1 Introduction and Classification of Infections of the CNS According to the Agent

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Despite modern antimicrobial therapies and vaccines, infections of the CNS still have an unacceptably high mortality and may generate permanent neurologic deficits in survivors. The bony structures of the skull and vertebral column and the blood-brain barrier (BBB) afford strong protection for the brain and spinal cord from invading pathogens. However, once the pathogen enters the CNS, the host defense mechanisms are often inefficient in preventing severe, life-threatening infections. The clinical severity of infection results from complex interactions between the host and the invading pathogen, but it is clear that CNS infections differ fundamentally from those in other organs and are usually more serious, partly because of the CNS's immunological privilege.

The growing numbers of patients with immune deficiency together with the increased displacement of people (i.e. migrants or international travelers) has expanded the spectrum of infectious diseases and its range, making the pathological diagnosis of CNS infectious disease more difficult. On the other hand, important advances in molecular medicine have improved our knowledge of the genetics of both the pathogens and the immunological characteristics of the host.

For these reasons, the International Society of Neuropathology devotes a volume of the established series of Pathology and Genetics textbooks to the pathology and genetics of infections in the CNS.

This volume *Infections of the Central Nervous System: Neuropathology and Genetics* consists of 50 chapters describing the most important infections involving the CNS. Numerous agents may infect the CNS, including viruses, bacteria, fungi, parasites, and arthropods (myiasis), and sequential chapters describing them have been laid out in this order. An exceptional case of meningitis resulting from an alga *Prototheca wickerhamii* in a patient with severe immunodeficient acquired

Infections of the Central Nervous System: Pathology and Genetics, First Edition. Edited by Fabrice Chrétien, Kum Thong Wong, Leroy R. Sharer, Catherine (Katy) Keohane and Françoise Gray.

immunodeficiency syndrome (AIDS) has been reported [1] but does not warrant a special chapter.

This introductory chapter proposes a classification of the different pathogens affecting the CNS; Chapters 2–4 discuss inflammation and sepsis, genetic and other host variations in infections, and the clinical approach to CNS infectious diseases.

The section on viral infections starts with DNA viruses, beginning with the large herpesvirus group, including herpes simplex 1 and 2, varicella-zoster and Epstein-Barr viruses, and cytomegalovirus, followed by adenovirus and polyomavirus (Table 1.1). For the RNA viruses, there are chapters on measles, rubella, henipavirus, rabies, hepatitis C and E viruses, alphaviral equine encephalitis viruses, Chikungunya virus, poliovirus (including postpolio syndrome), enterovirus A71, human immunodeficiency virus (HIV), human T-lymphocytic/leukemia virus I, and parechovirus. The large important group of flaviviruses are dealt with in four chapters with a general introduction to flaviviral encephalitides and a description of tick-borne encephalitis, followed by encephalitides caused by yellow fever, West Nile, St. Louis, dengue and Murray Valley encephalitis viruses, Zika virus, and Japanese encephalitis virus. Chapter 26 describes entities long known to be associated with viral infections (e.g. acute disseminated encephalomyelitis); the subsequent chapter deals with encephalitides of uncertain origin but that may be associated with viral infection (e.g. Rasmussen encephalitis).

Descriptions of CNS bacterial infections (Table 1.2) include chapters on *Mycoplasma* and *Rickettsia,* pyogenic bacteria, *Actinomyces, Tropheryma whipplei* (Whipple disease), *Nocardia, Mycobacterium tuberculosis,* nontuberculous *Mycobacteria,* spirochetes, *Brucella,* and *Legionella*. In addition to a chapter on general pathogenesis and pathophysiology of bacterial infections, the different types of pyogenic bacteria are discussed according to the clinicopathological entities they commonly cause: acute meningitis and abscess or suppuration; additionally, a separate chapter is devoted to bacterial infections following neurosurgical procedures. Disease entities such as neurosarcoidosis and chronic immunoglobulin G4 (IgG4) pachymeningitis are included because they are often a major differential diagnosis of bacterial infections. Toxin-induced neurological diseases are discussed in a separate chapter.

Numerous fungi (Table 1.3) cause CNS infections; according to their morphology, fungal pathogens can be divided into three major groups: molds, yeasts, and dimorphic fungi. This categorization does not relate to the taxonomic groups, but it may be helpful in guiding diagnosis because each category shares similar clinical features.

Parasitic infections of the CNS caused by protozoa include infections by *Plasmodium, Toxoplasma,* and other protozoa such as amebae, trypanosomes, *Microsporidium,* and *Leishmania* (Table 1.4). Helminthic cestodes (i.e. *Taenia, Echinoccocus, Spirometra*), trematodes (i.e. Schistosoma, Paragonimus), and nematodes (i.e. Angiostrongylus, *Gnathostoma, Toxocara, Trichinella*, filaria, *Strongyloides*) infections and CNS myiasis resulting from fly larvae infestation of the CNS are also described.

Many factors determine the incidence of different CNS infections in disparate geographical regions. Endemic and emerging infections in susceptible human populations depend on the dynamic interactions between (or changes in) microbe-environment-host factors. The increasing virulence of CNS pathogens because of antimicrobial resistance is of huge importance, resulting in increased incidence of more severe infections. Environmental factors caused by poor sanitation and hygiene and absence of vector control, and so on, enable diseases to spread rapidly. Host factors including changes in human behavior and demography, immunosuppression, genetic predisposition, and many others conspire to increase host susceptibility to CNS infections. In recent years, acquired immunosuppression resulting from HIV infection or associated with therapeutic modalities, including newer immunomodulating treatments, has dramatically increased host susceptibility to numerous opportunistic agents. A separate chapter on emerging CNS infections discusses more details about this phenomenon.

This book aims to describe and illustrate the various lesions and entities that may be encountered in CNS infections to help in pathological diagnosis. These include meningitis, abscess, encephalitis, myelitis, demyelination, vasculopathy, infarction, or combinations thereof (e.g. meningoencephalitis and encephalomyelitis). The

Table 1.1 Main viruses involving the CNS.

Virus	Genus/Species	Main CNS neurological syndromes[a]	Characteristics[b]
DNA viruses			
Herpes virus	Herpes simplex I, II HHV-1 and -2	Encephalitis	Virus targets neurons
	Varicella-zoster virus HHV-3	Myelitis Vasculitis/infarcts Meningoencephalitis Etc.	Virus targets neuroglial and Schwann cells, blood vessels.
	Epstein-Barr virus HHV-4	Myelitis Meningoencephalitis	Associated with immunosuppression
	Cytomegalovirus HHV-5	Myelitis Ventriculoencephalitis Congenital neurological syndrome	Associated with immunosuppression
Adenovirus	Adenovirus species	Meningoencephalitis	Associated with immunosuppression
Polyomavirus	JC virus	Progressive multifocal leukoencephalopathy	Virus targets oligodendroglia mainly
	BK virus		Associated with immunosuppression
RNA viruses			
Morbillivirus	Measles virus (rubeola)	Acute postinfectious encephalitis MIBE SSPE	Virus targets neuroglial cells and neurons in MIBE and SSPE MIBE mainly associated with immunosuppression SSPE associated with mutant virus
Rubivirus	Rubella virus	CRS (RE)	Cerebral blood vessel damage and microcephaly in CRS Neuronal degeneration in RE
Henipavirus	Hendra virus Nipah virus	Acute encephalitis Relapsing encephalitis	Virus targets cerebral blood vessels and neuroglial cells in acute encephalitis Virus targets only neuroglial cells in relapsing encephalitis
Lyssavirus	Rabies virus and other species	Encephalitis (Paralytic rabies; furious rabies)	Virus mainly targets neurons
Flavivirus	Tick-borne encephalitis virus	Encephalitis	Virus targets neurons
	West Nile virus	Encephalitis	Virus targets neurons
	St. Louis encephalitis virus	Encephalitis	Virus targets neurons
	Murray valley encephalitis virus	Encephalitis	Virus targets neurons
	Yellow fever virus	Encephalopathy	Mainly viscerotropic
	Dengue virus	Encephalopathy	Mainly viscerotropic
	Zika virus	Congenital Zika syndrome	Virus mainly targets neural progenitor cells
	Japanese encephalitis virus	Encephalitis	Virus targets neurons
	Hepatitis C virus	Neuropsychiatric-related (parainfectious) Meningoencephalitis/myelitis (rare)	Neurotropism unconfirmed
Hepevirus	Hepatitis E virus	Meningoencephalitis/myelitis (rare)	Neurotropism unconfirmed

(*continued*)

Table 1.1 (Continued)

Virus	Genus/Species	Main CNS neurological syndromes[a]	Characteristics[b]
Alphavirus	Eastern equine encephalitis virus	Encephalitis	Virus targets neurons
	Western equine encephalitis virus		
	Venezuelan equine encephalitis virus		
	Chikungunya virus	Encephalopathy Encephalitis	Specific neuropathology unknown
Enterovirus	Enterovirus A71	Acute flaccid paralysis Encephalomyelitis	Virus targets mainly lower motor neurons
	Poliovirus	Poliomyelitis Polioencephalitis Postpolio syndrome	Virus targets mainly lower motor neurons
Retrovirus	HIV	HIV-induced encephalitis and other encephalopathy/disorders Opportunistic infections	Virus targets CD4 lymphocytes and macrophages/microglia
	HTLV	Tropical spastic paraparesis/HTLV-1–associated myelopathy	Virus targets CD4 lymphocytes Pathogenesis may be associated with immune factors
Parechovirus	Parechovirus A	Encephalitis	Virus targets cerebral blood vessels

[a] Commonly used terms for the neurological syndromes in the CNS; peripheral nervous system disease not included.
[b] Selected characteristics only; cellular tropism is not well established in a significant number of viral CNS infections.
CRS, congenital rubella syndrome; HHV, human herpes virus; HIV, human immunodeficiency virus; HTLV, human T cell leukemia/lymphoma virus; JC virus, John Cunningham virus; MIBE, measles inclusion body encephalitis; RE, rubella encephalitis; SSPE, subacute sclerosing panencephalitis.

Table 1.2 Mycoplasmal rickettsial and bacterial infections of the CNS.

Organisms	Genus/Species	Type of CNS infection	Characteristics
Mycoplasma	*M. pneumoniae*	Encephalitis	Intracellular bacteria
	M. hominis	Brain abscess Meningitis	Intracellular bacteria
Rickettsia	*R. rickettsii*	Encephalitis Chronic leptomeningitis Cerebral infarction	Intracellular bacteria Tick-borne
	R. conorii	Meningoencephalitis Cerebral infarction Polyneuropathy and polyneuritis	Intracellular bacteria Tick-borne
	R. prowazekii	Meningoencephalitis Peripheral neuropathy Transverse myelitis	Intracellular bacteria Louse-borne
	R. typhi	Meningoencephalitis	Intracellular bacteria Flea-borne

Table 1.2 (Continued)

Organisms	Genus/Species	Type of CNS infection	Characteristics
Orientia	*O. tsutsugamushi*	Meningoencephalitis Cerebral vein thrombosis Guillain-Barré syndrome Transverse myelitis Cranial neuropathy Polyneuropathy	Intracellular bacteria Mite-borne
Ehrlichia	*E. chaffeensis*	Lymphocytic meningitis Cranial neuropathy Demyelinating polyneuropathy	Intracellular bacteria Tick-borne
Anaplasma	*A. phagocytophilum*	(same as ehrlichiosis?)	Intracellular bacteria Tick-borne
Gram-positive pyogenic bacteria	*Streptococcus pneumoniae*	Meningitis	Diplococcus
	Staphylococcus spp.	Brain abscess	Cocci
Gram-negative pyogenic bacteria	*Neisseria meningitidis*	Meningitis	Waterhouse-Friderichsen syndrome
	Escherichia coli	Meningitis	
	Haemophilus influenzae	Meningitis	Vaccine available
	Pseudomonas spp.	Abscess, meningitis	Hemorrhagic
Actinomycetaceae	*Actinomyces israelii* *Actinomyces meyeri* *Actinomyces viscosus*	Brain abscess	Filamentous
Actinobacteria	*Tropheryma whipplei*	Multifocal encephalitic nodules	Accumulation of partially degraded bacteria in macrophages
Nocardiaceae	*Nocardia asteroides complex* *Nocardia brasiliensis complex*	Brain abscess	Filamentous
Mycobacteria	*M. tuberculosis*	Basal meningitis Tuberculoma Abscesses (HIV)	Acid-alcohol resistant
	Non-tuberculous mycobacteria: MAC *M. haemophilium* *M. kansasii*	Brain abscess	Opportunistic pathogens
Spirochaetaceae	*Treponema pallidum*	Neurosyphilis	Humans only known natural hosts
	Borrelia burgdorferi	Lyme disease	Tick-borne
	Borrelia recurrentis	Relapsing fever	Louse-borne
	Other *Borrelia* species	Relapsing fever	Tick-borne
	Leptospira interrogans	Meningitis Meningoencephalitis Meningomyelitis Polyradiculoneuropathy Intracranial hemorrhage	Rodents are reservoirs

(*continued*)

Table 1.2 (Continued)

Organisms	Genus/Species	Type of CNS infection	Characteristics
Brucella	*B. melitensis* *B. suis* *B. abortus*	Neurobrucellosis	The most frequent zoonosis worldwide
Legionella	*58 species, 30 of which are pathogenic for humans*	Encephalopathy Transient focal neurological signs	Always associated with pulmonary disease

HIV, human immunodeficiency virus; MAC, *Mycobacterium avium-intracellulare complex.*

Table 1.3 Important fungal pathogens in the CNS.

Group/Genus	Species (common)	Types of CNS infections (common)	Distinct fungal characteristics
Molds (Filamentous fungi) **Hyaline (not pigmented)**			
Aspergillus	*A. fumigatus* *A. flavus* Other species	Brain abscess Skull-base syndromes Stroke/infarction Disseminated infection Hemorrhagic Myelitis	Branching septate hyphae Angiophilic
Fusarium	*F. solani species complex*	Meningoencephalitis Brain abscess	Branching septate hyphae
Mucorales			Branching nonseptate hyphae
Rhizopus	*R. arrhizus*	Brain abscess	Angiophilic
Rhizomucor	*R. pusillus*	Rhino-cerebral	
Mucor	*M. indicus*	Stroke/infarction Disseminated infection Hemorrhagic	
Lichtheimia	*L. corymbifera*	Brain abscess Rhino-cerebral	
Apophysomyces	*A. elegans*	Rhino-cerebral	
Pigmented molds (Dematiaceous)			
Cladophialophora	*C. bantiana*	Meningitis	Branching nonseptate pigmented hyphae
Exophiala	*E. dermatitidis*	Brain abscess	
Rhinocladiella	*R. mackenziei*		
Verruconis	*V. gallopava*		
Fonsecaea	*F. pedrosoi* *F. monophora*		
Curvularia	*C. spicifera* *C. hawaiiensis* *C. lunata*		
Alternaria	*A. infectoria*		

Table 1.3 (Continued)

Group/Genus	Species (common)	Types of CNS infections (common)	Distinct fungal characteristics
Yeasts			
Candida	*C. albicans* *C. parapsilosis*	Meningitis Meningoencephalitis Brain abscess Disseminated infection	Unicellular yeasts
Cryptococcus	*C. neoformans* *C. gattii*	Meningitis Meningoencephalitis Myelitis Cryptococcoma Disseminated infection	
Trichosporon	*T. asahii*	Meningitis Brain abscess	Yeast-like, arthroconidia
Dimorphic fungi			
Blastomyces	*B. dermatitidis*	Brain abscess Myelitis	Yeast form in vivo and filamentous form in vitro
Histoplasma	*H. capsulatum*	Meningitis Brain abscess Disseminated infection	
Coccidioides	*C. immitis* *C. posadasii*	Meningitis Meningoencephalitis Brain abscess Myelitis Disseminated infection	
Paracoccidioides	*P. brasiliensis*	Brain abscess Disseminated infection	

Table 1.4 Main parasitic infections of the CNS.

Category/Genus	Species	Main CNS neurological syndrome/disease	Characteristics
Protozoa			
Plasmodium	*P. falciparum*	Cerebral malaria	Parasitized RBCs in cerebral blood vessels
	P. knowlesi	Cerebral malaria	Parasitized RBCs in cerebral blood vessels
Toxoplasma	*T. gondii*	Encephalitis/abscess Congenital toxoplasmosis	Associated with immunosuppression
Amoeba	*Entamoeba histolytica*	Encephalitis/abscess	Non-free-living amoeba
	Naegleria fowleri	Primary meningoencephalitis	Free-living amoeba
	Acanthamoeba species	Granulomatous meningoencephalitis	Free-living amoeba
	Balamuthia mandrillaris *Sappinia pedata*	Granulomatous meningoencephalitis	Free-living amoeba
Trypanosoma			
	T. brucei gambiense *T. brucei brucei*	African trypanosomiasis/ meningoencephalitis	Unicellular hemoflagellate
	T. cruzi	South American trypanosomiasis/Chagas disease (acute, chronic, congenital)	Unicellular hemoflagellate
Microsporidia	*Microsporidium* spp.	Encephalitis	Associated with immunosuppression

(*continued*)

Table 1.4 (Continued)

Category/Genus	Species	Main CNS neurological syndrome/disease	Characteristics
Leishmania	*L. donovani*	Visceral leishmaniasis with CNS involvement (rare)	Nonflagellate amastigotes
Helminth (cestodes)			
Taenia	*T. solium*	Neurocysticercosis	Larva form (cysticerci) involved
	T. multiceps	Coenurosis	Larva form (coenurus) involved
Echinococcus	*E. granulosus*	Cerebral echinococcosis	Larva form (hydatid cysts) involved
Spirotmetra	*S. mansoni* *S. mansonoides* *S. poliferum*	Cerebral sparganosis	Plerocercoid larva (spargana) involved
Helminth (trematodes)			
Schistosoma	*S. haematobium*	Cerebral schistosomiasis	Ova involved
	S. mansoni	Cerebral schistosomiasis	Ova involved
	S. japonicum	Cerebral schistosomiasis	Ova involved
	S. mekongi	Cerebral schistosomiasis	Ova involved
Paragonimus	*P. westermani and other species*	Cerebral paragonimiasis	Immature flukes involved
Helminth (nematodes)			
Angiostrongylus	*A. cantonensis*	Neuroangiostrongylosis (eosinophilic meningitis)	Larva involved
Gnathostoma	*Gnathosoma* spp.	Cerebral gnathostomiasis	Larva involved
Toxocara	*T. canis* *T. cati* (other non-*Toxocara* spp.)	Visceral larva migrans Neurotoxocariasis	Larva involved
Trichinella	*T. spiralis* Other species	Neurotrichinosis	Larva involved
Filaria	*Loa loa* *Onchocerca volvulus*	CNS involvement not well established	Microfilaria involved
Strongyloides	*S. stercoralis*	Cerebral strongyloidiasis	Larva involved

CNS, central nervous system; RBCs, red blood cells; spp., species.

different types of lesions and their distribution in various parts of the CNS may be dictated by the different routes of neuroinvasion (e.g. hematogenous or along peripheral nerves or olfactory bulb); spread from adjacent extracranial structures; the nature of the pathogen and its predilection for different cellular or tissue targets; the tempo of the infection whether acute, subacute, or chronic; and the host immune response

The typical inflammation observed in many viral CNS infections consists of perivascular cuffing and parenchymal infiltration by inflammatory cells, often with microglial nodule formation, neuronophagia, and necrosis. Most viruses infecting the CNS are neuronotropic and, therefore, could potentially affect all areas where neurons are found. However, preferred routes of CNS invasion or even a predilection for different neuronal populations may determine the topography of the inflammation (e.g. in herpes simplex 1 and enterovirus A71 infections). Viral inclusions in different cellular compartments (i.e. nucleus or cytoplasm) may be observed in many DNA viruses and a few RNA viruses (e.g. paramyxoviruses: measles and henipavirus) and can be useful diagnostic features. Although relatively rare, vasculopathy (e.g. vasculitis and thrombosis)

is observed not only in henipavirus and varicella-zoster virus infections but may also be encountered in angioinvasive fungal and rickettsial infections and in CNS tuberculosis.

Abscesses are generally localized, circumscribed acute or subacute inflammations caused by pyogenic bacteria, fungi, and *Toxoplasma*. They may be found in most areas of the CNS. Certain bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae* are the main culprits for acute pyogenic meningitis. Granulomatous inflammation in the CNS is most often associated with more chronic infections, notably *Mycobacteria,* fungi, and spirochetes and in some parasitic infections like amoebiasis. Sarcoidosis, although not regarded as an infection, is included as it is an important differential diagnosis in granulomatous CNS inflammation.

Despite recent advances in molecular diagnosis using polymerase chain reaction (PCR)-based methods, sequencing, and so on, light microscopy using routine hematoxylin and eosin (H&E) stains may still be quite useful to help identify pathogens in infected tissues and other biological specimens based on morphology alone, especially if combined with special histochemical stains, immunohistochemistry, and in situ hybridization. Familiarity with diagnostic morphological features of certain fungi and parasites are particularly helpful. Commercial or proprietary specific primary antibodies for immunohistochemistry, if available, could also help detect some viral, bacterial, fungal, and parasitic infections to enable a more rapid diagnosis.

This volume also highlights the major historical and epidemiological characteristics of the different diseases, their clinical presentation and difficulties in diagnosis, and their pathogenesis, including information from animal models. It also gives some information on the microbiological characteristics of the agents, although it is not intended to be a detailed microbiological book. Genetic characteristics of both the agents and the hosts are discussed with reference to how these can favor disease development in particular hosts.

This monograph will be of interest to a wide variety of medical doctors, postgraduate students, and scientists involved in studying, diagnosing, or treating infections involving the CNS. We hope that it will become a reference book in neurology departments and microbiology and pathology laboratories because it approaches the topic in a way not dealt with in other books.

We have been fortunate in benefiting from numerous international authors who have written about their own area of expertise in CNS infectious diseases. Collaborating with the authors has been productive, interesting, and useful, and we sincerely thank them all for their generosity.

Reference

1. Kaminski, Z., Kapila, R., Sharer, L.R. et al. (1992). Meningitis due to *Prototheca wickerhamii* in a patient with AIDS. *Clin Infect Dis* 15: 704–706.