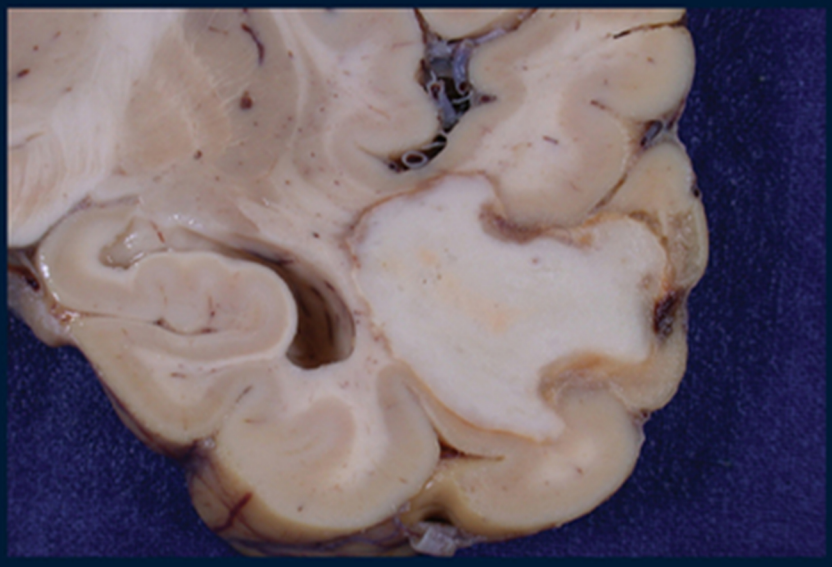
Institut Pasteur

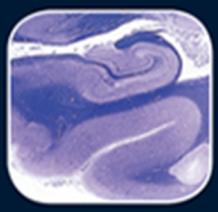
INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

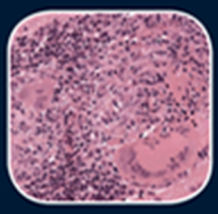
Pathology and Genetics

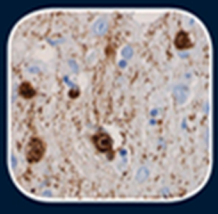
SERIES EDITORS
CATHERINE (KATY) KEOHANE | FRANÇOISE GRAY

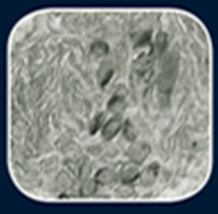
EDITED BY
FABRICE CHRÉTIEN
KUM THONG WONG
LEROY R. SHARER

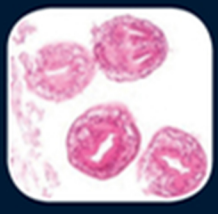












WILEY Blackwell

Infections of the Central Nervous System

Infections of the Central Nervous System: Pathology and Genetics

EDITORS

FABRICE CHRÉTIEN, MD, PhD

Department of Neuropathology, Sainte Anne Hospital, Paris;
Paris University, Paris;
Experimental Neuropathology Unit, Pasteur Institute, Paris, France

KUM THONG WONG, MBBS, MPath, FRCPath, MD

Department of Pathology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

LEROY R. SHARER, MD

Division of Neuropathology, Department of Pathology, Immunology, and Laboratory Medicine, Rutgers New Jersey Medical School and University Hospital, Newark, NJ, USA

SERIES EDITORS

CATHERINE (KATY) KEOHANE, MB, BCH, BAO, FRCPath, FFPath

Department of Pathology and School of Medicine, University College Cork, Brookfield Health Science Complex, Cork, Ireland

FRANÇOISE GRAY, MD, PhD

Retired from Department of Pathology, Lariboisière Hospital, APHP, Paris;
University Paris Diderot (Paris 7), Paris, France

WILEY Blackwell

Institut Pasteur

This edition first published 2020

Registered Office(s)
John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial Office
9600 Garsington Road, Oxford, OX4 2DQ, UK

For details of our global editorial offices, customer services, and more information about Wiley products visit us at www.wiley.com.

Wiley also publishes its books in a variety of electronic formats and by print-on-demand. Some content that appears in standard print versions of this book may not be available in other formats.

Library of Congress Cataloging-in-Publication Data

Names: Chrétien, Fabrice, editor. | Wong, Kum Thong, editor. | Sharer, Leroy R., editor. | Keohane, Catherine, editor. | Gray, Françoise, editor. | International Society of Neuropathology, issuing body.
Title: Infections of the central nervous system : pathology and genetics / edited by Fabrice Chrétien, Kum Thong Wong, Leroy R. Sharer, Catherine (Katy) Keohane, Françoise Gray.
Other titles: Infections of the central nervous system (Chrétien)
Description: Hoboken, NJ : Wiley-Blackwell, 2020. | Includes bibliographical references and index.
Identifiers: LCCN 2019033002 (print) | LCCN 2019033003 (ebook) | ISBN 9781119467762 (hardback) | ISBN 9781119467700 (adobe pdf) | ISBN 9781119467793 (epub)
Subjects: MESH: Central Nervous System Infections–pathology | Central Nervous System Infections–genetics
Classification: LCC RC359.5 (print) | LCC RC359.5 (ebook) | NLM WL 301 | DDC 616.8–dc23
LC record available at https://lccn.loc.gov/2019033002
LC ebook record available at https://lccn.loc.gov/2019033003

Cover Design: Wiley
Cover Images: Logo used with permission of Pasteur Institute, Main image, 1st and 6th images on right courtesy of Françoise Gray; 2nd image on right courtesy of Michael Farrell; 3rd and 4th images courtesy of Catherine (Katy) Keohane; 5th and 7th images courtesy of Gregory Jouvion

Set in 9.5/12pt Minion by SPi Global, Pondicherry, India

10 9 8 7 6 5 4 3 2 1

Contents

List of Contributors

Homa Adle-Biassette
Department of Pathology
Lariboisière Hospital
APHP, Paris;

Paris University, NeuroDiderot
INSERM F-75019
Paris, France

Philippe V. Afonso
Oncogenic Virus Epidemiology and Pathophysiology
Department of Virology
Pasteur Institute
Paris, France

Alan Beausang
Department of Neuropathology
Beaumont Hospital
Dublin, Ireland

Anne Beauvais
Aspergillus Unit
Pasteur Institute
Paris, France

Juan M. Bilbao
Department of Pathology
University of Toronto
Toronto, Ontario, Canada

Michael Blatzer
Aspergillus and Experimental Neuropathology Units
Pasteur Institute
Paris, France

Sandrine Bourdoulous
Inserm, U1016, Institut Cochin, CNRS
UMR8104, Paris University
Paris, France

Hervé Bourhy
Lyssavirus Epidemiology and Neuropathology Unit
French National Reference Centre for Rabies
WHO Collaborating Centre for Reference and Research on Rabies
Pasteur Institute
Paris, France

Stéphane Bretagne
Saint Louis Hospital
APHP, Paris;

University Paris Diderot
Sorbonne Paris Cité, Paris;

Molecular Mycology Unit
French National Reference Centre for Invasive Mycoses and Antifungal Treatments
Pasteur Institute
Paris, France

Clare Bryce
Department of Pathology, Neurology, and Neuroscience
Icahn School of Medicine
Mount Sinai, New York
NY, USA

Herbert Budka
Institute of Neurology
Medical University Vienna
Vienna, Austria

Olivier Cassar
Oncogenic Virus Epidemiology and Pathophysiology
Department of Virology
Pasteur Institute, Paris;

CNRS, UMR3569
Paris, France

Hugo Caire de Castro Faria Neto
Laboratory of Immunopharmacology
Oswaldo Cruz Institute, FIOCRUZ
Rio de Janeiro, Brazil

Leila Chimelli
Laboratory of Neuropathology and Molecular Genetics
State Brain Institute Paulo Niemeyer
Rio de Janeiro, Brazil;

Federal University of Rio de Janeiro (UFRJ),
Rio de Janeiro, Brazil

Fabrice Chrétien
Department of Neuropathology
Sainte Anne Hospital
Paris;

Paris University
Paris;

Experimental Neuropathology Unit
Pasteur Institute
Paris, France

Thérèse Couderc
Biology of Infection Unit
Pasteur Institute
Paris;

Inserm U1117
Paris, France

Jane B. Cryan
Department of Neuropathology
Beaumont Hospital
Dublin, Ireland

Laurent Dacheux
Lyssavirus Epidemiology and Neuropathology Unit
French National Reference Centre for Rabies
WHO Collaborating Centre for Reference and Research on Rabies
Pasteur Institute
Paris, France

Marine Le Dudal
Experimental Neuropathology Unit
Pasteur Institute
Paris;

Embryology, Histology and Pathology Unit
The National Veterinary School of Alfort
University Paris-Est
Maison-Alfort, France

Vanessa Estato
Laboratory of Immunopharmacology
Oswaldo Cruz Institute, FIOCRUZ
Rio de Janeiro, Brazil

Michael A. Farrell
Department of Neuropathology
Beaumont Hospital
Dublin, Ireland

Eoin R. Feeney
Department of Infectious Diseases
St. Vincent's Hospital
Dublin, Ireland

Antoine Gessain
Oncogenic Virus Epidemiology and Pathophysiology
Department of Virology, Pasteur Institute
Paris;

CNRS, UMR3569
Paris, France

Pierre L. Goossens
Experimental Neuropathology Unit
Pasteur Institute
Paris;

Yersinia, Pasteur Institute
Paris, France

Françoise Gray
Retired from Department of Pathology
Lariboisière Hospital
APHP, Paris;

University Paris Diderot (Paris 7)
Paris, France

Loic Le Guennec
Inserm, U1016, Institut Cochin
CNRS, UMR8104
Paris University, Paris;

La Pitie-Salpetriere Hospital
APHP, Paris, France

David Hardy
Experimental Neuropathology Unit
Pasteur Institute
Paris, France

Romana Höftberger
Institute of Neurology
Medical University of Vienna
Vienna, Austria

Ghazi Hmeydia
Department of Neuropathology
Sainte-Anne Hospital
Paris, France

Edward S. Johnson
Department of Laboratory Medicine
and Pathology
University of Alberta
Edmonton, Alberta, Canada

Grégory Jouvion
Experimental Neuropathology Unit
Pasteur Institute
Paris, France

Catherine (Katy) Keohane
Department of Pathology and School of Medicine
University College Cork
Brookfield Health Science Complex
Cork, Ireland

Bette K. Kleinschmidt-DeMasters
Department of Pathology, Neurosurgery,
and Neurology
University of Colorado School of Medicine
Aurora, CO, USA

Fanny Lanternier
Molecular Mycology Unit
French National Reference Centre
for Invasive Mycoses and Antifungal Treatments
Pasteur Institute, Paris;

Paris University,
Paris;

Department of Infectious Diseases and
Tropical Medicine
Necker-Sick Children University Hospital
and Imagine Institute
APHP, Paris, France

Hans Lassmann
Center for Brain Research
Medical University of Vienna
Vienna, Austria

Jean-Paul Latgé
Aspergillus Unit
Pasteur Institute
Paris, France

Emmanuèle Lechapt-Zalcman
Department of Neuropathology
Sainte Anne Hospital
Paris, France

Marc Lecuit
Biology of Infection Unit
Pasteur Institute
Paris;

Inserm U1117, Paris;

Department of Infectious Diseases and
Tropical Medicine

Necker-Sick Children University Hospital
and Imagine Institute
APHP, Paris;

Paris University
Paris, France

Anita Mahadevan
Department of Neuropathology
National Institute of Mental Health and
Neurosciences (NIMHANS)
Bangalore, India

Aurelien Mazeraud
Experimental Neuropathology Unit
Pasteur Institute, Paris;

Department of Anesthesiology and Intensive Care
Sainte Anne Hospital
Paris;

University Paris Diderot, Sorbonne Paris Cité
APHP, Paris, France

Guilherme Dias de Melo
Lyssavirus Epidemiology and Neuropathology Unit
French National Reference Centre for Rabies
WHO Collaborating Centre for Reference and
Research on Rabies
Pasteur Institute
Paris, France

Susan Morgello
Department of Pathology, Neurology, and
Neuroscience
Icahn School of Medicine
Mount Sinai, New York
NY, USA

Jamie Nakagiri
Department of Pathology and Laboratory Medicine
UC Irvine Medical Center
Orange, CA, USA

Kien Chai Ong
Department of Biomedical Science
Faculty of Medicine
University of Malaya
Kuala Lumpur, Malaysia

Catherine Oppenheim
Department of Neuroradiology
Sainte Anne Hospital
Paris;

Paris University
Paris;

Inserm U894, IMA-Brain
Psychiatry and Neurosciences Center
Paris, France

Johan Pallud
Department of Neurosurgery
Sainte Anne Hospital
Paris;

Paris University
Paris;

Inserm U894, IMA-Brain
Psychiatry and Neurosciences Center
Paris, France

Perrine Parize
Lyssavirus Epidemiology and Neuropathology Unit
French National Reference Centre for Rabies
WHO Collaborating Centre for Research
on Rabies
Pasteur Institute
Paris, France

Mari Perez-Rosendahl
Department of Pathology and Laboratory Medicine
UC Irvine Medical Center
Orange, CA, USA

Michel R. Popoff
Bacterial Toxins Unit
Pasteur Institute
Paris, France

Bishan Radotra
Department of Histopathology
Postgraduate Institute of Medical Education
and Research
Chandigarh, India

Patrícia Reis
Laboratory of Immunopharmacology
Oswaldo Cruz Institute, FIOCRUZ
Rio de Janeiro, Brazil

Roy H. Rhodes
School of Medicine
Department of Pathology
Louisiana State University
New Orleans, LA, USA

Alexandre Roux
Department of Neurosurgery
Sainte Anne Hospital
Paris;

Paris University
Paris;

Inserm U894, IMA-Brain
Psychiatry and Neurosciences Center
Paris, France

Aisling Ryan
Department of Neurology
Cork University Hospital
Cork, Ireland

Leroy R. Sharer
Division of Neuropathology
Department of Pathology, Immunology, and Laboratory Medicine
Rutgers New Jersey Medical School and University Hospital
Newark, NJ, USA

Tarek Sharshar
Experimental Neuropathology Unit
Pasteur Institute, Paris;

Department of Anesthesiology and Intensive Care
Sainte Anne Hospital
Paris;

University Paris Diderot
Sorbonne Paris Cité
Paris, France

Cássia Shinotsuka
Experimental Neuropathology Unit
Pasteur Institute
Paris, France

Romain Sonneville
Department of Anesthesiology and Intensive Care
Saint Anne Hospital
Paris;

Department of Intensive Care Medicine and Infectious Diseases
Inserm U1148, Bichat-Claude-Bernard Hospital
APHP, Paris;

University Paris Diderot
Sorbonne Paris Cité
Paris, France

Megan Still
Department of Neurosurgery
Sainte Anne Hospital
Paris, France

University of Texas Southwestern Medical Center
Dallas, TX, USA

Shankar Krishna Susarla
Department of Neuropathology
National Institute of Mental Health and Neurosciences (NIMHANS)
Bangalore, India

Masaki Takao
Department of Neurology
Saitama International Medical Center
Saitama Medical University
Hidaka, Japan

Arnault Tauziede-Espariat
Department of Neuropathology
Sainte Anne Hospital
Paris;

Paris University
Paris, France

Natacha Teissier
Department of Pediatric Otolaryngology
Robert Debre Hospital
APHP, Paris;

Paris University, NeuroDiderot
INSERM F-75019
Paris, France

Cédric Thépenier
Experimental Neuropathology Unit
Pasteur Institute
Paris, France

Melissa Umphlett
Department of Pathology, Neurology, and Neuroscience
Icahn School of Medicine
Mount Sinai, New York, NY, USA

Franck Verdonk
Experimental Neuropathology Unit
Pasteur Institute
Paris;

Department of Anesthesiology and Intensive Care
Saint Antoine Hospital
Paris;

Sorbonne University
Paris, France

Harry V. Vinters
Department of Pathology and Laboratory Medicine (Neuropathology) and Neurology
David Geffen School of Medicine UCLA and Ronald Reagan UCLA Medical Center
Los Angeles, CA, USA

Clayton A. Wiley
Division of Neuropathology
UPMC Presbyterian Hospital
Pittsburgh, PA, USA

Michel Wolff
Department of Anesthesiology and Neurological Intensive Care
Sainte Anne Hospital
Paris;

Department of Intensive Care Medicine and Infectious Diseases
Bichat-Claude-Bernard Hospital
APHP, Paris, France

Kum Thong Wong
Department of Pathology
Faculty of Medicine
University of Malaya
Kuala Lumpur, Malaysia

Gilles Zah-Bi
Department of Neurosurgery
Sainte-Anne Hospital
Paris, France

Marc Zanello
Department of Neurosurgery
Sainte Anne Hospital
Paris;

Paris University
Paris;

Inserm U894, IMA-Brain
Psychiatry and Neurosciences Center
Paris, France

Xinhai R. Zhang
Department of Pathology
RUSH University Medical Center
Chicago, IL, USA

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

Fabrice Chrétien[1,2,3], Kum Thong Wong[4], Leroy R. Sharer[5], Catherine (Katy) Keohane[6], and Françoise Gray[7,8]

[1] Department of Neuropathology, Sainte Anne Hospital, Paris, France
[2] Paris University, Paris, France
[3] Experimental Neuropathology Unit, Pasteur Institute, Paris, France
[4] Department of Pathology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia
[5] Division of Neuroptathology, Department of Pathology, Immunology and Laboratory Medicine, Rutgers New Jersey Medical School and University Hospital, Newark, NJ, USA
[6] Deparment of Pathology and School of Medicine, University College Cork, Brookfield Health Science Complex, Cork, Ireland
[7] Retired from Department of Pathology, Lariboisière Hospital, APHP, Paris, France
[8] University Paris Diderot (Paris 7), Paris, France

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.

2 Sepsis-Associated Encephalopathy

Franck Verdonk[1,2,3], Aurelien Mazeraud[1,2,4], Fabrice Chrétien[1,5,6], and Tarek Sharshar[1,2,4]

[1] Experimental Neuropathology Unit, Pasteur Institute, Paris, France
[2] Department of Anesthesiology and Intensive Care, Saint Antoine Hospital, Paris, France
[3] Sorbonne University, Paris, France
[4] University Paris Diderot, Sorbonne Paris Cité, Paris, France
[5] Paris University, Paris, France
[6] Department of Neuropathology, Sainte Anne Hospital, Paris, France

Abbreviations

AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
APACHE	acute physiology and chronic health disease classification system II
AQP4	aquaporin 4
Bax	proapoptotic factors
BBB	blood-brain barrier
BCL	B-cell lymphoma
CLP	cecal ligation and puncture
CNS	central nervous system
DAMPs	damage-associated molecular pattern molecules
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders*-5
EEG	electroencephalogram
ICU	intensive care unit
DIC	disseminated intravascular coagulopathy
IL	interleukin
MRI	magnetic resonance imaging
NMDAR	N-methyl-D-aspartate receptor
NOS	nitric oxide synthase
NSE	neuron-specific enolase
PAA	plasma anticholinergic activity
PAMPs	pathogen-associated molecular pattern molecules
SAE	sepsis-associated encephalopathy
TLR	toll-like receptor
TNF	tumor necrosis factor
ZO	zonula occludens

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.

Definition of the disorder, major synonyms, and historical perspective

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Sepsis is the most common causes of mortality in intensive care units (ICUs) and ranges from 10 to 50% [2]. During sepsis, CNS dysfunction, called sepsis-associated encephalopathy (SAE), occurs in more than 30% of patients. It is clinically characterized by impaired consciousness, which ranges from dizziness to coma and delirium, but it is also associated with an increased risk of stroke or epilepsy. SAE is associated with increased ICU and in-hospital mortality and long-term cognitive decline [3].

Epidemiologic characteristics

The incidence of SAE has been calculated in prospective and retrospective cohorts. In one of the first large prospective studies of 1333 patients with severe sepsis, Sprung et al. reported that 307 (23%) developed cognitive and behavioral changes [4]. More recently, in a retrospective study, Zhang et al. found a lower incidence of 17.7% [5]. This discrepancy is because the diagnostic criteria for SAE have evolved over the last decade and remain controversial. They should combine both clinical and neurophysiological parameters. Electroencephalogram (EEG) changes suggesting SAE are present in up to 80% of bacteremia cases [6, 7]. Considering the estimated number of patients treated for sepsis worldwide, the number of patients affected by SAE could range from 5.3 to 25.2 million annually.

Predictive factors

The risk factors in SAE include patients' comorbidities, clinical and microbiological characteristics of septic shock, and intensive-care interventions. Age, comorbid illness (notably neuropsychiatric), severity of organ failure (notably renal and liver), sedation, and drug side effects are all risk factors. Antibiotic overdose has to be excluded in this context. Encephalopathy is more frequent in cases of bacteremia or of infection with *Staphylococcus aureus, Enterococcus faecium, Acinetobacter* spp., *Pseudomonas aeruginosa,* or *Stenotrophomonas maltophilia*.

Consequences for survival

SAE is associated with increased morbidity and mortality. Sepsis-related mortality rises from 26 to 49% when complicated by encephalopathy [4]. Delirium is associated with a threefold increase in mortality rate in the general population of patients who are critically ill [8].

Consequences for long-term cognitive dysfunction

About one-third of patients will have cognitive impairment 12 months after their ICU discharge [9], and the degree of impairment is proportional to the duration of delirium during their ICU stay [10]. Similar to mild Alzheimer disease, memory, attention, verbal fluency, and executive functions are mainly affected [11, 12]. Patients with sepsis seem particularly susceptible to cognitive decline. Iwashyna et al. reported that hospitalization for sepsis tripled the risk of developing moderate to severe cognitive decline [13].

Patients with sepsis are also at risk of suicide and of developing psychological disorders, including depression, anxiety, and post-traumatic stress disorder [14].

Clinical features including appropriate investigations

Clinical examination

The fundamental features of SAE are the combination of sepsis and impairment of consciousness, ranging from delirium to coma. Delirium can be either hyperactive (i.e. agitation) or hypoactive. But before encephalopathy occurs, patients with sepsis usually develop a "sickness behavior," which is a physiological response to any systemic inflammation and characterized by lethargy, depression, anxiety, loss of appetite, drowsiness, hyperalgesia, difficulty concentrating, and thermal regulation disorder [15].

Motor signs, such as paratonic rigidity, asterixis, tremor, or myoclonus are rarely observed compared to hepatic, uremic, or toxic encephalopathies.

Intensivists have validated clinical test scales at their disposal for the detection of SAE. These include the Confusion Assessment Method for Intensive Care Units (CAM-ICU) [16] or the Intensive Care

Delirium Screening Checklist Worksheet (ICDSC) [17] for the diagnosis of delirium. Because the clinical spectrum of SAE is extremely broad and not limited to delirium, no single clinical examination is sufficiently specific and sensitive to be systematically applied, particularly in less-severe and early forms of SAE. It should be noted that the majority of clinical studies conducted on SAE only target delirium for the sake of diagnostic simplicity.

Once SAE is suspected, a thorough neurological examination is required, including an assessment of neck stiffness, motor responses, muscle strength, and deep tendon and cranial nerve reflexes. Although the frequent use of sedatives in ICU may limit the clinical examination, assessment of brainstem responses appears useful and loss of responses in patients who are sedated is predictive of mortality and altered mental status [18].

SAE blood markers

Serum S100β protein and neuron-specific enolase (NSE) have been proposed as biomarkers for SAE [19, 20], but their usefulness for predicting, diagnosing, and monitoring SAE awaits confirmation.

EEG

In patients with sepsis, two types of electroencephalographic abnormalities are visible affecting either the background activity or superimposed epileptic features. Background activity changes range from slowing of the normal alpha rhythm with the onset of theta activity in patients with mild encephalopathy (i.e. confusion or delirium), to an increase in slow waves, the onset of delta waves, and even "burst suppression" in severe encephalopathy associated with coma. The latter indicate damage to deep brain structures such as the central gray nuclei and midbrain [21].

Epileptic features are the second type of anomaly observed and have recently been precisely defined. Electrographic seizures are associated with delirium, whereas lack of EEG reactivity is associated with mortality [22]. EEG changes can also be observed in patients with sepsis who are asymptomatic, making it an interesting method for detecting and monitoring SAE. EEG anomalies are also associated with radiologic findings [23]. We, therefore, recommend that an EEG should always be performed in cases of SAE or suspected SAE.

Brain imaging

Brain imaging is not systematically carried out, but to exclude the usual causes of neurological deterioration (i.e. ischemic or hemorrhagic stroke, subarachnoid hemorrhage, abscess, etc.), it is required when seizures, focal neurological signs, persistent delirium, or coma occur.

Imaging usually reveals white matter hyperdensities, mainly related to vasogenic edema, and ischemic stroke, mainly related to DIC [15]. However, it can be normal in half the cases [15]. Magnetic resonance imaging (MRI) is useful to assess secondary cognitive impairment associated with white matter changes and hippocampal atrophy [24].

Physiopathology

Systemic inflammation is the main basis for SAE pathophysiology. Sepsis induces a dramatic immune inflammatory response associated with the clinical manifestations of SAE. Circulating levels of proinflammatory markers (namely interleukin (IL)-1, IL-6 or tumor necrosis factor (TNF)-soluble receptor decreased matrix metalloproteinase-9 [MMP-9] and protein C concentrations) are associated with an increased risk of delirium [25–27]. More generally, it has been shown that cognitive impairment relates to systemic inflammation whether as a result of sepsis or occurring after surgery [28, 29].

SAE is historically viewed as an aseptic insult of the CNS, justifying the term "encephalopathy" rather than "encephalitis" [30]. However, a recent study questions this view. In a mouse model of sepsis using cecal ligation and puncture (CLP) [31], Singer et al. found that sepsis is associated with polymicrobial spread within the CNS by viable bacteria during the acute phase up to the fifth day. The authors showed an increased expression of neuroinflammatory markers in microglial cells. These findings gain some support from a human study reporting brain abscesses in about 10% of patients [32]. If a microbial process is involved, encephalopathy is mainly secondary to the systemic inflammation.

The consequences of systemic inflammation on the brain can be separated into three nonexclusive mechanisms: ischemic, neuroinflammatory, and epileptic processes. In combination,

these processes result in impairment of neurotransmission and neurotoxicity. Particular structures are vulnerable to these phenomena: the frontal cortex and hippocampus, which accounts for acute and chronic neurological symptoms of sepsis, and central autonomic nuclei (i.e. amygdala, locus coeruleus, medullary nuclei), accounting for acute impairment of the response to stress [33].

Systemic or local inflammation is transmitted to the CNS via three major pathways [34]:

1. Circumventricular organs enable inflammatory mediators to pass directly into the brain parenchyma. They are thought to play a major role in the "humoral pathway" and induce neuroinflammation.

2. Blood-brain barrier (BBB) disruption increases the passage of inflammatory mediators to brain parenchyma, enabling their participation in micro- and macroangiopathy and neuroinflammation.

3. Neural pathways, notably via the vagus nerves, transfer the peripheral inflammatory signal to the medullary autonomic nuclei. The increased neuronal activity can produce excitotoxicity and is associated with neuroinflammation.

Ischemic processes

Macrocirculatory impairment

In addition to hypotension, hypovolemia, and cardiac dysfunction, impairment of autoregulation can compromise cerebral perfusion. Autoregulation is a physiological mechanism that aims to maintain a constant cerebral blood flow. In physiological conditions, the vessel diameter adapts to blood pressure. In patients with sepsis, this mechanism can be impaired. Schramm et al. showed that autoregulation is impaired in 60% at day 1 and 46% at day 4 [35]. Moreover, impaired autoregulation at day 1 was associated with delirium occurring at day 4, and this association was confirmed in a larger cohort of 50 patients with sepsis [36]. Interestingly, early decrease in cerebral flow correlates with long-term cognitive impairment [37].

Microcirculatory impairment

Sepsis frequently causes microvascular dysfunction that is considered an important mechanism in organ failure [38]. Microcirculatory dysfunction hampers diffusion of gases and induces a mosaic of tissue hypoxia and vascular shunts alongside well-oxygenated areas. Endothelial dysfunction, glycocalyx (pericellular matrix) changes, mechanisms inducing leukocyte translocation and platelet microthrombi, and pericyte dysfunction are its main mechanisms [39, 40]. This microcirculatory dysfunction can affect the brain, compromising its metabolism as oxygen demand and supply become unbalanced [41]. Microcirculation impairment impinges neurovascular coupling during sepsis [42]. So far, there are no preventive or therapeutic strategies for microcirculatory dysfunction.

Endothelial dysfunction

Endothelial activation at the early phase of sepsis results in increased permeability of the BBB, although tight junction proteins such as occludin, zonula occludens (ZO)-1 and ZO-2 [43], and claudin-3 and claudin-5 [44] seem preserved. Other factors contribute to BBB dysfunction, including astrocyte activation and overexpression of aquaporin 4 (AQP4). Endothelial activation contributes to the neuroinflammatory process by releasing inflammatory and neurotoxic factors or allowing their passage through an impaired BBB [45].

Ischemic lesions in sepsis

Ischemic lesions are constantly observed in patients who die from sepsis. They are found in areas of the brain sensitive to ischemia such as Ammon's horn, the lenticular nucleus, and frontal cortex but also and more specifically (in comparison to patients who died from causes other than sepsis) in autonomic nuclei involved in cardiovascular control (i.e. posterior and anterior hypothalamus, locus coeruleus). Pronounced neuronal apoptosis is also observed in these same areas. In addition, cerebral hemorrhages are found in 17–26% of patients who die of septic shock [32, 46]. Necrotizing multifocal leukoencephalopathy can also be found and correlates with brain expression of tumor necrosis factor alpha (TNF-α) and IL-1β and elevated circulating levels of TNF-α, IL-1β, IL-6, IL-8, IL-10, the soluble receptor for TNF II, and for IL-1 receptor antagonist [47]. Hypoxemia and hyperglycemia are frequent features of sepsis, which potentiate the deleterious effects of impaired cerebral perfusion. To date, there is no recommendation for monitoring and optimizing cerebral perfusion.