	12	0	0	13	0	0	0
JCV	5	0	0	5	0	0	5	0	0	0
RSV	1	0	0	1	0	0	1	0	0	0
TBEV	92	1	11	0	0	2	14	0	3	3
Toxoplasma spp.	8	0	1	8	0	0	9	0	0	0
Unspecified	1504	55	142	34	17	15	263	1	70	71
Total patients	2583	116	263	84	27	47	508	5	165	170

Co-NS Coagulase-negative staphylococci; *SFTV* sandfly fever Toscana virus; *WNV* West Nile virus; *TBEV* tick-borne encephalitis virus; *PIV* parainfluenza virus; *Mal* malignancy; *DM* diabetes mellitus; *Pg* pregnancy; *Primary* and *secondary* indicate primary and secondary immunodeficiencies, respectively

[a] *Eikenella* and *Kingella* were included in this group

Outcomes

In this study, 477 (18.5%) patients survived with sequelae and 227 (8.8%) died during hospital stay. Motor deficit (n = 128, 5%), cranial nerve involvement (n = 92, 3.6%), cognitive impairment (n = 70, 2.7%), persisting headache (n = 38, 1.5%), and epilepsy (n = 26, 1%) were the most frequent sequelae. Overall, 1879 (72.7%) patients were discharged with complete cure. Among the patients with any etiologically proven pathogen, 711 (65.9%) patients had complete cure, 261 (24.2%) survived with sequelae, and 107 (9.9%) patients died. Adverse clinical outcomes in patients with an etiologically proven pathogen [368/1079(34.1%)] were significantly more common than those without confirmed etiological diagnosis [336/1504 (22.7%)] ($p < 0.001$). The Glasgow Coma Scale (GCS) scores of the patients with a etiologically proven CNS pathogen on admission were significantly lower in patients with adverse clinical outcomes (mean: 11.94 ± 3.69) compared to survivors with complete cure (mean: 13.37 ± 2.86)

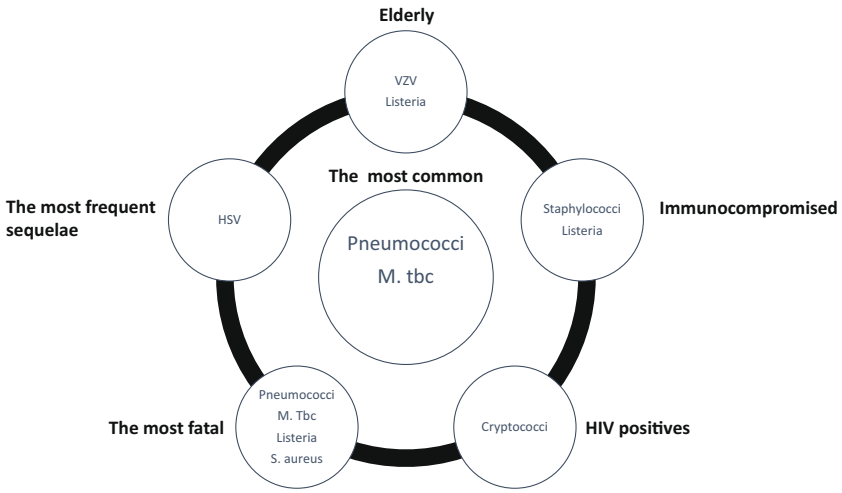

Fig. 1 Common pathogens in community-acquired central nervous system (CA-CNS) infections

($p < 0.001$). The outcome distributions in CA-CNS infection patients are presented in Table 5.

a) Mortality rate by specific pathogens: The fatality rate was significantly higher for *L. monocytogenes* [(8/107–19/972); ($p = 0.003$)], *S. aureus* [(10/107–38/972); ($p = 0.021$)], *M. tuberculosis* [(28/107–124/972); ($p < 0.001$)], and *S. pneumoniae* [(33/107–173/972); ($p = 0.002$)], while it was significantly lower in enterovirus [(1/107–90/972); ($p = 0.006$)] and TBEV [(1/107–91/972); ($p = 0.005$)] infections, and where no death was seen due to *Borrelia* spp. infections [(0/107–38/972); (non-applicable statistics)].
b) Rate of neurological sequelae by specific pathogens: Persistence of sequelae was significantly higher in herpes simplex virus (HSV) type 1 cases [(24/261–24/818); ($p < 0.001$)], while it was less frequent in enterovirus [(13/261–78/818); ($p = 0.029$)] and TBEV [(8/261–84/818); ($p < 0.001$)] infections.

Discussion

CNS infections have significant mortality and permanent neurological sequelae worldwide [17]. Despite the advances in management, 27.3% of patients with CA-CNS infections experienced unfavorable outcomes in this study, including persistent sequelae and death. The most frequent sequelae were motor deficits (5%) and cranial nerve involvements (3.6%), in accordance with the current literature [19]. Cognitive impairment, persisting headache, and epilepsy were seen in descending order (Table 5). We found that CA-CNS diseases due to *S. aureus*, *M. tuberculosis*, *S. pneumoniae*, and *Listeria* spp. were the most fatal etiologies, while the patients with CA-CNS infections due to enterovirus, TBEV, and *Borrelia* spp. were less likely to die. Furthermore, HSV-1 was associated with sequelae most commonly, while enteroviruses and TBEV were less likely to be complicated with sequelae.

Meningitis and encephalitis, known as two intersecting syndromes, were reported to be the most frequent CNS infections [17, 20, 21]. The use of neuroimaging before lumbar puncture has generated considerable debate, with some investigators pointing to delays in antibiotic administration, reduced likelihood of identifying a pathogen, and an increase in mortality [22]. In this study, half of the cases were classified as meningitis and 8% as encephalitis, and an unspecified 34% of patients were classified as meningoencephalitis. Considering the high frequency of cases presenting with encephalitic pattern in this study, the detection of brain parenchymal involvement with imaging together with positive EEG findings is directly suggestive of encephalitis [23] and leads to early administration of antivirals that reduce unfavorable outcomes [8]. Added to that, suppurative intracranial infections, where brain abscesses dominated in two-thirds and epidural abscesses in one-third, made up 5.6% of all CA-CNS infections. Thus, these data indicate the necessity of using radioimaging methods and EEG in an unspecified CA-CNS infection patient considering the high frequency encephalitis and suppurative intracranial infections.

Consequently, the diagnostic capacity of the hospitals treating CA-CNS infections determines the early diagnosis, which is key to rational therapies [2, 4, 8, 17]. We found that the etiological diagnosis was established in 41.8% of all patients. The data are scarce in the literature in that context. In an African study, 35% of the cases with meningitis [24] and in a Turkish systematic review, 32.6% of the cases [25] were reported to have an etiological diagnosis. In addition, 3% of the CA-CNS infections had multiple infecting agents, which must not be overlooked by the treating clinicians. The most frequent infecting pathogens in this study were *S. pneumoniae* and *M. tuberculosis*. TBEV, VZV, enteroviruses, and HSV infections are among the other most frequent CA-CNS infections. Hence, these data highlight the importance of pneumococcal immunization, producing herd immunity and decreasing invasive disease [22], and widespread tuberculosis elimination programs. Accordingly, *N. meningitidis*, which is the agent of epidemic meningitis, was a still noteworthy pathogen and had a share of 1.6% in CA-CNS patients. Although *Streptococcus suis* was reported to be one of the major causes of meningitis in some parts of Asia [22], *Streptococcus anginosus* was recovered mainly from patients in European countries among the non-pneumococcal species in this study. In a recent meta-analysis, the most frequent causes of brain abscesses were streptococci and *S. aureus* [26], and our data were in accordance with this. Pneumococcal CNS disease and VZV infections were the most frequent infections in the elderly, followed by *M. tuberculosis* and *L. monocytogenes* infections. In the literature, pneumococcal and listerial CNS diseases have been known to be quite frequent in elderly patients [4, 27]. However, our data affirm that, in accordance with the high tuberculous CNS disease worldwide [28], and as specific cell-mediated immunity declines in the elderly for VZV infections [29], they should not be underestimated in the elderly. According to our data, *S. pneumoniae*, *S. aureus*, *L. monocytogenes*, and VZV infections were seen relatively more frequently in older patients, while *M. tuberculosis* and enterovirus infections were observed in adult CA-CNS cases. These differences may be explained owing to the decreasing immunity with advancing age and epidemiological trends [4, 21, 30].

Listeria monocytogenes meningitis was more often found in patients with acquired immunodeficiencies [2, 31], while cryptococcal CNS disease was common in HIV-infected

Table 5 The outcomes of the CNS infection patients

		Cure	Cure with sequelae								Death	GCS[a]	
		No.	*n*, %	CNI	Epilepsy	Ataxia	MD	UI	CI	HA	Other[b]	*n* (%)	Mean	SD
Bacterial CNS infections														
T. pallidum	24	14	10 (42)	0	1	0	1	0	0	0	8	0	14.54	1.14
Brucella spp.	14	12	2 (14)	0	0	1	1	0	0	0	0	0	12.25	3.16
M. tuberculosis	152	90	34 (22)	9	3	1	10	0	0	1	10	28 (18.4)	12.56	3.18
S. pneumoniae	206	128	45 (22)	9	0	1	10	2	5	2	16	33 (16)	10.31	3.57
Streptococcus spp. (other)	55	31	17 (31)	2	2	0	8	0	3	1	1	7 (13)	12.44	3.1
S. aureus	48	24	14 (29)	1	2	0	5	0	1	0	5	10 (21)	12.72	3.22
Staphylococci (other)	23	19	4 (17)	1	0	0	1	1	0	0	1	0	12.27	3.85
Listeria spp.	27	15	4 (15)	0	0	0	1	0	2	0	1	8 (30)	10.65	4.01
Nocardia spp.	4	2	1 (25)	0	0	0	0	1	0	0	0	1 (25)	15	0
Klebsiella spp.	7	5	0	0	0	0	0	0	0	0	0	2 (29)	12.71	3.94
Haemophilus spp.	10	8	1 (10)	0	0	0	0	0	1	0	0	1 (10)	13.5	2.71
Capnocytophaga spp.	3	2	1 (33)	0	0	0	1	0	0	0	0	0	13	3.46
Neisseria spp.[c]	45	32	8 (18)	0	0	0	0	0	2	4	2	5 (11)	11.98	3.99
Fusobacterium spp.	2	1	1 (50)	0	0	0	1	0	0	0	0	0	14.5	0.70
Borrelia spp.	38	25	13 (34)	6	0	0	1	0	0	0	6	0	14.27	2.14
Enterococcus spp.	5	3	2 (40)	0	0	0	1	0	1	0	0	0	11	1.41
Micrococcus spp.	1	1	0	0	0	0	0	0	0	0	0	0	14	0
Gemella spp.	1	0	1 (100)	0	1	0	0	0	0	0	0	0	15	0
Peptococcus spp.	1	1	0	0	0	0	0	0	0	0	0	0	8	0
Peptostreptococcus spp.	3	1	2 (67)	0	0	0	2	0	0	0	0	0	10.33	4.04
Lactobacillus	1	0	1 (100)	0	0	0	1	0	0	0	0	0	15	0
Corynebacteria	1	0	0	0	0	0	0	0	0	0	0	1 (100)	14	0
Actinomyces	5	2	3 (60)	0	0	0	3	0	0	0	0	0	15	0
Escherichia coli	9	6	1 (11)	0	0	0	0	0	0	0	1	2 (22)	12.57	2.99
Enterobacter spp.	3	2	1 (33)	0	0	0	1	0	0	0	0	0	9	8.48
Proteus spp.	2	1	1 (50)	1	0	0	0	0	0	0	0	0	13.5	2.12
Morganella spp.	3	3	0	0	0	0	0	0	0	0	0	0	14.67	0.57
Campylobacter spp.	1	1	0	0	0	0	0	0	0	0	0	0	15	0
Aggregatibacter spp.	3	2	1 (33)	0	0	0	1	0	0	0	0	0	14.67	0.57
Pseudomonas spp.	7	4	2 (29)	0	0	0	0	0	0	2	0	1 (14)	12.14	4.56
Acinetobacter spp.	4	2	2 (50)	1	1	0	0	0	0	0	0	0	10.67	4.04
Moraxella spp.	2	1	1 (50)	0	0	0	1	0	0	0	0	0	12	6.36
Sphingomonas spp.	2	2	0	0	0	0	0	0	0	0	0	0	15	0
Prevotella spp.	2	0	2 (100)	0	0	0	2	0	0	0	0	0	15	0
Bacteroides spp.	1	0	1 (100)	0	0	0	1	0	0	0	0	0	13	0
Xanthomonas spp.	1	1	0	0	0	0	0	0	0	0	0	0	15	0
Aerococcus urinae	1	1	0	0	0	0	0	0	0	0	0	0	14	0
Fungal CNS infections														
Saccharomyces cerevisiae	1		1 (100)	0	0	0	1	0	0	0	0	0	10	0
Cryptococcus spp.	27	18	5 (19)	2	1	0	0	0	1	0	1	4 (15)	13.97	2.55
Candida spp.	5	3	0	0	0	0	0	0	0	0	0	2 (40)	11.5	4.04
Viral CNS infections														
HSV-1	48	22	24 (50)	2	3	0	0	0	19	0	0	2 (4)	12.81	3.33
HSV-2	34	25	7 (21)	0	1	0	0	0	4	1	1	2 (6)	14.06	2.13
HSV-1/2	1		1 (100)	0	0	0	0	0	0	0	1	0		
EBV	16	11	4 (25)	1	1	0	1	1	0	0	0	1 (6)	12.75	3.45

Table 5 (continued)

		Cure	Cure with sequelae								Death	GCS[a]	
		No.	*n*, %	CNI	Epilepsy	Ataxia	MD	UI	CI	HA	Other[b]	*n* (%)	Mean	SD
CMV	5	2	3 (60)	0	0	0	0	1	0	1	1	0	15	0
VZV	91	61	25 (27)	14	0	0	4	0	4	0	3	5 (5.5)	14.39	1.63
SFTV	1	1	0	0	0	0	0	0	0	0	0	0	15	0
WNV	36	24	9 (25)	1	1	0	4	0	1	2	0	3 (8)	13.17	3.47
Parechovirus	1	1	0	0	0	0	0	0	0	0	0	0	15	0
Mumps virus	6	5	1 (17)	1	0	0	0	0	0	0	0	0	15	0
Measles virus	1	1	0	0	0	0	0	0	0	0	0	0	15	0
Adenovirus	4	2	1 (25)	0	0	0	0	0	0	1	0	0	15	0
PIV	2	1	1 (50)	0	0	0	0	0	0	0	1	0	15	0
Enterovirus	91	77	13 (14)	1	0	0	0	0	3	9	0	1 (1.1)	14.72	1.2
HHV-6	3	3	0	0	0	0	0	0	0	0	0	0	13	3.46
HIV	12	5	7 (58)	2	0	0	0	0	5	0	0	0	13.25	3.59
JCV	5	1	4 (80)	0	0	0	1	0	2	0	1	0	14.2	1.30
RSV	1	1	0	0	0	0	0	0	0	0	0	0	15	0
TBEV	92	83	8 (8.6)	3	0	0	3	0	1	0	1	1 (1.1)	14.57	0.95
Toxoplasma spp.	8	5	3 (38)	0	0	0	0	0	1	0	2	0	11.88	4.96
Undermined etiology	1504	1168	216 (14)	35	9	3	62	1	14	14	78	120 (8)		
Total	2583	1879	477 (18)	92	26	6	128	7	70	38	141	227 (9)		

CNI Cranial nerve involvement; *MD* motor deficit; *UI* urinary incontinency; *CI* cognitive impairment; *HA* persisting headache; *GCS* Glasgow Coma Scale; *SD* standard deviation; *SFTV* sandfly fever Toscana virus; *WNV* West Nile virus; *TBEV* tick-borne encephalitis virus; *PIV* parainfluenza virus

[a] On admission data

[b] Depression, spinal abscess, cerebellar syndrome, etc.

[c] *Eikenella* and *Kingella* were included in this group

patients [32, 33]. Our data were in accordance with that for both pathogens. In addition, we have disclosed that *S. aureus* was a significant agent in diabetic patients, while coagulase-negative staphylococci were common in patients with secondary immunosuppression and malignancy patients. These two groups of pathogens were reported to be the leading agents in various subgroups of immunocompromised patients [34, 35]. However, to the best of our knowledge, this is the first report interrelating immunosuppressive states and staphylococcal CA-CNS infections. Our data may, therefore, support the recommendations in using anti-Gram-positive agents as part of the combination regimen in bacterial CA-CNS infections [2, 3, 7].

In the literature of the past two decades [32, 33, 36], the most frequent agents causing chronic CNS infections were cryptococci and *M. tuberculosis*, depending on the HIV status. In HIV-positive patients, cryptococcal disease predominated [32, 33] and in HIV-negative patients, CNS tuberculosis [36] was the most frequent diagnosis in chronic CNS infections. In this study, 4.3% of the cases presented with a chronic pattern extending over 4 weeks, and neurosyphilis, brucellar meningitis, neuroborreliosis, and CNS tuberculosis were significantly more likely to present chronic courses. In contrast, cryptococcal meningitis was seen only in 2.2% of cases with chronic CNS disease, although it was still the most frequent CA-CNS infection in HIV-positive individuals. This shift was most probably due to the increasing efficiency of HIV treatment worldwide, with the resultant decrease in opportunistic infections [37].

We believe that our study has important implications for the management of CA-CNS infections. *Streptococcus pneumoniae* and *M. tuberculosis* were the leading CA-CNS pathogens. Considering the high frequency of patients predisposed as encephalitis, meningoencephalitis, or suppurative intracranial infections, both MRI and EEG should be applied to all patients with probable CA-CNS infections. The need to improve the diagnostic capacity in centers treating CNS infections is another serious concern. Accordingly, high sequelae forming infections like HSV-1 were important in the differential diagnosis. In addition to pneumococcal disease and CNS tuberculosis, both common in all ages, VZV, *S. aureus*, and *L. monocytogenes* should be taken into consideration in the elderly population. Accordingly, staphylococcal, cryptococcal, and listerial infections should be considered for immunocompromised patients. Finally, clinicians need to consider that neurosyphilis, brucellar meningitis,

neuroborreliosis, and CNS tuberculosis may have a predilection for prolonged courses where alternative strategies are needed.

Compliance with ethical standards

Funding We did not receive any kind of funding.

Ethical approval Yes, it is obtained from the Review Board of Fatih Sultan Mehmet Education and Research Hospital in Istanbul.

Informed consent Not applicable. The study has a retrospective design.

Conflict of interest We have no competing interests to declare.

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