26.1 Clinical Signs and Symptoms

Signs and symptoms of (Table 26.1):

- Meningitis
- Encephalitis
  - Cerebral dysfunctions (delirium, lethargy, confusion, stupor, coma)
  - Seizures
  - Focal neurologic deficits

26.2 Classification of Viruses

Classification of viruses based on their nuclei acid into (Tables 26.2 and 26.3):

- DNA viruses
- RNA viruses

The diseases caused by viruses are listed in Table 26.4 while brain diseases caused by viruses are depicted in Tables 26.5 and 26.6.

26.3 Epidemiology

Incidence

- 1.5–7 cases/100,000 inhabitants/year, excluding epidemics
- True incidence of these infections is difficult to determine because

**Table 26.1** Neurologic signs and syndromes related to affected regions

| Localization               | Syndrome          | Neurologic signs                                      |
|----------------------------|-------------------|-------------------------------------------------------|
| Meninges                   | Meningitis        | Headache, Vomiting, Photophobia, Focal neurologic deficits, Alterations in consciousness |
| Brain parenchyma diffuse    | Encephalitis      | Alterations in consciousness, Seizures, Multifocal neurologic deficits |
| Brain parenchyma focal      | Encephalitis      | Focal neurologic deficits, Seizures                   |
| Brain stem and posterior cranial fossa | Brain stem encephalitis | Opto- and pupillomotor disturbances, Nuclear cranial nerve lesions, Dysarthria, Bilateral pyramidal tract signs, Alterations in consciousness, Breathing insufficiency, Vegetative signs |
| Spinal cord                | Myelitis          | Paraplegia, Brown Séquard syndrome                     |
| Arteries                   | Arteritis         | Sudden focal neurologic deficit                       |
| Veins                      | Septic venous sinus thrombosis | Headache, Seizures, Raised brain pressure, Focal neurologic deficits |
Many cases are unreported.
The diagnosis may not be considered.
A specific viral etiology is never confirmed.

**Age Incidence**
- all ages possible
- CMV: congenital, adulthood
- HIV: adulthood

**Sex Incidence**
- dependent on virus
  - HIV: predominantly males
  - CMV: equal distribution

### Table 26.2 Subdivision of viruses

| DNA viruses | Enveloped | Naked capsid |
|-------------|-----------|--------------|
| +RNA        | Pox       | Polyoma, Papilloma, Adeno, Parvo |
| -RNA        | Herpes    |              |
| ±RNA        | Hepadna   |              |
| +RNA via DNA| Polyoma, Papilloma, Adeno, Parvo |

### Table 26.3 A detailed subdivision of viruses

| Viral genome | Family name of virus | Family members |
|--------------|----------------------|----------------|
| DNA Double-stranded | Herpesviridae | • HSV-1  
• HSV-2  
• Varicella-zoster virus  
• Cytomegalovirus  
• Epstein-Barr virus  
• Human herpesvirus 6  
• Human herpesvirus 7  
• Human herpesvirus 8  
• Herpes simiae  
• Adenoviridae  
• Papovaviridae |
| DNA Single-stranded | Parvoviridae | • Parvovirus B19  
• JC virus  
• Simian virus 40 |
| RNA Double-stranded | Reoviridae | • Coltivirus  
• Seadornaviruse |
| RNA Single-stranded sense non-segmented | Retroviridae | • Deltaretrovirus  
• Lentivirus  
• Coronaviridae  
• Coronavirus  
• Togaviridae  
• Alphavirus  
• Flaviviridae  
• Flavivirus  
• Picornaviridae  
• Enterovirus |
| RNA Single-stranded antisense segmented | Bunyaviridae | • Orthobunyavirus  
• Phlebovirus  
• Arenaviridae  
• Arenavirus |
| RNA Single-stranded antisense non-segmented | Orthomyxoviridae | • Influenza viruses  
• Paramyxoviridae  
• Henipavirus  
• Morbillivirus  
• Rubulavirus  
• Rhabdoviridae  
• Rabies  
• Borna  
• Filoviridae  
• Ebola |
| Viral family    | Virus                        | Disease                                                                 |
|---------------|-----------------------------|--------------------------------------------------------------------------|
| DNA Papillomavirus |                             | • Warts                                                                 |
|                |                             | • Condylomas                                                            |
|                |                             | • Cervical cancer                                                       |
| Polyomaviridae | BK virus                    | • Renal disease                                                         |
|                | JC virus                    | • Progressive multifocal leukoencephalopathy                             |
| Adenoviridae  |                             | • Respiratory disease                                                  |
|                |                             | • Meningoencephalitis                                                  |
| Alphaherpesvirinae | Herpesvirus 1             | • Encephalitis                                                          |
|                | Herpesvirus 2               | • Encephalitis                                                          |
|                | Varicella-zoster virus      | • Encephalitis                                                          |
| Gammaherpesvirinae | Epstein-Barr virus         | • Encephalitis                                                          |
| Betaherpesvirinae | Cytomegalovirus            | • Encephalitis                                                          |
| Poxviruses    |                             | • Smallpox                                                              |
| Parvoviruses  |                             | • Erythema infectiosum                                                 |
| Picornaviruses | Enterovirus                 | • Encephalitis                                                          |
|                |                             | • Meningitis                                                            |
|                |                             | • Poliovirus infections (polyomyelitis, paralytic polio)                |
|                | Hepatovirus                 | • Hepatitis                                                             |
| RNA Picornaviridae | Poliovirus               | • Poliomyelitis                                                         |
|                |                             | • Postpolio syndrome                                                   |
| Enteroviruses |                             |                                                                         |
| Cardiovirus genus |                             |                                                                         |
|                | Encephalomyocarditis virus |                                                                         |
| Arboviruses   | Togaviridae, alphavirus genus | • Eastern equine encephalitis                                       |
|                |                             | • Western equine encephalitis                                           |
|                |                             | • Venezuelan equine encephalitis                                        |
| Flaviviridae  |                             | • Japanese encephalitis                                                |
|                |                             | • St. Louis Encephalitis                                               |
|                |                             | • Russian spring-summer encephalitis                                    |
|                |                             | • Central European encephalitis                                        |
|                |                             | • Kyasanur forest disease                                              |
|                |                             | • Murray valley encephalitis                                           |
|                |                             | • Rocio                                                                 |
| Bunyaviridae  |                             | • La Crosse encephalitis                                               |
| Reoviridae    |                             | • Snowshoe hare virus                                                  |
| Paramyxoviruses | Measles virus              | • California encephalitis                                              |
|                |                             | • Jamestown canyon encephalitis                                        |
| Orthomyxoviruses | Influenza A and B viruses | • Influenza                                                             |
| Rhabdoviruses | Rhabdovirus                 | • Rabies                                                                |
| Retroviruses  | Oncovirinae (HTLV)         | • Tropical spastic paraparesis                                         |
|                | Lentivirinae (HIV)          | • Acquired immune deficiency syndrome (AIDS)                            |
Table 26.5 Viral infections of the brain and their causative viral agents

| Encephalitis | • HSV-1  
|             | • Toga, Flavi, Bunya encephalitis viruses  
|             | • Picornaviruses  
|             | • Arboencephalitis virus  
|             | • Varicella-zoster virus  
|             | • Rabies virus  
|             | • Polioviruses  
|             | • Coxsackie A and B viruses  

| Meningitis | • HSV-2  
|           | • Picornaviruses  
|           | • Mumps virus  
|           | • Enteroviruses  
|           | – Echoviruses  
|           | – Coxsackie virus  
|           | – Poliovirus  
|           | • Adenoviruses  

| Paralysis | • Poliovirus  
|          | • Enterovirus 70 and 71  
|          | • Coxsackie A7 virus  

| Postinfectious encephalitis (immune mediated) | • Measles virus  
|                                               | • Mumps virus  
|                                               | • Rubella virus  
|                                               | • Varicella-zoster virus  
|                                               | • Influenza virus  

| Other | • JC virus-progressive multifocal leukoencephalopathy (PML)  
|      | • Human Immunodeficiency Virus (HIV)  
|      | • Human T-cell lymphotropic virus 1 (HTLV-1) (tropical spastic paraparesis)  
|      | • Measles variant (subacute sclerosing panencephalitis)  

Table 26.6 Acute and chronic viral infection affecting the brain

| Acute viral infection | • Aseptic meningitis  
|                      | • Polymyelitis  
|                      | • Neonatal enteroviral encephalitis  
|                      | • Herpesvirus infections  
|                      | – Herpes simplex virus infection  
|                      | – Atypical herpes simplex encephalitis  
|                      | – Chronic granulomatous herpes simplex encephalitis  
|                      | – Necrotizing myelopathy  
|                      | – Neonatal HSV encephalitis  
|                      | • Varicella-zoster virus (ZVZ) infection  
|                      | • Epstein-Barr virus (EBV) infection  
|                      | • Cytomegalovirus (CMV) infection  
|                      | • Human herpesviruses 6 and 7  
|                      | • Adenovirus  
|                      | • Paramyxoviruses  
|                      | – Mumps virus  
|                      | – Measles  
|                      | • Rubella encephalitis  
|                      | • Rabies  
|                      | • Arbovirus infections  

| Chronic and subacute viral infections | • Chronic enteroviral encephalomyelitis  
|                                      | • Subacute measles encephalitis  
|                                      | • Subacute sclerosing panencephalitis (SSPE)  
|                                      | • Progressive rubella panencephalitis  
|                                      | • Progressive multifocal leukoencephalopathy (PML)  
|                                      | • Human T-cell leukemia/lymphotropic virus-1 (HTLV-1)  
|                                      | • Human immunodeficiency virus (HIV)  
|                                      | • Rasmussen encephalitis  

Localization
• Brain, any region  
• Temporal lobe for HSV

26.4 Neuroimaging Findings

General Imaging Findings
• Viral CNS infections can either lead to meningitis or (meningo-)encephalitis.  
• Imaging of viral encephalitis often nonspecific—like focal or diffuse edema (acute infection) or focal atrophy (chronic infection)—except HSV encephalitis showing an almost pathognomonic involvement of limbic system.  
• Location depends on causative agent.

CT Non-Contrast-Enhanced
• Meningitis: Normal  
• Encephalitis: Hypodense edema, loss of gray-white matter differentiation, chronic infection may cause brain atrophy

CT Contrast-Enhanced
• Meningitis: Meningeal enhancement often missing  
• Encephalitis: Enhancement possible

MRI-T2
• Encephalitis: Hyperintensity of involved brain areas
MRI-FLAIR
• Encephalitis: Hyperintensity of involved brain areas

MRI-T1
• Encephalitis: Hypointense edema with loss of gray-white matter differentiation

MRI-T1 Contrast-Enhanced
• Meningitis: Weak meningeal enhancement
• Encephalitis: Variable enhancement

MRI-T2*/SWI
• Encephalitis: Hemorrhages (HSV, VZV, Japanese encephalitis)

MR-Diffusion Imaging
• Encephalitis: Diffusion restriction common

Typical MR imaging patterns of specific viral encephalitides are listed in Table 26.7.

Nuclear Medicine Imaging Findings
• In HIV-infected patients
  – Reduced brain perfusion SPECT and reduced FDG-PET uptake of cortical structures (medial frontal, temporoparietal) are described.
  – FDG shows diffuse hypermetabolism in subcortical and deep white matter, basal ganglia, and thalami in some cases.
• In herpes simplex encephalitis
  – HMPAO showed increased uptake followed by a decrease in tracer uptake in the recovery phase and ECD decreased uptake of the affected temporal lobe (most likely due to disturbed membrane and intracellular metabolism).
  – FDG-PET shows hippocampal hypermetabolism in the acute phase of herpes simplex encephalitis followed by hypometabolism after 3–9 months, but it is reported, that hypometabolism can persist for years.
• Studies with various imaging agents are performed to assess different pathologic steps in neuroinflammation.

26.5 Neuropathology Findings

Macroscopic Features
• No discernible lesion
• Hemorrhagic lesion
• Necrotic lesion

Table 26.7 Typical MR imaging patterns of specific viral encephalitides

| Virus         | Patterns Description                                                                 |
|---------------|--------------------------------------------------------------------------------------|
| HSV           | • Limbic system and temporal lobe<br>• Often hemorrhages and enhancement             |
| CMV           | • Periventricular white matter, subependymal enhancement<br>• Calcifications in perinatal CMV |
| EBV           | • Symmetric involvement of basal ganglia, thalami, cortex, or brain stem<br>• Rarely EBV-cerebellitis |
| VZV           | • Multifocal cortical areas<br>• Hemorrhagic infarctions possible                      |
| HIV           | • Brain atrophy<br>• Symmetric confluent white matter lesions (periventricular, basal ganglia, centrum semiovale, brain stem, cerebellum),<br>• No enhancement |
| Rabies virus  | • Diffuse involvement of basal ganglia, thalami, periventricular white matter, brain stem, and hippocampi |
| TBEV (Tick-borne encephalitis virus) | • MRI and CT often normal<br>• Rarely lesions in thalamus, cerebellum, caudate nucleus, and brain stem |
| JC Virus (PML) | • Confluent subcortical white matter lesions, predominantly in parieto-occipital lobes<br>• U-fibers involved |
| JEV (Japanese encephalitis virus) | • Bilateral symmetric lesions in thalami, basal ganglia, and midbrain |
| Enteroviruses | • Posterior medulla oblongata and pons, dentate nuclei, and midbrain                 |
Microscopic Features
- See specific subchapters
- Perivascular lymphocytic cuffing
- Gliomesenchymal nodules
- Multinucleated giant cells
- Large cells with inclusion bodies
- Reactive astrogliosis
- Leukoencephalopathies

Immunohistochemical Staining Characteristics
- Antibodies directed against a specific virus or part of the virus
- HIV: p24, gp41

Differential Diagnosis
- Necrosis of malignant tumors or metastases
- Necrosis from other infectious agents

### 26.6 Molecular Neuropathology

Properties of viruses, i.e., DNA versus RNA viruses (Table 26.8)
- Entry into the body
  - Viral receptors (Table 26.9)
- Delivery of the virus to the target tissue
- Interaction of virus with target tissue
  - Stability of virus in the body
  - Ability to establish viremia
  - Ability to spread through the reticuloendothelial system
- Cytopathogenesis
  - Failed infection (abortive infection)
  - Cell death (lytic infection)
  - Replication without cell death (persistent infection)
  - Presence of virus without production but with potential for reactivation (latent-recurrent infection)
- Host responses
  - Antigen-nonspecific (innate) host defenses
  - Antigen-specific immune responses
  - Viral mechanisms of escape to immune responses
- Immunopathology
  - Interferon
  - T-cell responses: cell killing, inflammation, and inflammation

| Table 26.8 | Properties of DNA viruses and RNA viruses |
|------------|------------------------------------------|
| DNA viruses | RNA viruses |
| - DNA is not transient or labile. | - RNA is labile and transient. |
| - Many DNA viruses establish persistent infections. | - Most RNA viruses replicate in the cytoplasm. |
| - DNA genomes reside in the nucleus. | - Cells cannot replicate RNA. RNA viruses must encode an RNA-dependent RNA polymerase. |
| - Viral DNA resembles host DNA for transcription and replication. | - The genome structure determines the mechanism of transcription and replication. |
| - Viral genes must interact with host transcriptional machinery. | - RNA viruses are prone to mutation. |
| - Viral gene transcription is temporally regulated. | - The genome structure and polarity determine how viral messenger RNA is generated and proteins are processed. |
| - Early genes encode DNA-binding proteins and enzymes. | - RNA viruses, except (+) RNA genome, must carry polymerases |
| - Late genes encode structural and other proteins. | - All (−) RNA viruses are enveloped. |
| - DNA polymerases require a primer to replicate the viral genome. | |
| - The larger DNA viruses encode means and promote efficient replication of their genome. | |

| Table 26.9 | Viral receptors |
|------------|----------------|
| Virus | Target cell | Receptor |
| Epstein-Barr virus | B-cell | C3d complement receptor CR2 (CD21) |
| Human immunodeficiency virus | Helper T-cell | CD4 molecule and chemokine co-receptor |
| Rhinovirus | Epithelial cells | ICAM-1 (immunoglobulin superfamily protein) |
| Polioivirus | Epithelial cells | Immunoglobulin superfamily protein |
| Herpes simplex virus | Many cells | Herpesvirus entry mediator (HVEM), nectin 1 |
| Rabies virus | Neuron | Acetylcholine receptor, NCAM |
| Influenza A virus | Epithelial cells | Sialic acid |
| B19 parvovirus | Erythroid precursors | Erythrocyte P antigen (globoside) |
Antibody: complement, antibody-dependent cellular cytotoxicity, immune complexes

Other inflammatory responses

Virus production in a tissue with release of the virus to other people (contagion)

Transmission of viruses depends
- On source of the virus (tissue site of viral replication and secretion)
- Ability of the virus to endure hazards and barriers of the environment

26.7 Treatment and Prognosis

Treatment
Antiviral drugs aim at altering:

- Virion disruption
- Attachment
- Penetration and uncoating
- RNA synthesis
- Genome replication
- Protein synthesis
- Virion assembly and release

Antiviral drugs include:

- Nucleoside analogs
  - Acyclovir
  - Ganciclovir
- Nonnucleoside polymerase inhibitors
- Protease inhibitors
- Immunomodulators

Biologic Behavior–Prognosis–Prognostic Factors

- Age of infection
  - Congenital
- Nature of disease
  - Target tissue
  - Portal of entry of virus
  - Access of virus to target tissue
  - Tissue tropism of virus
  - Permissiveness of cells for viral replication
  - Pathogenic activity (strain)
- Severity of disease
  - Cytopathic ability of virus
  - Immune status
  - Competence of the immune system
  - Prior immunity to the virus
  - Immunopathology
- Progression of viral disease
  - Acquisition
  - Activation of innate protections
  - Incubation period
  - Target tissue
  - Host responses
  - Contagion
  - Resolution or persistent infection/chronic disease

26.8 Unspecified Nodular Encephalitis

The only histological finding in unspecified nodular encephalitis is the presence of gliomesenchymal nodules (GMN) (Fig. 26.1a–d). The finding is indicative of a viral infection.

GMN are:

- composed of microglia, macrophages, and reactive astrocytes
- found in the gray and white matter
- absence of multinucleated giant cells (MGC) or large cells containing inclusion bodies

The differential diagnosis for GMN includes

- HIV-1 encephalopathy/leukoencephalopathy
- Cytomegalovirus encephalitis
  - The nodules are very suspicious to contain CMV when further serial sectioning is performed.
- Toxoplasma gondii encephalitis

Complete clarification and identification of an infectious agent is sometimes not possible.
RNA Viruses: Human Immunodeficiency Virus (HIV)-1

Human immunodeficiency virus (HIV)-1 infection is a serious health problem worldwide as 33 million adults and 2 million children are infected with HIV-1. Despite preventive efforts, the epidemic continues to spread rapidly and the socioeconomic consequences of the neurologic dysfunction caused by HIV-1 infection are of enormous proportions. Most of the affected patients live in developing countries, where antiretroviral medications are not available.

HIV-viruses (1, 2) are

- Retroviruses, lentivirinae subfamily
- Roughly spheric, enveloped, RNA viruses
- Diameter of 80–120 nm
- RNA-dependent DNA polymerase
- Encode accessory genes
  - Gag: group-specific antigen: core and capsid proteins
  - Int: integrase
  - Pol: polymerase: reverse transcriptase, protease, integrase
  - Pro: protease
  - Env: envelope: glycoproteins
  - Tat: transactivation of viral and cellular genes
  - Rev: regulation of RNA splicing and promotion of export to cytoplasm
  - Nef: decreases cell surface CD4, facilitates T-cell activation, progression to AIDS
  - Vif: virus infectivity, promotion of assembly, blocks a cellular antiviral protein

Fig. 26.1 Unspecified nodular encephalitis (a–d) (Stain: H&E)
– Vpu: facilitates virion assembly and release, induces degradation of CD4
– Vpr: transport of complementary DNA to nucleus, arresting of cell growth, replication in macrophages
– LTR: promoter, enhancer elements

Following involvement of the lung (75–85%), the brain is the second most frequently affected organ (60–80%) in HIV-1 infection.

Neurological signs and symptoms are seen:

• In about 50% of HIV-1-infected patients.
• In approximately 10% of the cases, they are the first presentation of the disease.

The term “AIDS dementia complex (ADC)” was coined in 1986 (Navia et al. 1986a, b) to describe impaired memory and concentration, psychomotor slowing and behavioral disturbances in 65% of patients, and has been attributed mainly to subcortical damage of AIDS brains (subcortical dementia). The name ADC was later changed into HIV-1-associated cognitive and motor complex with HIV-1-associated dementia complex (motor)/behavior (HAD) and HIV-1-associated myelopathy as its severe manifestations and HIV-1-associated minor cognitive/motor disorder as its mild manifestation (Force 1991).

Classification of HIV-associated neurocognitive disorders (HAND) (Antinori et al. 2007)

• Asymptomatic neurocognitive impairment (ANI)
  – No evidence of pre-existing cause. Cognitive impairment must be attributable to HIV and no other etiology (e.g., dementia, delirium).
  – The cognitive impairment does not interfere with activities of daily living.
  – Involves at least two cognitive areas (memory, attention, language, processing speed, sensory perceptual, motor skills) documented by performance of >1 standard deviation below the mean of standardized neuropsychological testing.

• Mild neurocognitive disorder (MND)
  – No evidence of pre-existing cause. Cognitive impairment must be attributable to HIV and no.
  – Other etiology (e.g., dementia, delirium).
  – At least mild interference in >1 activities of daily living including mental acuity, inefficiency at work, homemaking or social functioning.

• HIV-associated dementia (HAD)
  – No evidence of another pre-existing cause for dementia (i.e., CNS infections, CNS neoplasm, cerebrovascular disease).
  – Marked interference in activities of daily living.
  – Marked cognitive impairment involving at least two cognitive domains by performance of >2 standard deviation below the mean of standardized neuropsychological tests, especially in learning of new information, slowed information processing and defective attention or concentration.

– 2–8% prevalence in combination antiretroviral therapies (CART)-treated HIV+ individuals.

Despite the introduction of antiretroviral therapies with a greater life expectancy of HIV-1-infected individuals, epidemiologic data suggest that involvement of the brain in AIDS patients continues to be a frequent autopsy finding.

Neuropathological examinations show in up to 95% of the brains changes that may be due to:

• primary effect of HIV-1
• probable effect of HIV-1
• opportunistic agents
• neoplasias

The neuropathological changes seen in the brains (Table 26.10) and peripheral nerve and skeletal muscle (Table 26.11) of HIV-1-infected patients are manifold.
Since HIV-1 is rarely the cause of focal macroscopic lesions even in severely infected patients, systematic sampling of specimens for histological examination is required. If focal lesions are present, they are almost always due to opportunistic infections, cerebrovascular complications, or neoplasms.

### 26.9.1 HIV-1 Encephalitis (HIVE)

Since HIV-1 is rarely the cause of focal macroscopic lesions even in severely infected patients, systematic sampling of specimens for histological examination is required. If focal lesions are present, they are almost always due to opportunistic infections, cerebrovascular complications, or neoplasms.

### 26.9.1.1 Neuroimaging Findings

#### General Imaging Features
- Brain atrophy and symmetric confluent white matter lesions (periventricular, basal ganglia, centrum semiovale, brain stem, cerebellum), no enhancement

#### CT Non-Contrast-Enhanced
- Brain atrophy
- Symmetric confluent white matter hypodensities

#### CT Contrast-Enhanced
- No enhancement

#### MRI-T2/FLAIR (Fig. 26.2a–d)
- Focal white matter hyperintensities
- Diffuse white matter hyperintensities

#### MRI-T1 (Fig. 26.2e, f)
- Lesions usually not seen

#### MRI-T1 Contrast-Enhanced (Fig. 26.2g, h)
- No enhancement
MRI-DWI (Fig. 26.2i, j)
- No restricted diffusion.

### 26.9.1.2 Microscopical Findings
HIV-1 encephalitis is characterized by (Fig. 26.3a–j)

- Multiple disseminated foci composed of microglia, macrophages, and multinucleated giant cells (MGCs). The foci are predominantly located in the cortex, deep gray matter, and the white matter.
- The multinucleated giant cells (MGC) are the hallmark for HIV-1 encephalitis.
  - They contain up to 20 round or elongated and basophilic nuclei which are usually arranged at the periphery of the cell.
  - The cytoplasm is eosinophilic and appears densely stained in the center and vacuolated at the periphery.
  - The cells are of monocyte/histiocyte lineage which includes microglia and macrophages.
  - They are derived from HIV-1-mediated fusion of infected microglia and macrophages.
  - The nucleic acids of HIV proteins have been demonstrated to be located in their cytoplasm.
- In their absence, the presence of HIV-antigen or HIV nucleic acids has to be demonstrated either by immunohistochemistry, i.e., gp41 and p24 (Fig. 26.3j) or by in situ hybridization.
- HIVE usually occurs in the later stages of the AIDS infection.
- The electron microscopical analysis revealed retroviral particles either free in the cytoplasm or in cytoplasmic cisternae.
- Microglia/macrophages and MGC are capable of HIV synthesis and, thus, constitute the major reservoir and vehicle for the spread of the virus.
- Synonyms previously used: giant cell encephalitis, multifocal giant cell encephalitis, multinucleated cell encephalitis, subacute encephalitis

There is no strong correlation between HIVE and the clinical stages of the HAD.

Despite the introduction of HAART with a greater life expectancy of infected individuals, epidemiologic data suggest that the prevalence of HIVE is on the rise.

### 26.9.2 HIV-1 Leukoencephalopathy (HIVL)

HIV-1 leukoencephalopathy is characterized by (Fig. 26.4a–j)

- diffuse damage to the white matter including
  - myelin loss
  - reactive astrogliosis
  - macrophages
  - multinucleated giant cells
- Myelin pallor is usually found around the gliomesenchymal nodule containing the MGC.
- Little or no inflammatory infiltrates are seen.
- In the absence of multinucleated giant cells, the presence of HIV-antigen or HIV nucleic acids has to be demonstrated either by immunohistochemistry or by in situ hybridization.
- Axonal damage can be demonstrated with immunohistochemistry for β-amyloid precursor protein.
- HIVL usually occur in the later stages of the AIDS infection.
- Synonyms previously used: progressive diffuse leukoencephalopathy

### 26.9.3 Lymphocytic Meningitis (LM) and Perivascular Lymphocytic Infiltration (PLI)

Lymphocytic meningitis (LM) is characterized by (Fig. 26.5a–f)

- Significant lymphocytic infiltrates in the leptomeninges.
- No opportunistic pathogens are encountered in the meninges.
Fig. 26.2  HIV encephalopathy, T2 (a, b), FLAIR (c, d), T1 (e, f), T1 contrast (g, h), DWI (i, j)
Fig. 26.2 (continued)
Perivascular lymphocytic infiltration (PLI) is characterized by (Fig. 26.5g–j)

- Significant lymphocytic infiltrates in the perivascular spaces of the brain tissue.
- No opportunistic pathogens are encountered in the perivascular brain tissue.

It seems that lymphocytic infiltrates in the leptomeninges and in the perivascular spaces of the brain tissue constitute changes occurring in the early stages of the HIV-1 infection.

26.9.4 Vacuolar Myelopathy (VM) and Vacuolar Leukoencephalopathy (VL)

Vacuolar myelopathy is characterized by (Fig. 26.6a–f)

- Numerous vacuolar myelin swellings.
- Macrophages in multiple areas of the spinal cord.
- Predominant involvement of the dorsolateral spinal tracts.

- Some macrophages may be found in the vacuoles.
- Might not be specific for HIV-1 since they can occur in the absence of HIV.
- The axon is at first unaffected, but it is damaged in the later stages of the disease.
- VM might not be specific for HIV-1

Vacuolar leukoencephalopathy is characterized by

- Numerous vacuolar myelin swellings in the central white matter.
- Some macrophages may be found in the vacuoles.
- VL is a rare condition.

26.9.5 Neuropathological Changes in Early Stages of HIV-1 Infection

Brain changes in HIV-1 seropositive, non-AIDS cases include:

- Cerebral vasculitis was significantly more frequent and marked in HIV seropositive cases and was often associated with lymphocytic
Fig. 26.3  HIV-1 encephalitis: multinucleated giant cells (a–i) (a–h: Stain: H&E; i: Stain: cresyl violet). HIV-1 antigen shown in a small gliomesenchymal nodule (j: stain: immunohistochemistry for p24)
meningitis (Gray et al. 1992).

- Granular ependymitis, myelin pallor with reactive astrocytosis, and microglial proliferation were also more frequent and more severe in HIV seropositive cases. Immunohistochemistry was negative for HIV-antigens. Highly expressed cytokines (tumor necrosis factor-α, interleukin (IL)-1,4,6) (Gray et al. 1992).

- Perivascular lymphocytic infiltrates (PLI) as well as lymphocytic infiltrates in the meninges (MLI) were found in 62.8% of the cases. PLI alone was seen in 61% of the cases, MLI alone in 43% of the cases, and the combination of PLI and MLI in 34% of the cases (Weis et al., unpublished data).

26.9.6 Neuropathological Changes in HIV-1-Infected Children

Children born to HIV-1-infected mothers are in 10–40% of the cases also infected by the virus (Kozlowski et al. 1993). These children develop symptoms before the age of 2 years.

- About 30% of the HIV-1 children develop opportunistic infection or HIV-1 encephalopathy within the first year of life.
- Brain growth is impaired leading to intellectual deficiency.
- The gross-anatomical analysis shows brains which are too small for the age.
- Sometimes atrophic gyri may be noted.
Fig. 26.4 HIV-leukoencephalopathy: presence of multinucleated giant cells in the white matter (a, b: H&E, c: LFB, d: cresyl violet) and myelin pallor loss (e–j)
Microcephaly and/or brain atrophy is present.

The most common findings in brains of HIV-1-infected children are
- Mineralization of predominantly small vessels found in 95% of the case.
- Myelin pallor and gliosis are the noted changes of the white matter that occur in 78% of the cases.
- MGC are seen in 62% of HIV-1-infected children.

Opportunistic infections are comparatively uncommon.

26.9.7 Therapy: HAART Effects and Therapy-Induced Immune Restitution Inflammatory Syndrome (IRIS)

In 1995/1996, highly active antiretroviral therapies (HAART) were introduced which combine

- nucleoside reverse transcriptase inhibitors (NRTI)
  - specifically inhibit the viral reverse transcriptase enzyme necessary for DNA chain elongation of the virus
- protease inhibitors (PI)
  - prevent the production of active virus by interfering with the cleavage of proteins necessary for viral assembly

Effects of the therapy results in:

- The frequency of HIV-1-related CNS diseases has been reduced through
  - the reduction of both viral load in the blood
  - the reduced continuous penetration of virus into the brain (Tardieu 1999)
- HIV-positive patients live longer.
- The median survival
Fig. 26.5 Meningeal lymphocytic infiltrates (a–f: Stain: H&E). Perivascular lymphocytic infiltrates (g–j: Stain: H&E)
– following AIDS increased from 19.6 months in 1993–1995 to 39.6 months for those diagnosed in 1996–2000
– following ADC increased from 11.9 months in 1993–1995 to 48.2 in 1996–2000.
• The proportion of patients with AIDS dementia complex (ADC) increased from 5.2% in 1993–1995 to 6.8% in 1996–2000.

Larger cohort autopsy studies of HIV-infected patients over longer time periods suggest that, despite the beneficial effects of modern antiretroviral combination therapy, involvement of the brain in AIDS subjects continues to be a frequent autopsy finding (Gray et al. 1988, 2003; Jellinger et al. 2000; Langford et al. 2003) (Tables 26.12 and 26.13).

Immune reconstitution inflammatory syndrome (IRIS) is a syndrome that emerges when the immune system recovers after an immune deficiency state (Table 26.14) (Nelson et al. 2017; Chahroudi and Silvestri 2012; McCarthy and Nath 2010). IRIS is an adverse clinical manifestation that occurs in HIV-infected individuals treated successfully with ART and consists of a paradoxical deterioration of clinical status despite improved CD4-T-cell counts and immunologic conditions.

A new variant of HIVE has emerged in the era of HAART as a severe leukoencephalopathy with significant perivascular infiltration of macrophages and lymphocytes which is assumed to be the result of an exaggerated response from a newly reconstituted immune system (Persidsky and Gendelman 2003).
Fig. 26.6 Spinal cord showing vacuolar myelopathy of the dorsal tracts (a–d: stain LFB, e: stain H&E, f: stain: Woelcke’s myelin stain)
Table 26.12  Review of 1597 consecutive autopsies of HIV-1-positive patients performed between 1984 and 2000, and division into four time periods on the basis of the therapeutic regimens available (Vago et al. (2002) reproduced with kind permission by Wolters Kluver Health)

| Year        | Therapy                                                        | n   | HIV--E/L | Opportunistic infections |
|-------------|----------------------------------------------------------------|-----|----------|--------------------------|
| 1984–1987   | No therapy                                                     | 119 | 53.8     | 40.3                     |
| 1988–1994   | Monotherapy (zidovudine)                                      | 1116| 32.2     | 46.8                     |
| 1995–1996   | Dual combination therapy with nucleoside reverse transcriptase inhibitors | 256 | 17.9     | 42.6                     |
| 1997–2000   | Triple combination therapy including two NRTIs and at least one protease inhibitor or non-NRTI | 106 | 15.1     | 42.5                     |

Table 26.13  Frequencies for various neuropathological changes in pre-HAART era compared to HAART era

| Author (year) | Pre-HAART | HAART | Pre-HAART | HAART | Pre-HAART | HAART | Pre-HAART | HAART | Pre-HAART | HAART | Pre-HAART | HAART |
|---------------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|
| Gray et al. (1988) | 40 | 37.5 | Nip | 20.0 | 5.0 | 47.5 | 2.5 |
| Gray et al. (2003) | 23 | 17.4 | Nip | 8.7 | 17.4 | 13.0 | 13.0 |
| Jellinger et al. (2000) | 352 | 8.5 | 4.3 | 18.5 | 7.1 | 22.2 | 8.5 |
| Langford (2003) | 62 | 25.8 | Nip | 16.1 | 6.4 | 6.4 | 19.3 |
| Langford (2003) | 89 | 43.8 | Nip | 16.8 | 5.6 | 0.0 | 8.9 |

n sample size, HIVE HIV-1 encephalitis, HIVL HIV-1 leukoencephalopathy, CMV cytomegalovirus encephalitis, PML progressive multifocal leukoencephalopathy, TOXO toxoplasma gondii encephalitis, LYM primary non-Hodgkin lymphoma

*Frequencies for pre-HAART could not be calculated due to lack of original data in their paper

Table 26.14  Clinical manifestations of IRIS in patients with HIV-1 infection on cART modified after McCarthy and Nath (2010) reproduced with kind permission by Springer Nature

| Infection             | Typical clinical manifestations                      | Atypical clinical manifestations                          |
|-----------------------|------------------------------------------------------|----------------------------------------------------------|
| HIV encephalitis      | • Asymptomatic                                       | • Fulminant decline in mental status over days with brain swelling and inflammation |
|                       | • Mild cognitive decline                             |                                                          |
| PML with JCV          | • Subacute focal neurologic deficits                 | • Focal areas of contrast enhancement and swelling       |
| Varicella-zoster virus| • Shingles                                           | • Strokes without skin rash                               |
|                       | • CNS vasculitis                                     |                                                          |
| Cytomegalovirus       | • Retinitis                                          | • Vasculitis                                             |
|                       | • Cerebritis                                         |                                                          |
| Epstein-Barr virus    | • CNS lymphoma                                       | • Optic neuropathy                                       |
| Tuberculosis          | • Meningitis                                         | • Cerebral infarcts                                      |
|                       | • Subarachnoid hemorrhage                            | • Subarachnoid hemorrhage                                |
| Cryptococcus          | • Meningitis                                         | • Enhancing mass lesions in posterior fossa             |
| Candida               | • Meningitis                                         | • Vasculitis with strokes                                |
Neuropathological examination revealed

- Severe inflammatory lesions.
- Demyelinating lesions with marked intraparenchymal and perivascular infiltration by macrophages and T-lymphocytes.
- In some cases, abundant viral proliferation was identified by immunocytochemistry or in situ hybridization, but in others the infectious agent could only be detected using PCR.
- T-lymphocytes were predominantly CD8(+).
- In those cases with the more favorable course, inflammation was less severe with marked macrophage activation and a number of CD4(+) lymphocytes.
- In the lethal cases, inflammation was severe and mostly composed of CD8(+) cytotoxic lymphocytes.

### 26.9.8 The Sequelae of HIV-1 Infection of the Nervous System

In summary, the following changes of the brain have been described to be due to the HIV-1 infection:

- **Brain weight** (Weis, unpublished data)
  - no changes
- **Brain edema** (Weis, unpublished data)
  - no significant difference
- **Gross-anatomy** (Gelman and Guinto 1992)
  - No apparent macroscopical signs of atrophy are seen by bare visual inspection.
  - Cerebrospinal fluid (CSF) space greater than two standard deviations above the mean of the age-matched control subjects.
  - CSF spaces expanded most in the frontal and temporal lobe.
- **Ventricular system** (Weis, unpublished data) (Gelman and Guinto 1992)
  - Widening of the lateral ventricles.
  - Ventricular spaces expanded more than the sulcal spaces.
- **Volume of brain regions** (Oster et al. 1993; Subbiah et al. 1996; Weis et al. 1993c)
  - No significant changes in volume, surface area, mean cortical thickness.
  - Reduction of the mean volume of the neocortex.
  - Reduction in volume of the central brain nuclei.
  - Reduction in volume of the internal capsule.
  - Mean neocortical thickness was reduced by 12%.
  - There were no differences in white matter volumes between groups.
  - The mean volume of the white matter was reduced by 13%.
  - Mean ventricular volume was increased by 55%.
  - There were no significant differences between the AIDS groups with and without HIV-associated dementia.
- **Neuronal number**
  - Cerebral cortex (Ketzler et al. 1990; Weis et al. 1993b)
    - Loss of neurons in different cortical regions.
    - Neuronal loss is not be correlated with development of dementing symptoms and of HIV-specific neuropathology.
  - Basal ganglia
    - decrease in neuronal density (21%) in the putamen especially in those cases with HIV-1 encephalitis (Everall et al. 1993).
- Cerebellum
  - significant reduction of the volume density, the numerical density of neurons as well as neuronal size was apparent in the cerebellar dentate nucleus and in both inferior olivary nuclei (Abe et al. 1996)
- Substantia nigra
  - The total number of neuronal cell bodies was 25% lower in AIDS than in age-matched controls although the volume density of neuronal melanin did not differ from that of controls because the percentage of pigmented cell bodies was higher and the cell bodies were more fully packed with melanin in AIDS (Reyes et al. 1991).
  - The size of total neurons (pigmented and non-pigmented neurons) and of pigmented neurons was significantly reduced in all investigated nuclei (antero-medial, antero-intermediolateral, posterolateral, and posteromedial nuclei) of HIV-1-infected brains.
  - Furthermore, the nigral neuronal loss showed no relationship with immunohistochemical detection of HIV-1 antigens (gp41, p24).
  - The numerical density of non-pigmented large neurons (type II neurons) was significantly increased in HIV-1-infected brains suggesting that (1) non-pigmented, dopaminergic neurons or non-pigmented, non-dopaminergic neurons might be relatively preserved in the SN of HIV-1 infection, or (2) that pigmented dopaminergic neurons loose their melanin pigments during the early stages of degeneration, which also might be responsible for functional deterioration (Itoh et al. 2000).
- Neuronal size (Weis et al. 1993b)
  - no changes in perikaryal size
- Synapses (Wiley et al. 1991)
  - Loss of synapses as shown by a decrease in the immunoreactivity against synaptophysin
- Dendrites (Masliah et al. 1992a, b)
  - Apical dendrites
    - dilated, vacuolated, and tortuous
    - decreased length and branching
  - Basal and oblique dendrites
    - show the same alterations, but to a lesser extent
    - Some dendrites present lacunae and filopodia consistent with remodeling.
    - 40–60% decrease in spine density throughout the entire length of dendrites.
    - Fewer spines on neurons; 55% fewer on the first segment, 40% fewer on the second, 45% fewer on the third, 60% fewer on the fourth, and 65% fewer in the fifth segment.
    - Aberrant spines in regions of abnormal second-order dendritic branches.
- Nerve fibers
  - White matter
    - Loss of nerve fibers in the white matter
  - Corpus callosum (Wohlschlaeger et al. 2009)
    - Reduced thickness of the myelin sheath of nerve fibers in the corpus callosum.
    - Calculation of the g-ratio revealed a relative increase in size of the axon and a relative decrease in the myelin sheath thickness.
    - The data indicated a reduction in the size of nerve fibers and axons as well as thinner myelin sheaths, whereas in other callosal regions axons and myelin sheaths were swollen and enlarged.
    - These changes were observed in regions which are unaffected, as revealed by light-microscopic analysis of sections stained for myelin.
  - Optic nerve (Tenhula et al. 1992)
    - Degeneration was often severe and was scattered throughout all of the AIDS-affected optic nerves.
    - Despite the approximate 40% loss of axons in the AIDS-affected optic nerves, the mean axonal population was markedly lower than the mean obtained from normal optic nerves (880,000 vs. 1,507,000).
    - The mean axonal diameters were not markedly different, that the changes may not only be secondary to damage at the
retina, but may reflect an AIDS-associated primary optic neuropathy.

- **Astroglia** (Weis et al. 1993a; Ciardi et al. 1990)
  - no change in the number of all astrocytes (i.e., GFAP-positive and GFAP-negative astrocytes)
  - reduction of the number of GFAP-negative cells
  - increase of reactive GFAP-positive astrocytes
  - not correlated with loss of nerve cells
  - increase in nuclear size of GFAP-negative and GFAP-positive astrocytes
  - increase of the size of the cytoplasm of GFAP-positive astroglia
  - no correlation between the neuronal loss and the pattern of reactive astrogliosis
- **Oligodendroglia** (Esiri et al. 1991)
  - significant increase in the number of oligodendrocytes associated with mild degree of myelin damage
  - decrease of oligodendrocytes in severely affected areas
  - slight increase in immunoreactivity for the enzymes carbonic anhydrase II and 2',3'-cyclic nucleotide 3'-phosphodiesterase
  - significant increase in the numerical density of transferrin-immunopositive cells of the white matter
  - an initial reactive hyperplasia which may represent an attempt to repair myelin damage taking place already early during the HIV-1 infection
- **Microglia/macrophages** (Weis et al. 1994)
  - Activated in gray and white matter of all brain regions.
  - Activation pattern is not correlated with the presence of HIV-antigen gp41 and p24 in the brain tissue.
- **Vessels** (Buttner et al. 1996; Weis et al. 1996)
  - Significant increase in the diameter of cortical vessels
  - Increase of the volume fraction, surface area of vessels
  - No changes in length density indicating no changes in the number of vessels
  - Increase of the numerical density of vessels in the gray matter
  - No changes in the numerical density of vessels in the white matter
  - Thinning of the basal lamina as seen by electron microscopy
  - Reduced immunoreactivity for collagen IV and laminin (thinning of the basal lamina)
- **Vascular endothelial cell** (Buttner et al. 1996; Weis et al. 1996)
  - loss of glycoproteins SBA, UEA-I, and WGA of the endothelial cell membrane
  - decrease of immunoreactivity for von Willebrand factor (Factor VIII)
  - no significant differences RCA-I
  - No changes in size at the electron microscopic level
- **Capillaries** (Weis and Haug 1989)
  - region-specific changes
  - increased capillary profile area
  - increased capillary diameter
  - decreased basal lamina thickness
  - increased endothelial cell size
  - unchanged pericyte size

### 26.9.9 Pathogenetic Mechanisms

#### 26.9.9.1 Mode of Entrance of HIV-1 to the Brain

HIV-1 enters the CNS by

- HIV-1 is passively carried by T-lymphocytes and monocytes—the “Trojan Horse” hypothesis.
- Cell-free HIV-1 particles may also penetrate brain microvascular endothelial cells.
- After crossing the BBB into the CNS, macrophages spread productive HIV-1 infection to neighboring microglia.
- Microglia serve as
  - a reservoir for persistent viral infection and replication
  - a vehicle for viral dissemination throughout the brain
  - a major source of neurotoxic products that affect glial function, the blood–brain
barrier and neuronal function, and finally lead to cell death

- Microglia and monocyte-derived macrophages express both the CD4 and chemokine coreceptors (CCR5, CXCR4), the prerequisite for HIV-1 to enter a cell.
- The potential role of the cerebrospinal fluid or the choroid plexus as a means for HIV-1 entry in the brain is still unclear.
- At the time of primary HIV-1 infection, an acute aseptic meningitis or encephalitis indicates central nervous system invasion.
- The point in time when the migration of HIV-1-infected lymphocytes into the brain takes place is not known. It has been shown that, at the time of seroconversion, HIV-1 can be detected in the CSF; this is the time when, clinically, a subacute meningitis develops, thus, suggesting that HIV-1 enters the CNS at a very early stage of the disease.
- Opportunistic infectious agents or drugs of abuse disturbing the BBB may further attract more HIV-1-infected T-lymphocytes and macrophages into the brain.

26.9.9.2 Target Cells of HIV-1 Infection

The cells in the brain identified to contain HIV-1 are:

- Microglia
- Macrophages
- Multinucleated giant cells
- Astrocytes (possibly)
- Endothelial cells (possibly)
- Oligodendrocytes (possibly)

Mechanisms of Brain Lesions

- The development of brain lesions due to opportunistic infections and lymphomas might be explained by the lack of a competent immunologic defense system.
- One might assume that the changes described in Sect. 26.5.8 might result by direct infection with HIV-1.
  - However, it has been shown that neither neurons, nor astrocytes nor endothelial cells are infected with HIV-1.
  - Thus, these changes more probably result from indirect toxic factors that are produced either by infected multinucleated giant cells or by activated microglia.
- Neuronal dropout occurs in brain regions
  - That are free from any neuropathological changes.
  - Neuronal damage in AIDS was, at least, partly due to apoptosis.
  - No correlation was found between the presence and severity of neuronal loss or of neuronal apoptosis and a history of cognitive disorders.
  - No correlation between the presence of HIV-1 proteins and neuronal loss.
- The reactive astrogliosis was not correlated with the loss of nerve cells, indicating that this reaction pattern is rather a response to toxic factors secreted into the brain tissue.
- The number of activated microglia/macrophages is significantly increased in all brain regions. This activation of microglia is not correlated with the presence of HIV-1 antigen in the brain tissue. Activated microglia/macrophages, rather than MGCs, most probably secrete toxic factors.
- The neurotoxicity associated with HIV-1 infection is mediated, in part, through
  - cytokines
  - arachidonic acid metabolites
  - produced during cell-to-cell interactions between HIV-1-infected brain macrophages and astrocytes
- Pathobiological events underlying the neurodegenerative processes in HIV-1-associated dementia are believed to begin with productive infection of monocytes/macrophages by HIV-1.
  - Peripheral activation causes the differentiation of macrophages to produce a variety of immune products that lead to the upregulation of adhesion molecules on brain microvascular endothelial cells and the expression of adhesins on the monocyte-macrophage cell surface.
  - After penetration of the BBB, the differentiated brain macrophages and microglia can be vehicles for viral dissemination.
throughout the brain and focal reservoirs for productive HIV-1 replication.

- The neurotoxic events in the brain are caused by neurotoxins produced by these cells which are primed by HIV-1 and secondarily activated by factors such as immune stimuli or by T-cells trafficking through the nervous system.

- The primed and immune-activated brain macrophages/microglia secrete a variety of factors which affect neural and glial function and eventually lead to CNS inflammation.

- A pro-inflammatory cytokine response from blood-derived monocytes/macrophages, microglia, and astrocytes is amplified and leads finally to neurodegeneration.

- Immune neurotoxic factors may contribute to the breakdown of the BBB and affect the generation of chemokines, leading to transendothelial migration of monocytes into the brain perpetuating the inflammatory cascade.

- As a result of the neurotoxic activities of activated macrophages/microglia, astrocytes may suppress or increase macrophages/microglia secretory functions and toxicity, depending on the astrocytic functional status.

- Cytolytic T-lymphocytes serve to eliminate infected cells, but are lost in late-stage HIV-1 disease, allowing the virus-induced, neurodegenerative response to continue unabated.

Other factors include:
- viral proteins
- CA²⁺ channels
- NMDA receptors
- chemokines and cytokines

- Expression of developmental proteins (Malik and Eugenin 2016):
  - Dickkopf homolog 1 (DKK1): upregulated
  - Rho-associated, coiled-coil containing protein kinase 2 (ROCK2)—upregulated
  - Low density lipoprotein receptor-related protein-associated protein 1 (LRPAP1)—upregulated
  - Low density lipoprotein receptor-related protein 5-like (LRP5L)—downregulated
  - Low density lipoprotein-related protein 12 (LRP12)—upregulated

- Low density lipoprotein receptor-related protein 8, apolipoprotein e receptor (LRP8)—downregulated
- Catenin (cadherin-associated protein), alpha-like 1 (CTNNAL1)—upregulated
- Catenin, beta-like 1 (CTNNBL1)—downregulated
- Catenin (cadherin-associated protein), delta 1 (CTNND1)—downregulated
- Catenin (cadherin-associated protein), alpha-like 1 (CTNNAL1)—upregulated
- Glycogen synthase kinase 3 beta (GSK3B)—downregulated
- Wingless-type MMTV integration site family, member 10A (WNT10A)—downregulated

- For more details, see (Zayyad and Spudich 2015; Singh 2016; Ru and Tang 2017; Rao et al. 2014; Malik and Eugenin 2016; Lamers et al. 2016; Joseph et al. 2016; Chen et al. 2014; Carroll and Brew 2017).

Interactions between the blood–brain barrier (BBB) and HIV (Hong and Banks 2015)

Mechanisms involving the BBB in HIV-infection

- Passage of HIV cell-free virus across the BBB
  - Transcytotic (mannose 6 phosphate receptor dependent)
  - Paracellular (tight junction dissolution)
- Passage of HIV-1 proteins (gp120, Tat) across the BBB
- Increased immune cell trafficking across the BBB
  - Activated and infected T cells
  - Activated and infected monocytes
- Transport of cytokines across the BBB
- Induction of cytokine release from barrier cells
- Increased BBB leakiness
- Brain-to-blood efflux of antivirals
  - Protease inhibitors by P-glycoprotein
  - AZT by organic ion transporter
- Altered BBB transporter expression and function (e.g., P-glycoprotein)
- Neurovascular unit effects
Therapeutic effects on involved pathways are illustrated in Table 26.15.

### Table 26.15  Therapy and effects on involved pathways (Sanchez and Kaul 2017) reproduced with kind permission from MDPI open access

|                        | HIV or methamphetamine or HIV + Meth | HIV + cART | HIV + METH + cART |
|------------------------|--------------------------------------|------------|-------------------|
| Microglia activation   | ↑                                    | ↑          | ↑                 |
| Astrocytosis           | ↑                                    | ↑          | ↑                 |
| Alteration of neurotransmission | ↑                              |            | ↑                 |
| HAND/HAD               | ↑                                    | ↓          | ↑                 |
| Oxidative stress       | ↑                                    | ↑          | ↑                 |
| Mitochondrial impairment | ↑                                   |            | ↑                 |
| ER stress              | ↑                                    |            | ↑                 |
| Autophagy              |                                      | ↓          |                   |
| Neuronal dendrites     | ↓                                    |            | ↓                 |
| Synapses               | ↓                                    |            | ↓                 |
| Neuronal ATP           | ↓                                    | ↓          | ↓                 |
| Viral load             |                                      |            | ↓                 |

MRI-T1 (Fig. 26.7e)
- Subependymal enhancement

MRI-T1 Contrast-Enhanced (Fig. 26.7e)
- Subependymal enhancement

MRI-T2*/SWI (Fig. 26.7f)
- Periventricular hypointense calcifications in perinatal CMV

### 26.10  DNA-Virus: Cytomegalovirus Infection (CMV)

#### Cytomegalovirus
- Herpesviruses, subfamily Betaherpesvirinae
- Large, enveloped viruses containing double-stranded DNA
- 150 nm in diameter

#### 26.10.1 Neuroradiology Findings

**General Imaging Features**
- Periventricular white matter lesions, subependymal enhancement
- Calcifications in perinatal CMV

**CT Non-Contrast-Enhanced** (Fig. 26.7a)
- Periventricular hypodense lesions
- Periventricular hyperdense calcifications in perinatal CMV

**CT Contrast-Enhanced**
- Subependymal enhancement possible

**MRI-T2/FLAIR** (Fig. 26.7b, c)
- Periventricular hyperintensities

MRI-T1 (Fig. 26.7e)
- Subependymal enhancement

MRI-T1 Contrast-Enhanced (Fig. 26.7e)
- Subependymal enhancement

MRI-T2*/SWI (Fig. 26.7f)
- Periventricular hypointense calcifications in perinatal CMV

#### 26.10.2 Neuropathology Findings

**Macroscopic Features**
- In general, there are no gross-anatomical changes.
- Rarely, some small areas of necrosis are seen lining the ventricles, i.e., necrotizing ependymitis.

**Microscopic Features** (Fig. 26.8a–j)
- Microglial nodules are seen scattered throughout the nervous system.
- Large cells containing inclusion bodies are found within the microglial nodules.
- The microglial nodules located in the gray and white matter are usually not surrounded by a necrotic area.
- Along the periventricular spaces CMV-containing cells are found within the necrotic areas.
Fig. 26.7 Cytomegalovirus (CMV) infection: periventricular calcifications after perinatal CMV. CT non-contrast (a), T2 (b, c), T1 (d), T1 contrast (e), T2* (f)
John Cunningham Virus (JCV) is a member of the Polyomaviridae family
Polyomaviruses BK and JC are ubiquitous.

- Are 45 nm in diameter.
- Contain less than 5000 base pairs.
- Genomes of BK and JC are closely related.
  - divided in early, late, and non-coding regions

- JC virus etiological agent of the progressive multifocal leukoencephalopathy (PML)
- JC is an ubiquitous, neurotropic virus:
  - 50–90% of adult healthy individuals have been exposed to this virus.
  - 19–27% of those people shedding JCV in their urine.
- The seroprevalence increases with age but acquisition of this virus is not associated with a clinical syndrome.
- JC binds to sialylated carbohydrates and serotonin receptors to enter glial cells by endocytosis.
- DNA genome is uncoated and delivered to the nucleus.

### 26.11.1 Clinical Signs and Symptoms

- The pre-AIDS era
  - Impaired vision
    - homonymous hemianopsia
  - Motor weakness
    - hemiparesis or hemiplegia
  - Changes in mentation:
    - personality change
    - difficulty with memory
    - emotional lability
    - dementia
- AIDS-related PML
  - weakness (42%)
  - speech abnormalities (40%)
  - cognitive abnormalities (36%)
  - gait abnormalities (29%)
  - sensory loss (19%)
  - visual impairment (19%)
  - seizures
Fig. 26.8 Cytomegalovirus (CMV) infection (a–n). Cells with inclusion bodies (a–j) (stain: H&E); cytomegalic cell with inclusion body (k–n) (stain: immunohistochemistry for CMV)
Fig. 26.8 (continued)
- diplopia
- limb incoordination

- PML associated with monoclonal antibody therapy
  - cognitive disorders (48%)
  - motor abnormalities (37%)
  - language disturbances (31%)
  - visual defects (26%)

- PML-IRIS immune reconstitution inflammatory syndrome
  - Paradoxical worsening of clinical or radiographic finding with recovery of the immune system
  - New or increased neurologic deficits
  - Increase in the number or size of lesions on neuroimaging
  - Contrast enhancement of brain lesions
  - Brain edema
  - Concurrent with diagnosis of PML

26.11.2 Neuroimaging Findings

General Imaging Features
- Confluent subcortical white matter lesions, predominantly in parieto-occipital or frontal lobes, U-fibers involved

CT Non-Contrast-Enhanced (Fig. 26.9a)
- Multiple hypodensities in white matter
- No mass effect
- If bilateral often asymmetric
- Natalizumab-associated PML often monofocal

CT Contrast-Enhanced (Fig. 26.9b)
- Usually no enhancement
- Enhancement possible in HIV-associated PML and natalizumab-associated PML

MRI-T2 (Fig. 26.9c)
- Hyperintense

MRI-FLAIR (Fig. 26.9d)
- Hyperintense

MRI-T1 (Fig. 26.9e)
- Hypointense

MRI-T1 Contrast-Enhanced (Fig. 26.9f)
- Usually no enhancement
- Enhancement possible in HIV-associated PML and natalizumab-associated PML

MRI-DWI (Fig. 26.9g)
- Acute lesions hyperintense

MRI-ADC (Fig. 26.9h)
- Acute lesions hypointense

26.11.3 Neuropathology Findings

Macroscopic Features (Fig. 26.10a–d)
- Multiple areas of discoloration of the white matter.
- Sometimes, the white matter may appear softened and mottled.
Fig. 26.9 Progressive multifocal leukoencephalopathy (PML). CT non-contrast (a), CT contrast (b), T2 (c), FLAIR (d), T1 (e), T1 contrast (f), DWI (g), ADC (h)
26.7 Progressive Multifocal Leukoencephalopathy (PML)

Fig. 26.9 (continued)
Fig. 26.10 Progressive multifocal leukoencephalopathy: macroscopically, the white matter shows a moth-eaten appearance (a–d). The myelin of the left hemisphere is completely lost (stain: Woelcke’s myelin stain) (e, f). Histology shows degeneration of myelin accompanied by the presence of reactive astrocytes, bizarre astrocytes/oligodendrocytes with large eccentric cytoplasm and lymphocytic infiltrates (g–j). Reactive astrogliosis (stain: GFAP) (k, l) and reactive microgliosis (stain: HLA-DRII) (m, n). Lymphocytes (stain: CD45) (o, p) are found in the perivascular spaces and within the brain tissue.
Fig. 26.10 (continued)
Microscopic Features (Fig. 26.10e–p)
- Multiple foci of demyelination in the white matter consisting of loss of myelin sheaths.
- The oligodendrocytes are enlarged, amphophilic, and contain intranuclear inclusions.
- Enlarged, bizarre astrocytes.

26.11.4 Molecular Neuropathology

Development of PML (Berger and Khalili 2011)
- Infection with JC virus
- Establishment of latent and/or persistent JC virus infection
- Rearrangement of JC virus into a neurotropic strain if initial infection has been with the archetype strain
- Reactivation of the neurotropic JC virus strain from sites of viral persistence-latency
- Entry into the brain

- Establishment of productive infection of oligodendrocytes
- Ineffective immune system that prevents immunosurveillance from eliminating the infection

Drugs which cause PML are listed in Table 26.16.

The differences between progressive multifocal leukoencephalopathy (PML), progressive multifocal leukoencephalopathy—immune reconstitution inflammatory syndrome (PML–IRIS) and multiple sclerosis (MS) with regard to anatomical, neuropathological, and MRI features are shown in Table 26.17.

Prognostic factors of the evolution of progressive multifocal leukoencephalopathy have been described (Gheuens et al. 2013) and include:

- Favorable factors:
  - Detectable JCV-specific cellular immune response in blood or CSF
– Rapid clearance of JCV from CSF
– CD4 count >200 μL − 1 at onset

Unfavorable factors:
– Undetectable JCV-specific cellular immune response in blood or CSF
– Mass effect on MRI
– Posterior fossa lesions
– High JC viral load in CSF
– CD4 count <200 μL − 1 at onset

### 26.12 Herpes Simplex Virus (HSV) Encephalitis

Herpesviruses are large, enveloped viruses.
- Contain double-stranded DNA.
- 150 nm in diameter.
- DNA core surrounded by an icosadeltahedral capsid containing 162 capsomeres.
- Capsid is enclosed by a glycoprotein-containing envelope.
- Encode proteins that manipulate the host cell and immune response.
- DNA replication and capsid assembly occurs in the nucleus.
- Virus is released by
  – Exocytosis
  – Cell lysis
  – Through cell-to-cell bridges
- Cause lytic, persistent, latent, and immortalizing infections

### 26.12.1 Clinical Signs and Symptoms

- Headache
- Neck stiffness
- Drowsiness
- Coma
- Dysphagia
- Hemiparesis
- Focal seizures

### 26.12.2 Neuroimaging Findings

**General Imaging Features**
- Involvement of limbic system and temporal lobe
- Often hemorrhages and enhancement
- Often bilateral, but asymmetric

**CT Non-Contrast-Enhanced** (Fig. 26.11a)
- Normal (early) to mild hypodense, swollen temporal lobes and insula

**CT Contrast-Enhanced**
- Patchy enhancement possible

**MRI-T2/FLAIR** (Fig. 26.11b–d)
- Hyperintense, swollen white matter and cortex of affected areas.
- Hemorrhages may be hypointense.

| Medication          | Treatment                                      |
|---------------------|------------------------------------------------|
| Azathioprine        | Transplantation/autoimmune disease             |
| Cyclosporine        | Transplantation                                |
| Cyclophosphamide    | Cancer/transplantation/autoimmune disease      |
| Dimethylfumarate    | Autoimmune disease                             |
| Efalizumab          | Autoimmune disease (psoriasis)                 |
| Fingolimod         | Autoimmune disease                             |
| Infliximab         | Autoimmune disease                             |
| Leflunomide        | Autoimmune disease                             |
| Methotrexate      | Cancer/autoimmune disease                     |
| Mycophenolate     | Transplantation/autoimmune disease             |
| Natalizumab        | Autoimmune disease                             |
| Rituximab          | Cancer/autoimmune disease                     |
| Tacrolimus         | Transplantation                                |
Table 26.17 Comparative anatomical, neuropathological, and MRI features of progressive multifocal leukoencephalopathy (PML), progressive multifocal leukoencephalopathy—immune reconstitution inflammatory syndrome (PML–IRIS) and multiple sclerosis (MS) (Bauer et al. 2015) reproduced with kind permission by Springer Nature

|                  | PML                     | PML–IRIS                | MS                     |
|------------------|-------------------------|-------------------------|------------------------|
| **Anatomical features** |                         |                         |                        |
| • Lesions mostly reside in cerebral hemispheres but periventricular lesions are rare. | • Lesion distribution is similar to PML. | • Lesions can be found in white and gray matter, but are often found in a periventricular position. |                        |
| • Lesions predominantly affect the deep and subcortical white matter and can expand into the cortical gray matter. |                                        | • Unlike in PML, lesions can be found in spinal cord and optic nerves. |                        |
| • Intracortical lesions are present. |                                        |                         |                        |
| • Spinal cord and optic nerves are spared. |                                        |                         |                        |
| **Neuropathological features** |                         |                         |                        |
| • Demyelinating lesions reveal oligodendrocytes with enlarged nucleus and cytoplasm. The nucleus may show inclusion bodies. | • Like PML, lesions contain infected cells, especially on the border. | • Unlike in PML, lesions are perivenous and show finger-like extensions (i.e., Dawson fingers). |                        |
| • Oligodendrocytes are mostly found on the border of the lesion. | • In small samples (biopsies) however, infected cells may be low in numbers or may be absent. | • Subpial lesions are present and are specific for MS. |                        |
| • Subpial lesions are absent. | • Subpial lesions are absent. | • Lesions contain bizarre astrocytes. |                        |
| • Remyelination is absent. | • Remyelination is absent. | • Lesions contain extremely high numbers of T-cells and B-cells. |                        |
| • Within the demyelinated lesions, large (the so-called bizarre) astrocytes are found. | • Like in PML, lesions contain bizarre astrocytes. | • Lesions contain moderate to high numbers of T-cells. |                        |
| • Lesions contain low to moderate numbers of T-cells. | • Lesions contain extremely high numbers of T-cells and B-cells. | • Numbers of microglia and macrophages do not differ with PML. |                        |
| • few B-cells | • Numbers of microglia and macrophages do not differ with PML. | • Numbers of microglia and macrophages do not differ from PML or PML–IRIS. |                        |
| • few plasma cells |                                        |                         |                        |
| • Activated microglial cells and macrophages are present in high numbers. |                                        |                         |                        |
| **MRI features** |                         |                         |                        |
| • Usually larger than 3 cm | • Usually larger than 3 cm | • All MRI features seen in PML and/or PML–IRIS also can be seen in MS. |                        |
| • Lesions always start in subcortical regions, probably related to a high blood flow. | • Lesions always start in subcortical regions, probably related to a high blood flow. | • However, MS lesions usually are and stay smaller in size than in PML or PML–IRIS. |                        |
| • Borders are sharp towards the GM and ill-defined towards the WM. | • Borders are sharp towards the GM and ill-defined towards the WM. | • Homogeneous or open-ring enhancing lesions are present in MS but not observed in PML. |                        |
| • In first scans of 28% of patients, lesions extend in deep GM. | • In first scans of 71% of patients, lesions extend in deep GM. |                                        |                        |
| • 23–57% of (HIV-associated) cases have contrast-enhancing lesions. | • 86% of PML–IRIS cases have contrast-enhancing lesions. |                                        |                        |
| • T1 lesions are mostly hypointense. | • T1 lesions may have hyperintense rims. |                                        |                        |
| • Diffusion-weighted images are always hyperintense. | • Diffusion-weighted images are always hyperintense. |                                        |                        |
| • Punctate T2-hyperintense lesions can be found in the immediate vicinity of the main lesion. | • Punctate T2-hyperintense lesions can be found in the immediate vicinity of the main lesion. |                                        |                        |
Fig. 26.11 Herpes encephalitis with characteristic involvement of right limbic system, temporal and basal frontal lobe, restricted diffusion and weak enhancement; CT non-contrast (a), T2 ax/cor (b, c), FLAIR (d), T1 (e), T1 contrast (f), DWI (g), ADC (h)
Fig. 26.11 (continued)

MRI-T1 (Fig. 26.11e)
- Hypointense edema
- Loss of gray-white matter differentiation

MRI-T1 Contrast-Enhanced (Fig. 26.11f)
- Diffuse enhancement

MRI-T2*/SWI
- Hemorrhages hypointense

MR-Diffusion Imaging (Fig 26.11g)
- Often restricted diffusion

MRI-ADC (Fig. 26.11h)
- Often restricted diffusion

Nuclear Medicine Findings (Fig. 26.12)
- Decreased FDG uptake
- After recovery FDG uptake appears regular
Fig. 26.12  Herpes encephalitis: decreased FDG uptake (left 3 rows) in a patient during the recovery phase of Herpes simplex encephalitis and regular FDG uptake after recovery (right 3 rows).

Fig. 26.13  Herpes encephalitis: macroscopically, necrosis is seen in both temporal lobes (arrow) (a, b). The virus is demonstrated by immunohistochemistry mainly in neurons (c, d).
26.12.3 Neuropathology Findings

Macroscopic Features (Fig. 26.13a, b)
- Congestion
- Hemorrhagic necrosis of the
  - Temporal lobe
  - Insula
  - Cingulate gyrus
  - Posterior orbitofrontal cortex

Microscopic Features (Fig. 26.13c, d)
- Acute phase
  - parenchymal inflammation
  - lymphocytes and macrophages in the leptomeninges
  - necrotic cells
  - foci of hemorrhages
  - perivascular and interstitial infiltrate of lymphocytes
  - microglial nodules
  - neuronophagia
- Chronic phase
  - glial scar tissue
  - clusters of lymphocytes

26.12.4 Molecular Neuropathology

Pathogenesis
- Primary mucocutaneous infection
  - mucocutaneous border of lips or oropharyngeal mucosa
- Latency in trigeminal ganglion
  - by retrograde axonal transport along sensory fibers to the trigeminal ganglion
  - further replication
  - latent infection (latency-associated transcripts)
- Reactivation of virus
  - anterograde transport to the skin or mucose
  - development of cold sores
  - reactivation
    - spontaneously
    - mucocutaneous trauma
    - ultraviolet irradiation
    - emotional stress
    - pyrexia
    - fluctuations in estrogen and progesterone concentrations
    - immnosuppression

26.12.5 Treatment and Prognosis

Outcome
- Fatal outcome within a few days when untreated
- Treatment

26.13 Tick-Borne Encephalitis

Tick-borne encephalitis (TBE) is an infection of the central nervous system (CNS) caused by tick-borne encephalitis virus (TBEV) and transmitted by ticks, with a variety of clinical manifestations (Table 26.18). The incidence of TBE in Europe is increasing due to an extended season of the infection and the enlargement of endemic areas.

Causative agents:
- Togaviridae
- Flaviviridae
- Reoviridae
- Bunyaviridae

TBE is a caused by flavivirus
- Western Europe subtype, tick vector: *Ixodes ricinus*
- Siberian subtype, tick vector: *Ixodes persulcatus*
- Far eastern subtype, tick vector: *Ixodes persulcatus*

26.13.1 Clinical Signs and Symptoms

- Meningitis typically manifests with
  - High fever
  - Headache
  - Nausea
  - Vomiting
- Encephalitis can be manifested by
  - Impaired consciousness
  - Somnolence
  - Stupor
  - Coma
- Myelitis
- Other manifestations comprise
  - Personality changes
  - Behavioral disorders
– Concentration and cognitive function disturbances
– Tongue fasciculations and tremor of extremities
– Focal or generalized seizures
– Delirium
– Psychosis

### 26.13.2 Epidemiology

#### Incidence
- Highly endemic areas (≥5 cases/100,000/year)

### 26.13.3 Neuroimaging Findings

#### General Imaging Features
- MRI and CT often normal, rarely lesions in thalamus, cerebellum, or basal ganglia

#### CT Non-Contrast-Enhanced
- Usually normal

#### MRI-T2/FLAIR (Fig. 26.14a, b)
- Lesions hyperintense

#### MRI-T1 (Fig. 26.14c)
- Lesions hypointense

#### MRI-T1 Contrast-Enhanced (Fig. 26.14d)
- Meningeal or parenchymal enhancement possible

#### MR-Diffusion Imaging (Fig. 26.14e)
- Restricted diffusion possible

#### MRI-ADC (Fig. 26.14f)
- Restricted diffusion possible

#### Nuclear Medicine Imaging Findings
- Decreased FDG uptake

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**Table 26.18 Viruses causing tick-borne encephalitis**

| Virus                        | Brain region affected | Mortality | Morbidity                                      | Geographic distribution                      |
|------------------------------|-----------------------|-----------|------------------------------------------------|---------------------------------------------|
| Eastern equine encephalitis  |                       | 50–75%    | 90% of survivors have persistent neurologic disability. | • Eastern and Gulf coast states of the USA.  |
| Western equine encephalitis  | • Basal ganglia       | <5%       |                                                | • Caribbean                                  |
|                              | • Thalamus            |           |                                                | • South America                              |
|                              | • Brain stem          |           |                                                |                                             |
| St. Louis encephalitis       | • Midbrain            | <5%       | 25% of survivors have persistent neurologic disability. | • The USA                                    |
|                              | • Thalamus            |           |                                                | • Central America                            |
| Japanese encephalitis        | • Thalamus            | Up to 50% | High percentage of survivors have persistent neurologic disability. | • Southeast Asia                             |
|                              | • Substantia nigra    |           |                                                | • Bangladesh                                 |
|                              | • Brain stem          |           |                                                | • Pakistan                                   |
|                              | • Spinal cord         |           |                                                |                                             |
| West Nile virus              | • Thalamus            | 3–15%     | 50–75% of survivors have residual neurologic disability. | • Africa                                     |
|                              | • Cerebellum          |           |                                                | • Eastern Europe                             |
|                              | • Substantia nigra    |           |                                                | • West Asia                                  |
|                              | • Pons                |           |                                                | • Middle East                                |
|                              | • Medulla oblongata   |           |                                                | • North America                              |
|                              | • Medulla oblongata   |           |                                                |                                             |
|                              | • Spinal cord         |           |                                                |                                             |
| Tick-borne encephalitis      |                       | 1–10%     | Small percentage develop chronic encephalitis with intractable epilepsy and progressive paralysis (Russian spring-summer encephalitis). | • Africa                                     |
Fig. 26.14  Tick-borne encephalitis with T2-hyperintensity and mild enhancement of thalami and basal ganglia. T2 (a), FLAIR (b), T1 (c), T1 contrast (d), DWI (e), ADC (f)
26.13.4 Neuropathology Findings

**Macroscopic Features**
- moderate to severe congestion (Fig. 26.15)
- petechial hemorrhages

**Microscopic Features** (Fig. 26.16a–l)
- lymphocytic infiltrates
- leptomeningeal
- perivascular
- parenchymal
- microglial nodules and macrophages
- focal necrosis of white matter myelinated fibers
- thrombosed small vessels

Fig. 26.14 (continued)

Fig. 26.15  Tick-borne encephalitis: totally decreased FDG uptake in cerebral cortex
Fig. 26.16 Tick-borne encephalitis: histological examination reveals perivascular lymphocytic infiltrates (a, b) and the presence of gliomesenchymal nodules (c, d) which may contain multinucleated giant cells (e, f). The perivascular infiltrates are mainly made up of CD3-positive T-lymphocytes (g) which are also homing in the surrounding brain tissue (h). Reactive astrogliosis (stain: GFAP) (i, j) and reactive microgliosis (stain: HLA-DRII) (k, l) might be moderate.
26.13.5 Molecular Neuropathology

- Virus enters the vector (mosquito or tick) while it is feeding on the blood of an infected host.
- Is transmitted to other hosts in the salivary secretions of the vector.
- Natural hosts are birds or small mammals (rodents).
- Humans are dead-end hosts.
- Virus replicates at the site of host inoculation.
- Spreads to regional lymph nodes and other lymphoreticular tissues.
- Disseminates hematogenously to systemic tissues (CNS).
26.13.6 Treatment and Prognosis

Treatment
- No specific drug therapy
- Corticosteroids
- Tracheal intubation and respiratory support

Outcome
- Complete restitution to fatal
- Prevention:
  - Vaccination

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