Infections: Viruses

26

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

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 • Cerebritis	• Focal neurologic deficits • Seizures
Brain stem and posterior cranial fossa	• Brain stem encephalitis • Cerebellitis	• 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

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

S. Weis et al., *Imaging Brain Diseases*, https://doi.org/10.1007/978-3-7091-1544-2_26

Table 26.2 Subdivision of viruses

DNA viruses	Enveloped	• Pox • Herpes • Hepadna
	Naked capsid	• Polyoma, Papilloma, Adeno • Parvo
RNA viruses	+RNA	• Naked capsid: Picorna, Calici • Enveloped: Toga, Flavi, Corona
	–RNA	• Enveloped: Rhabdo, Filo, Orthomyxo, Paramyxo, Bunya, Arena
	±RNA	• Double capsid: Reo
	+RNA via DNA	• Enveloped: Retro

  - 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 26.3 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	• Adenovirus
		Papovaviridae	• JC virus • Simian virus 40
	Single-stranded	Parvoviridae	• Parvovirus B19
RNA	Double-stranded	Reoviridae	• Coltivirus • Seadornavirus
	Single-stranded sense non-segmented	Retroviridae	• Deltaretrovirus • Lentivirus
		Coronaviridae	• Coronavirus
		Togaviridae	• Alphavirus
		Flaviviridae	• Flavivirus
		Picornaviridae	• Enterovirus
	Single-stranded antisense segmented	Bunyaviridae	• Orthobunyavirus • Phlebovirus
		Arenaviridae	• Arenavirus
	Single-stranded antisense non-segmented	Orthomyxoviridae	• Influenza viruses
		Paramyxoviridae	• Henipavirus • Morbilivirus • Rubulavirus
		Rhabdoviridae	• Rabies • Borna
		Filoviridae	• Ebola

Table 26.4 List of viruses and related diseases of viruses

	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 • Snowshoe hare virus • California encephalitis • Jamestown canyon encephalitis
		Reoviridae	• Colorado tick fever
	Paramyxoviruses	Measles virus	• Measles
		Parainfluenza virus	• Limited respiratory tract infection
		Mumps virus	• Mumps
	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 • Polyomyelitis • 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
Chromic 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

HSV	• Limbic system and temporal lobe • Often hemorrhages and enhancement
CMV	• Periventricular white matter, subependymal enhancement • Calcifications in perinatal CMV
EBV	• Symmetric involvement of basal ganglia, thalami, cortex, or brain stem • Rarely EBV-cerebellitis
VZV	• Multifocal cortical areas • Hemorrhagic infarctions possible
HIV	• Brain atrophy • Symmetric confluent white matter lesions (periventricular, basal ganglia, centrum semiovale, brain stem, cerebellum), • 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 • Rarely lesions in thalamus, cerebellum, caudate nucleus, and brain stem
JC Virus (PML)	• Confluent subcortical white matter lesions, predominantly in parieto-occipital lobes • 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

Table 26.8 Properties of DNA viruses and RNA viruses

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

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)
Poliovirus	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
- Immunomudulators

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.

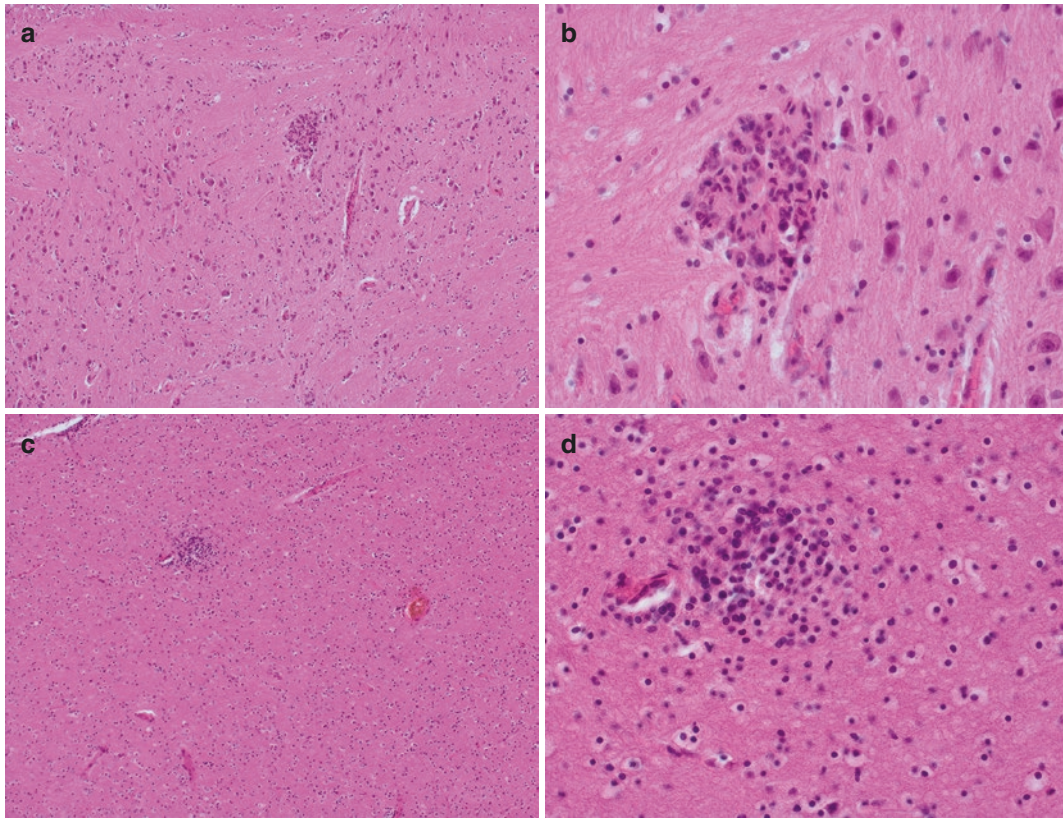


Fig. 26.1 Unspecified nodular encephalitis (**a**–**d**) (Stain: H&E)

26.9 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

- *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.
  - 30% prevalence in combination antiretroviral therapies (CART)-treated HIV+ individuals.
- 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.
  - 20–30% prevalence in combination antiretroviral therapies (CART)-treated HIV+ individuals.
- 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.

Table 26.10 The neuropathological changes seen in the brains of HIV-1-infected patients

Changes primarily due to HIV-1	• HIV-1 encephalitis (HIVE) • HIV-1 leukoencephalopathy (HIVL) • HIV-1 myelitis • Lymphocytic meningitis (LM) • Meningeal lymphocytic infiltration (MLI) • Perivascular lymphocytic infiltration (PLI)
Changes probably due to HIV-1	• Vacuolar myelopathy • Vacuolar leukoencephalopathy
Opportunistic infections—viruses	• Cytomegalovirus infection (CMV) • Progressive multifocal leukoencephalopathy (PML) • Herpes simplex virus 1 • Herpes simplex virus 2 • Herpes zoster • HTLV-1 • Varicella-zoster virus
Opportunistic infections—parasites	• Toxoplasma gondii • Acanthamoeba • Leptomyxid amoeba • Trypanosoma cruzi • Strongyloides
Opportunistic infections—fungi	• Aspergillus fumigatus • `Candida albicans` • `Cryptococcus neoformans` • Others including: Histoplasma, Phycomyces, Coccidioides, Blastomyces, Acremonium, Cladosporium
Opportunistic infections—bacteria	• Pyogenic: *Escherichia coli*, Listeria, Staphylococcus, Salmonella • Mycobacterial: *Mycobacterium tuberculosis*, *Mycobacterium avium* intracellulare • Spirochetal: Treponema pallidum • Filamentous: Nocardia • Miscellaneous: Whipple's disease
Neoplasias	• Lymphoma (primary and secondary) • Kaposi sarcoma

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.

Table 26.11 The changes occurring in the peripheral nervous system and in skeletal muscles of HIV-1-infected patients

Peripheral nervous system	• Acute inflammatory demyelinating (poly) (radiculo) neuropathy • Chronic inflammatory demyelinating (poly) (radiculo) neuropathy • Axonal neuropathy • Ganglionitis, ganglioradiculitis, (poly) (radiculo) neuritis • necrotizing vasculitis, vasculitic neuropathy
Skeletal muscle	• (Poly) myositis • Necrotizing myopathy • Nemaline rod myopathy • Vesicular myopathy, mitochondrial myopathy • Necrotizing vasculitis

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 chararcterized 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.

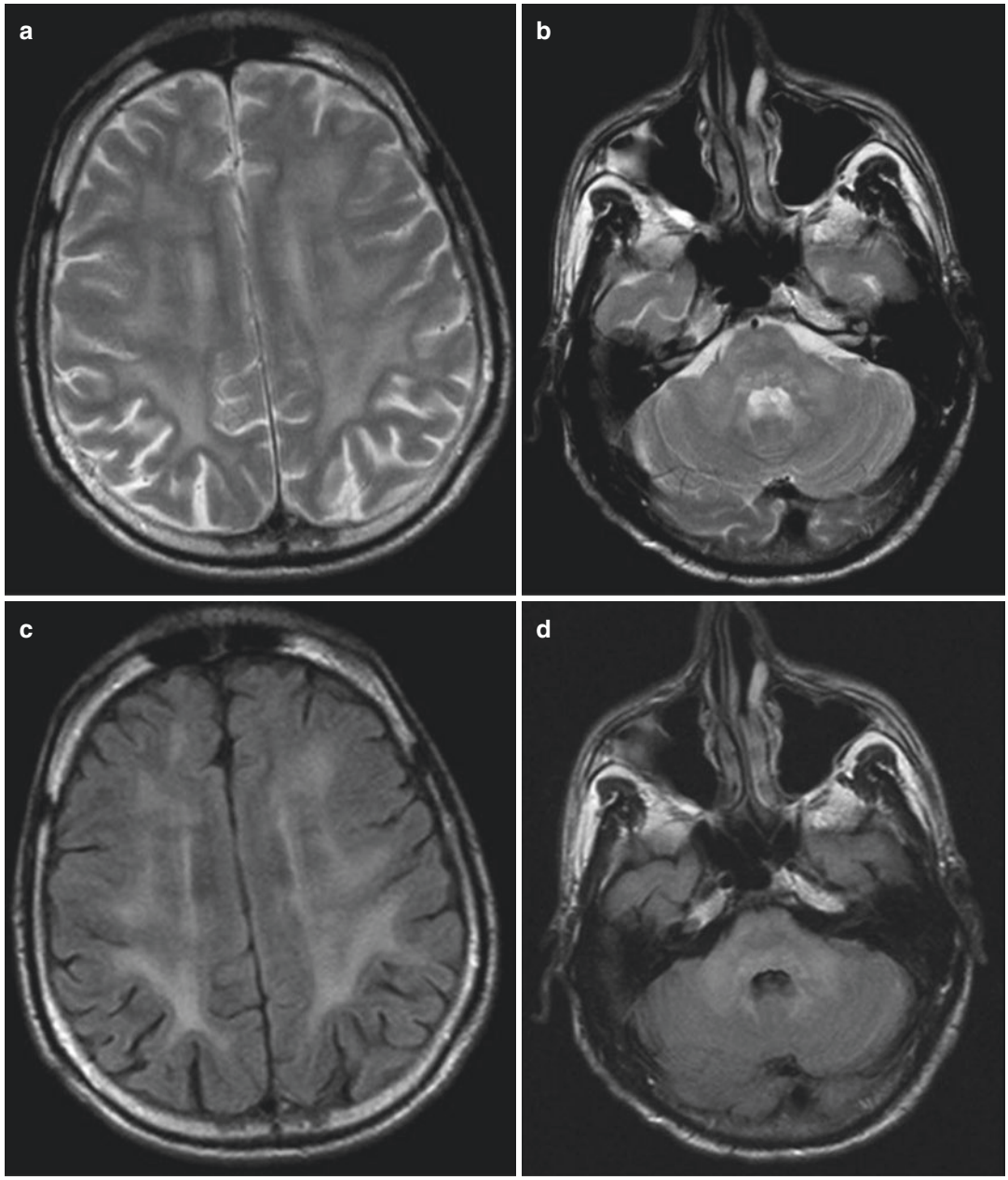


Fig. 26.2 HIV encephalopathy, T2 (**a**, **b**), FLAIR (**c**, **d**), T1 (**e**, **f**), T1 contrast (**g**, **h**), DWI (**i**, **j**)

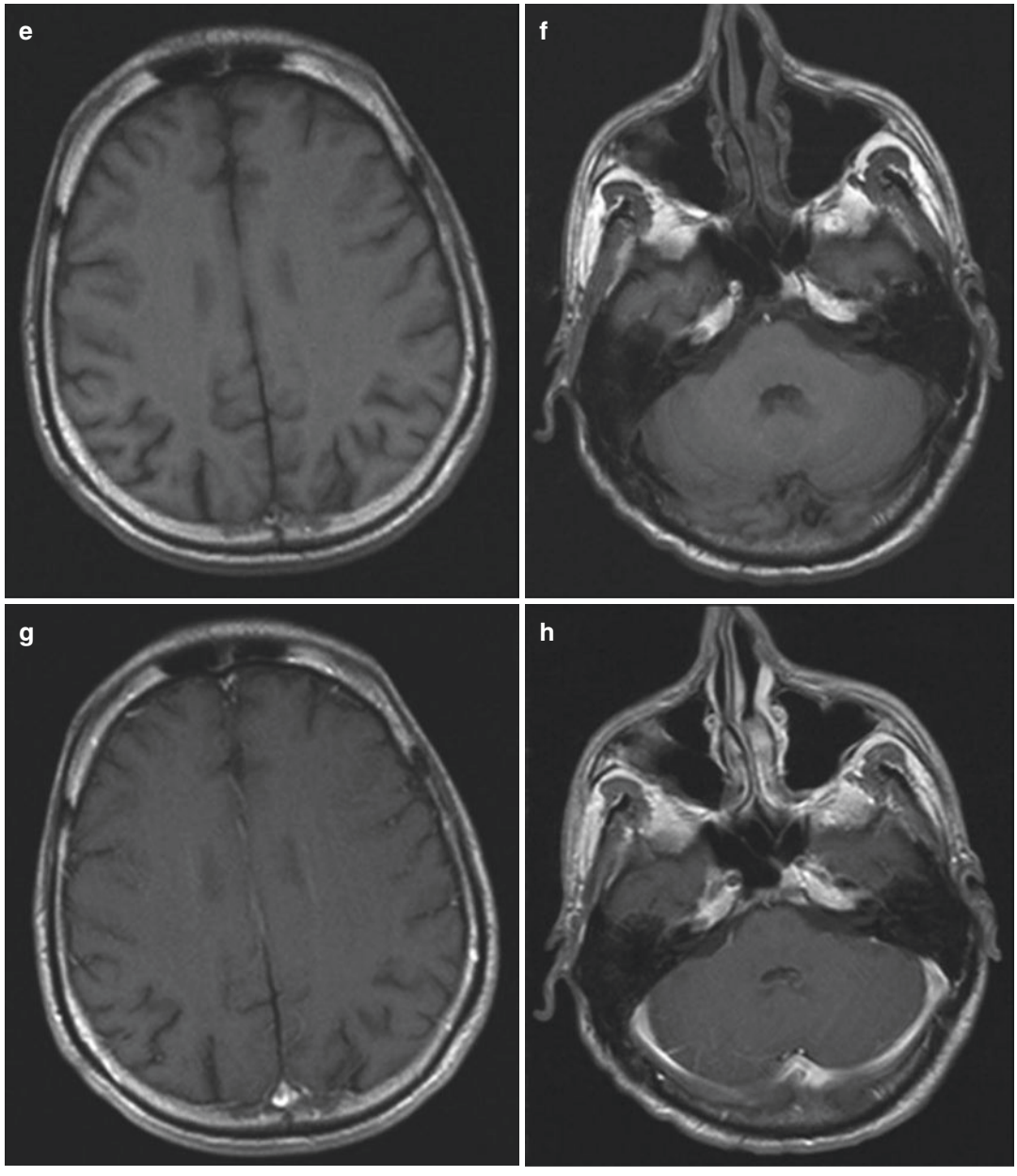


Fig. 26.2 (continued)

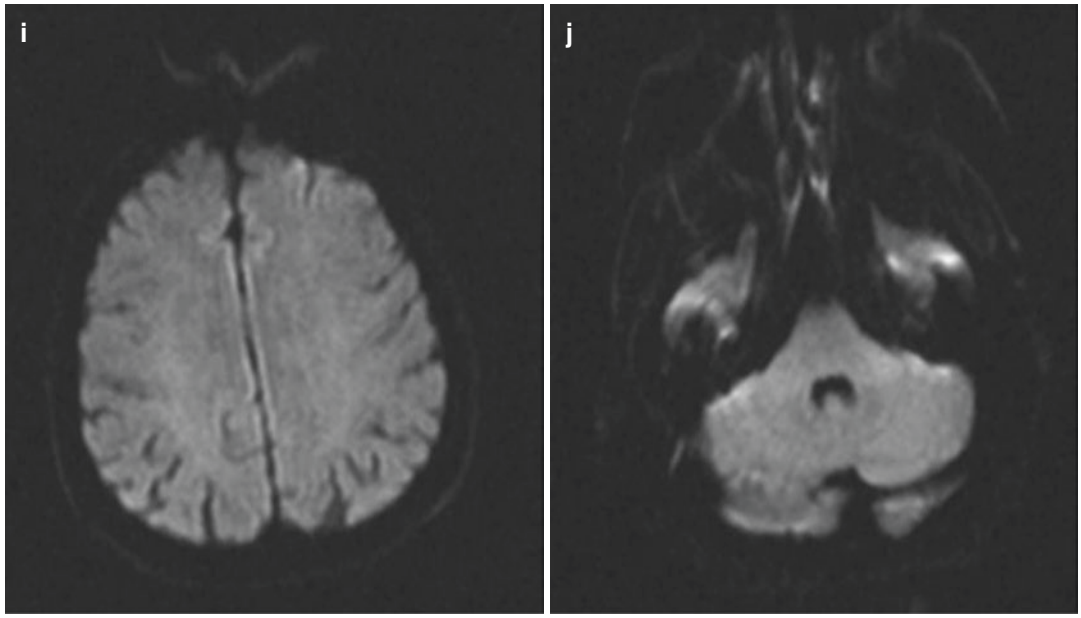


Fig. 26.2 (continued)

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

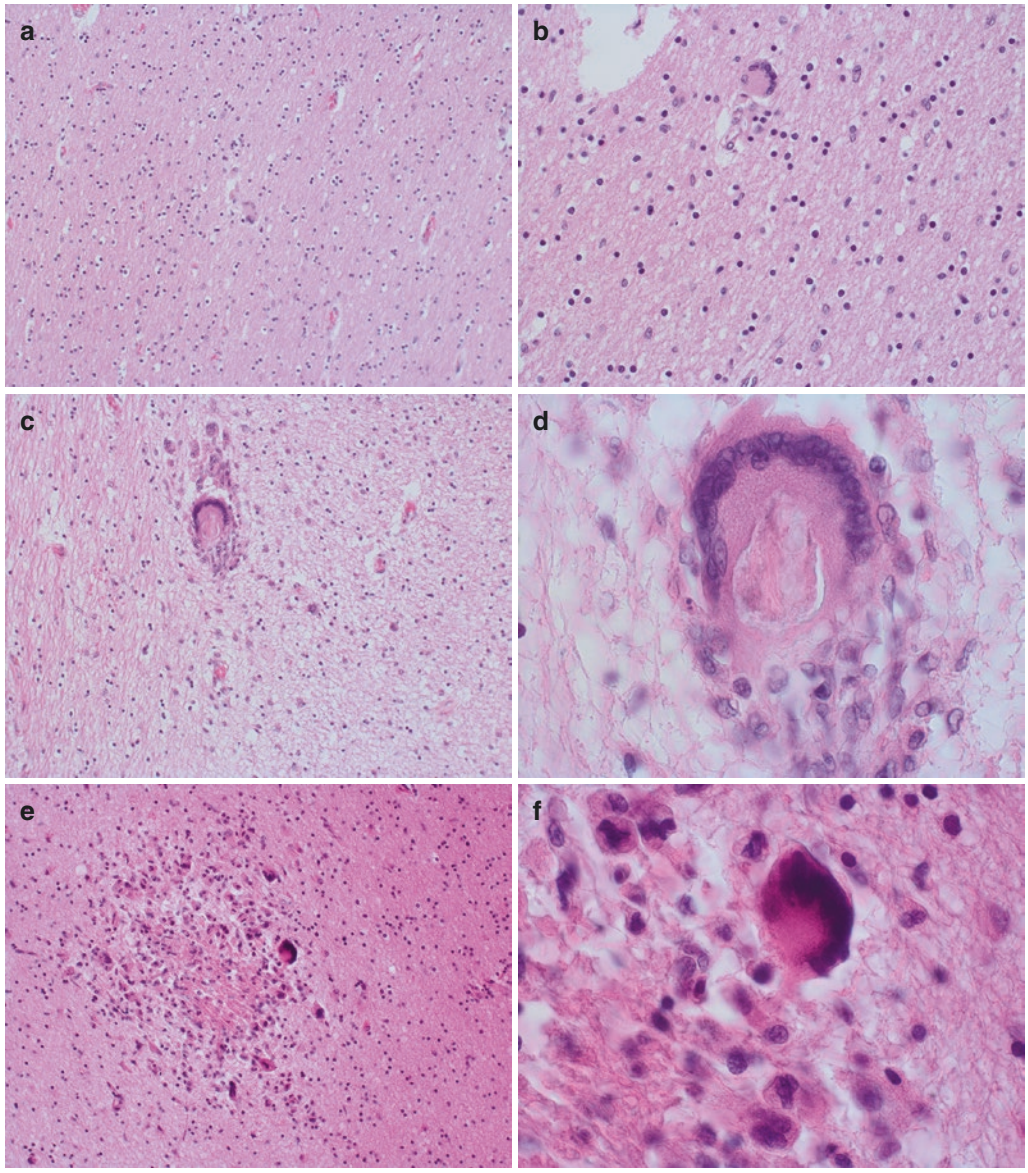


Fig. 26.3 HIV-1-encephalitis: multinucleated giant cells (**a**–**i**) (**a**–**h**: Stain: H&E; **i**: Stain: cresyl violet). HIV-1 antigen shown in a small gliomesenchymal nodule (**j**: stain: immunohistochemistry for p24)

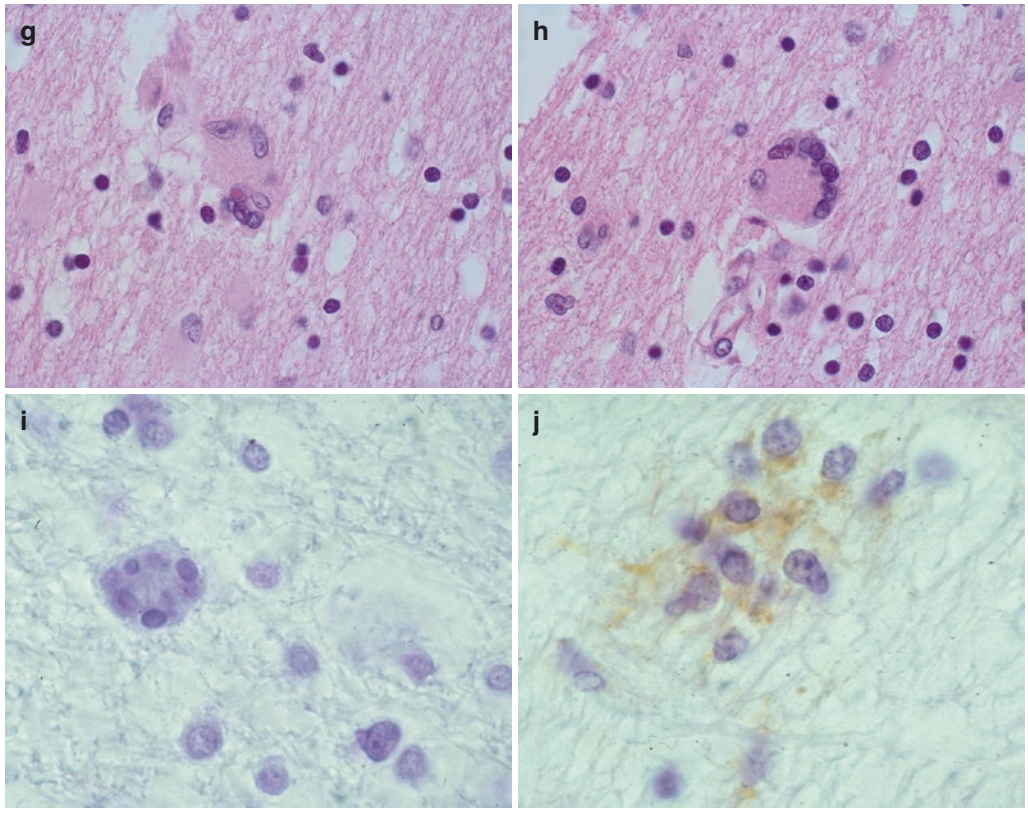


Fig. 26.3 (continued)

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.

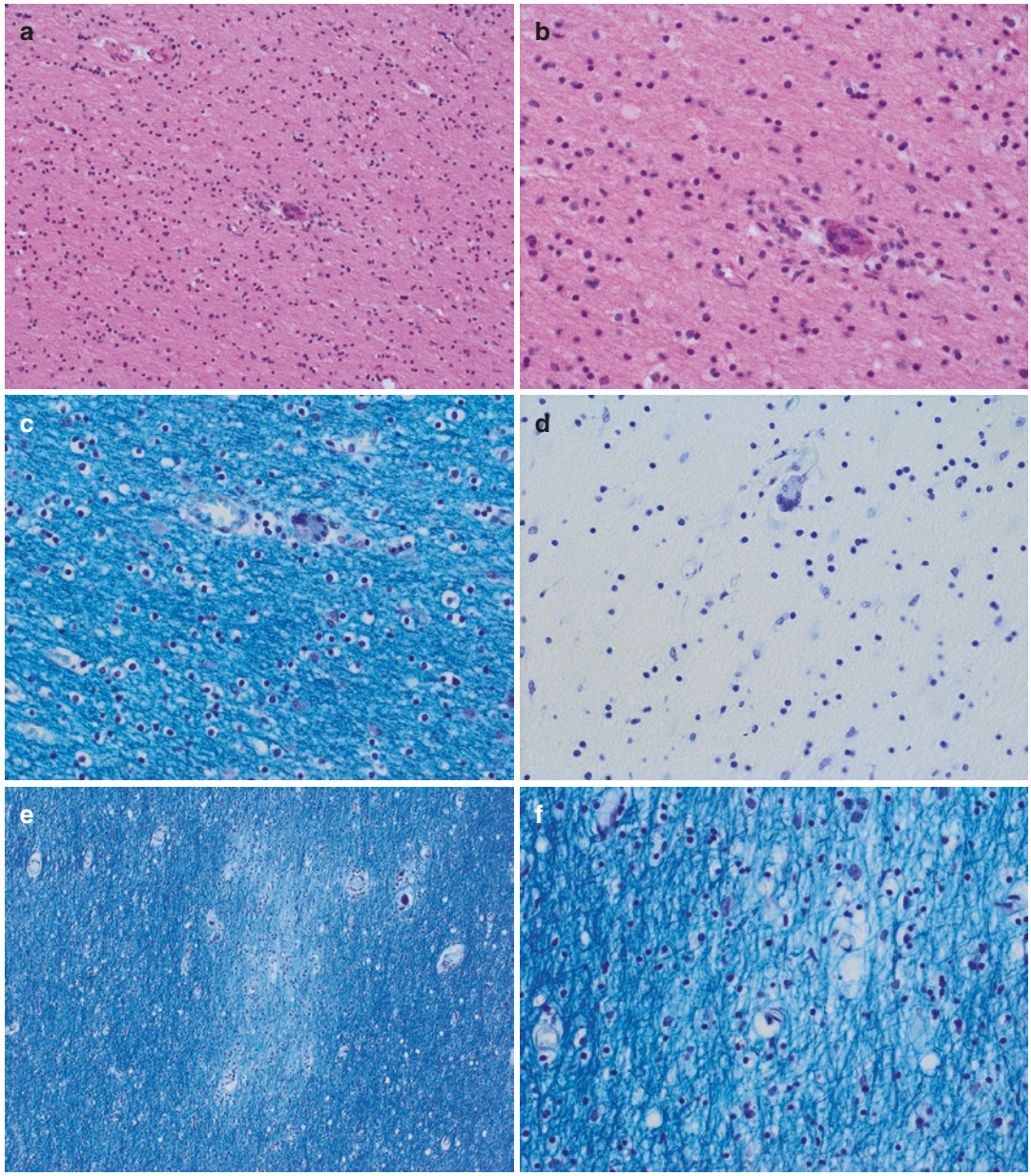


Fig. 26.4 HIV-leukoencephalopathy: presence of multinucleated giant cells in the white matter (**a**, **b**: H&E, **c**: LFB, **d**: cresyl violet) and myelin pallor loss (**e**–**j**)

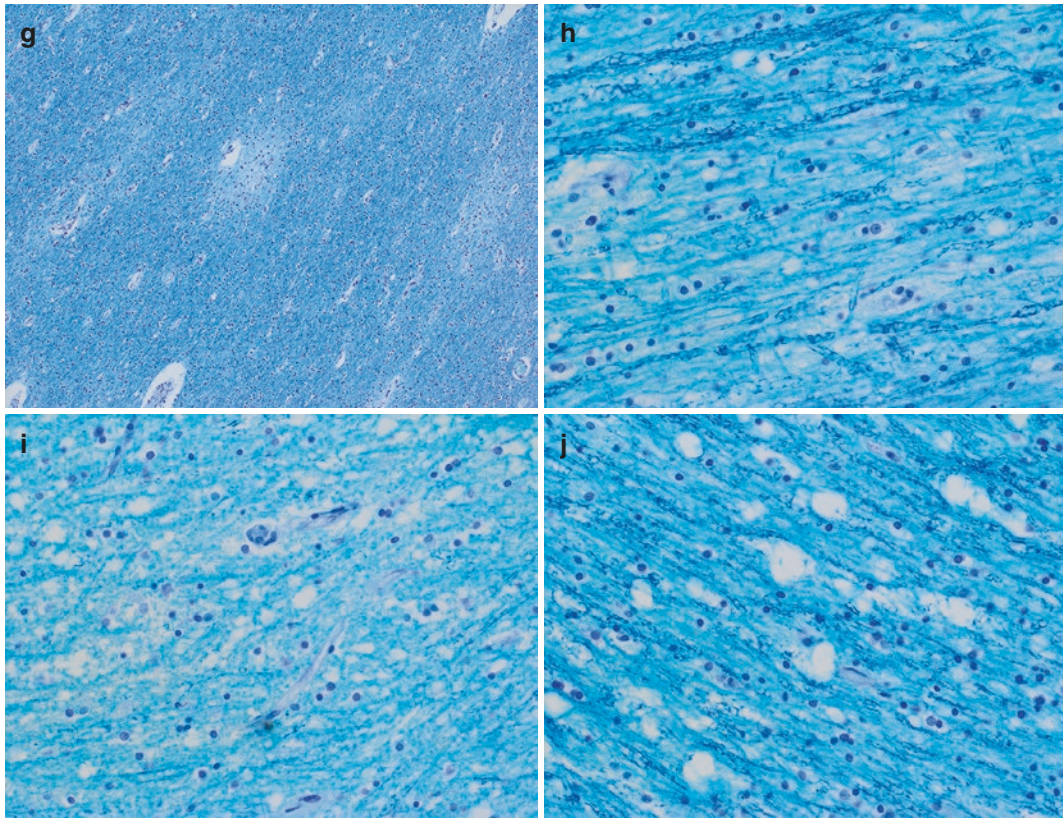


Fig. 26.4 (continued)

- 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

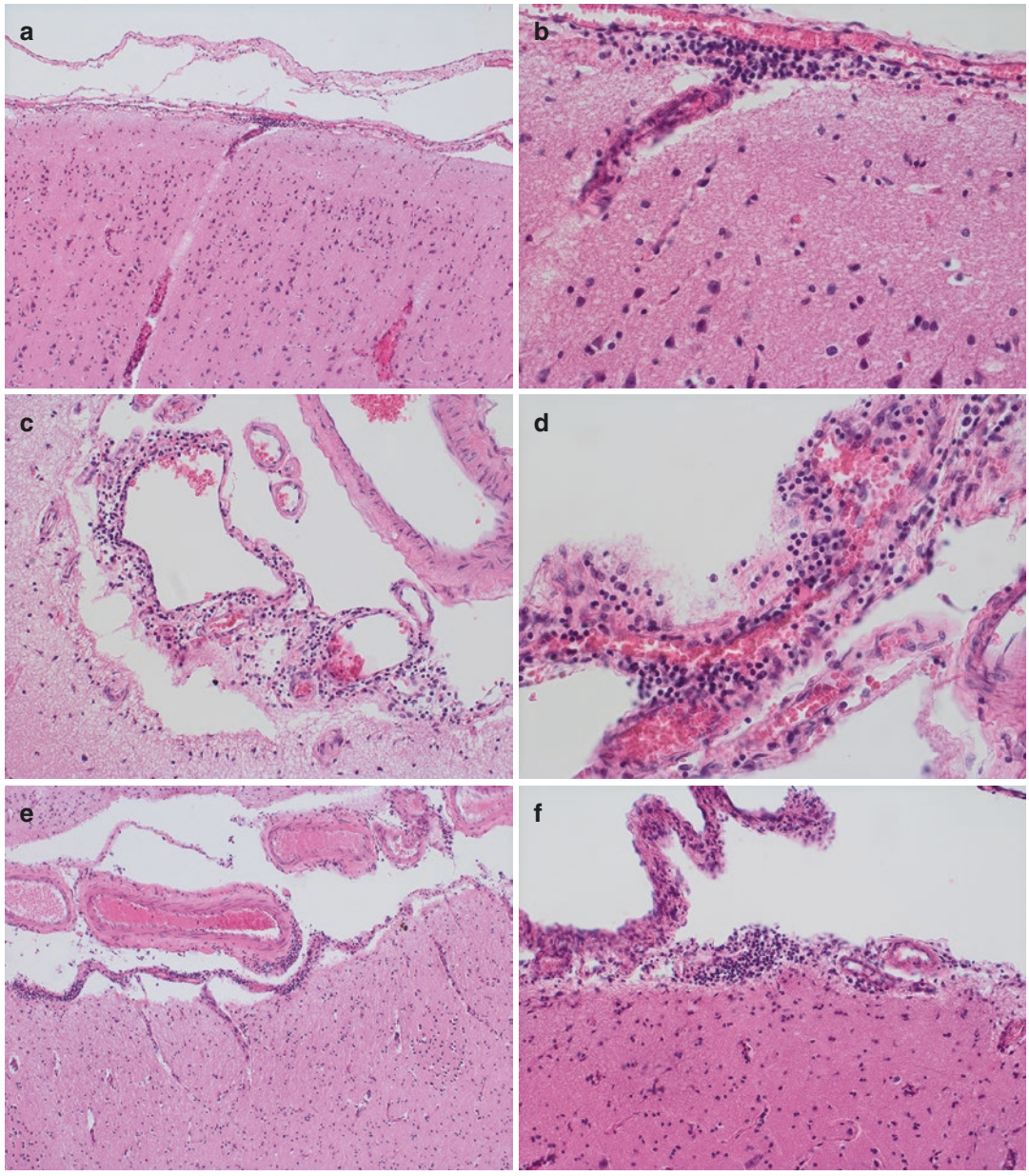


Fig. 26.5 Meningeal lymphocytic infiltrates (**a**–**f**: Stain: H&E). Perivascular lymphocytic infiltrates (**g**–**j**: Stain: H&E)

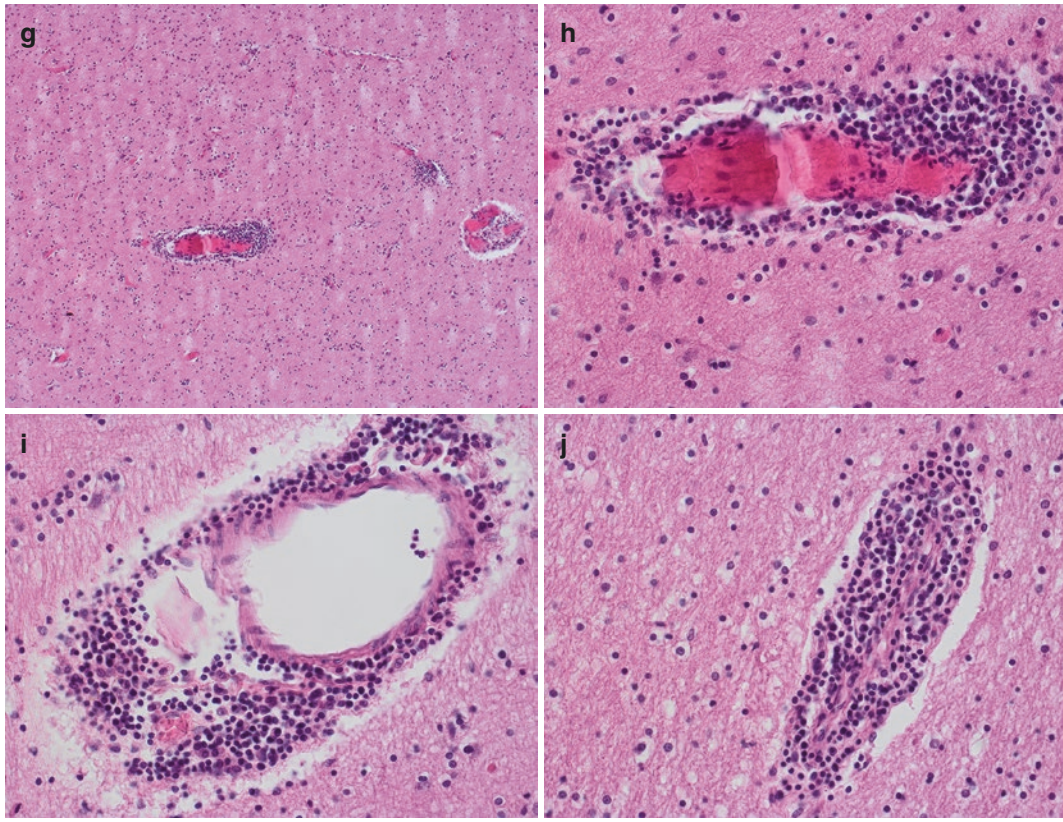


Fig. 26.5 (continued)

  - 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).

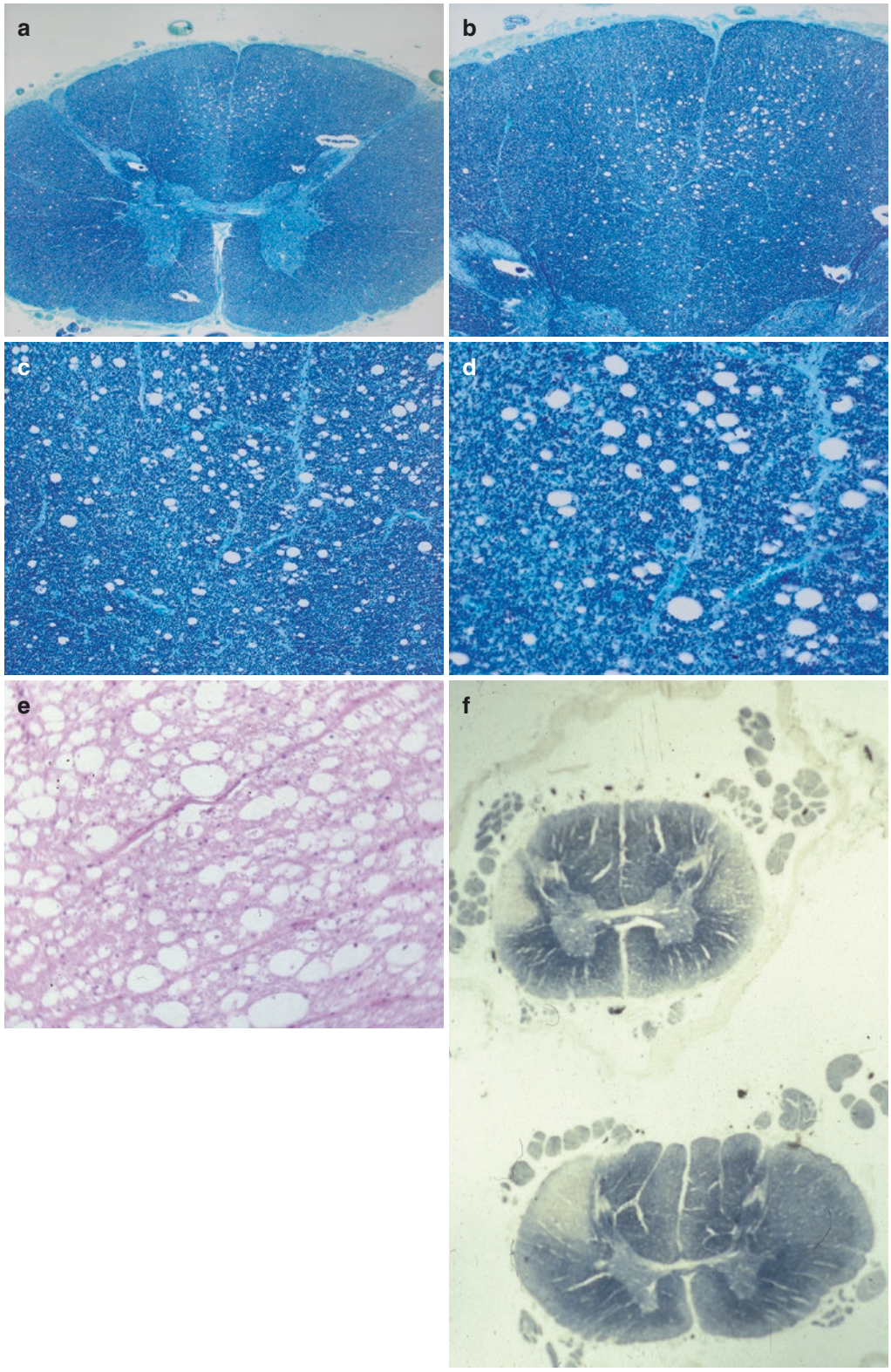


Fig. 26.6 Spinal cord showing vacuolar myelopathy of the dorsal tracts (**a**–**d**: stain LFB, **e**: stain H&E, **f**: stain: Woelcke's myelin stain)

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)		*n*	HIVE	HIVL	CMV	PML	TOXO	LYM
Gray et al. (1988)	Pre-HAART	40	37.5	Nip	20.0	5.0	47.5	2.5
Gray et al. (2003)[a]	HAART	23	17.4	Nip	8.7	17.4	13.0	13.0
Jellinger et al. (2000)	Pre-HAART	352	8.5	4.3	18.5	7.1	22.2	8.5
	HAART	98	8.0	5.0	11.0	5.0	8.0	6.0
Langford (2003)	Pre-HAART	62	25.8	Nip	16.1	6.4	6.4	19.3
	HAART	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

[a]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 • Mild cognitive decline	• Fulminant decline in mental status over days with brain swelling and inflammation
PML with JCV	• Subacute focal neurologic deficits	• Focal areas of contrast enhancement and swelling
Varicella-zoster virus	• Shingles • CNS vasculitis	• Strokes without skin rash
Cytomegalovirus	• Retinitis • Cerebritis	• Vasculitis
Epstein-Barr virus	• CNS lymphoma	• Optic neuropathy
Tuberculosis	• Meningitis	• Cerebral infarcts • 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 Sequalae 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 astrocytosis
- 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
  - CA^{2+} 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 Ccll 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

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		↓	

Therapeutic effects on involved pathways are illustrated in Table 26.15.

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.

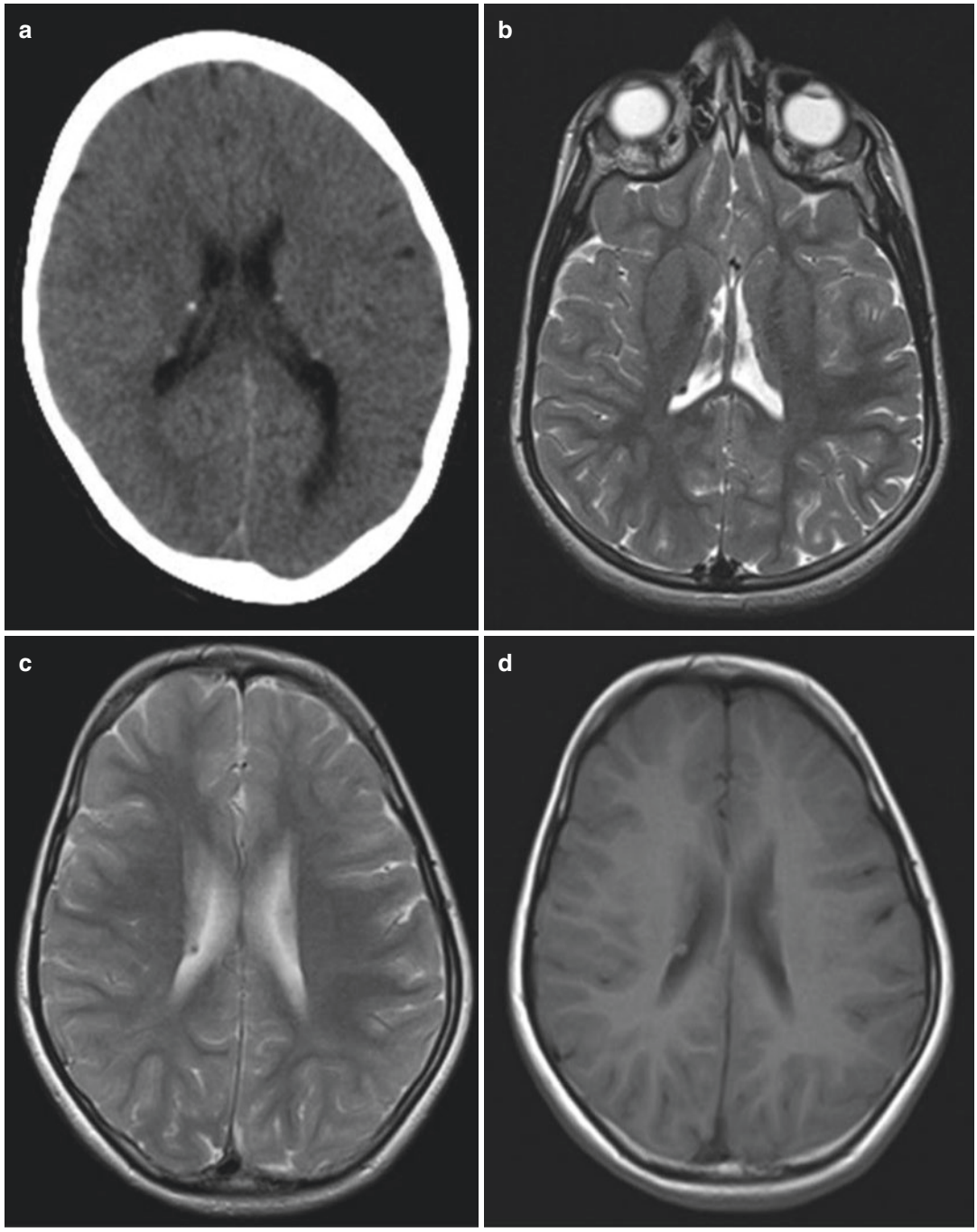


Fig. 26.7 Cytomegalovirus (CMV) infection: periventricular calcifications after perinatal CMV. CT non-contrast (**a**), T2 (**b**, **c**), T1 (**d**), T1 contrast (**e**), T2∗ (**f**)

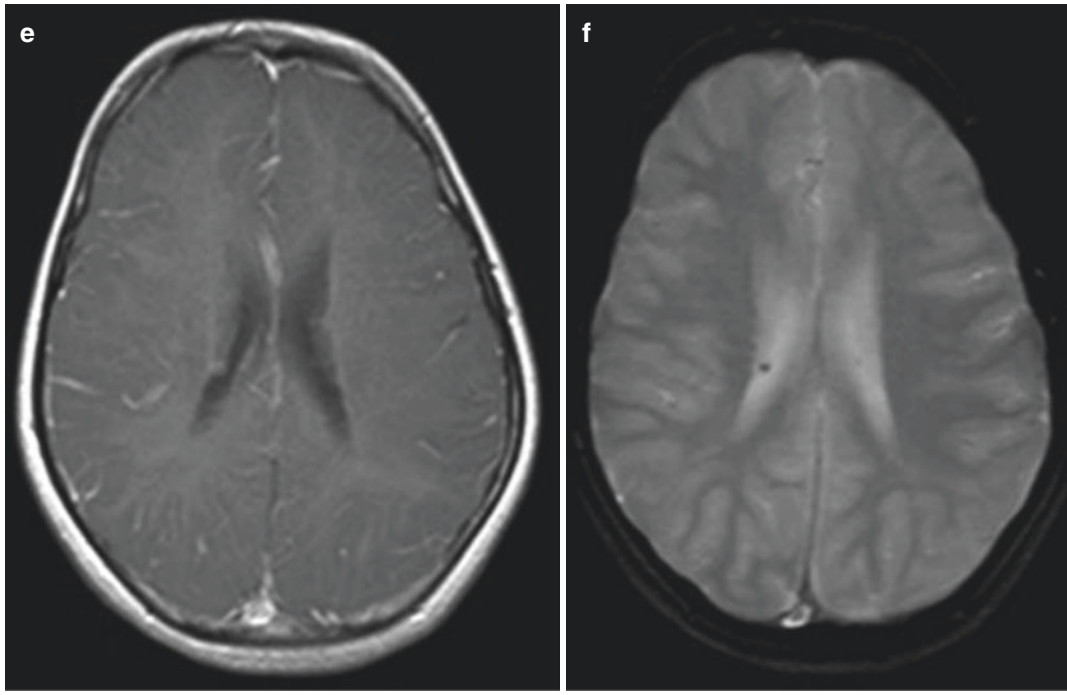


Fig. 26.7 (continued)

26.11 Progressive Multifocal Leukoencephalopathy (PML)

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

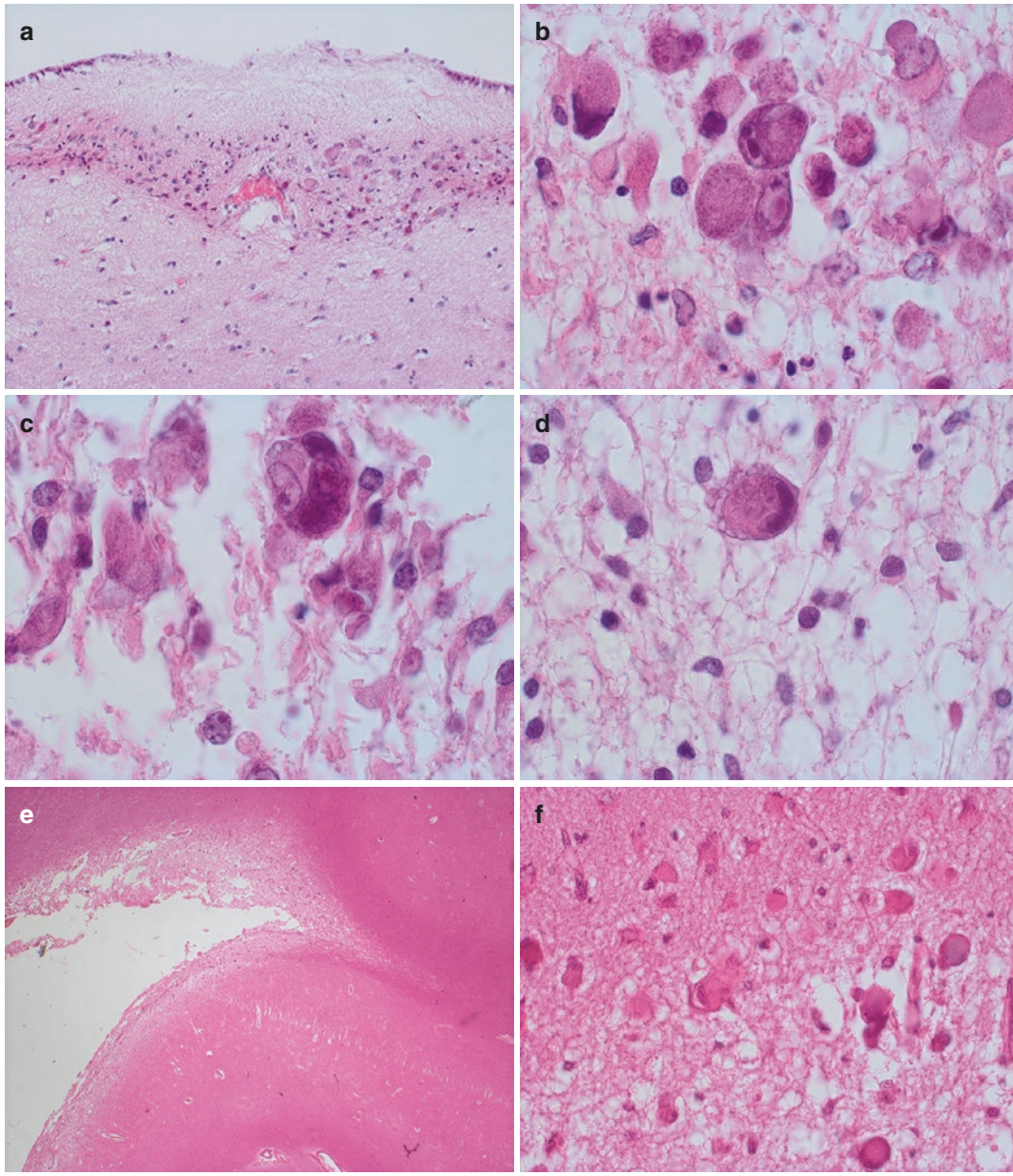
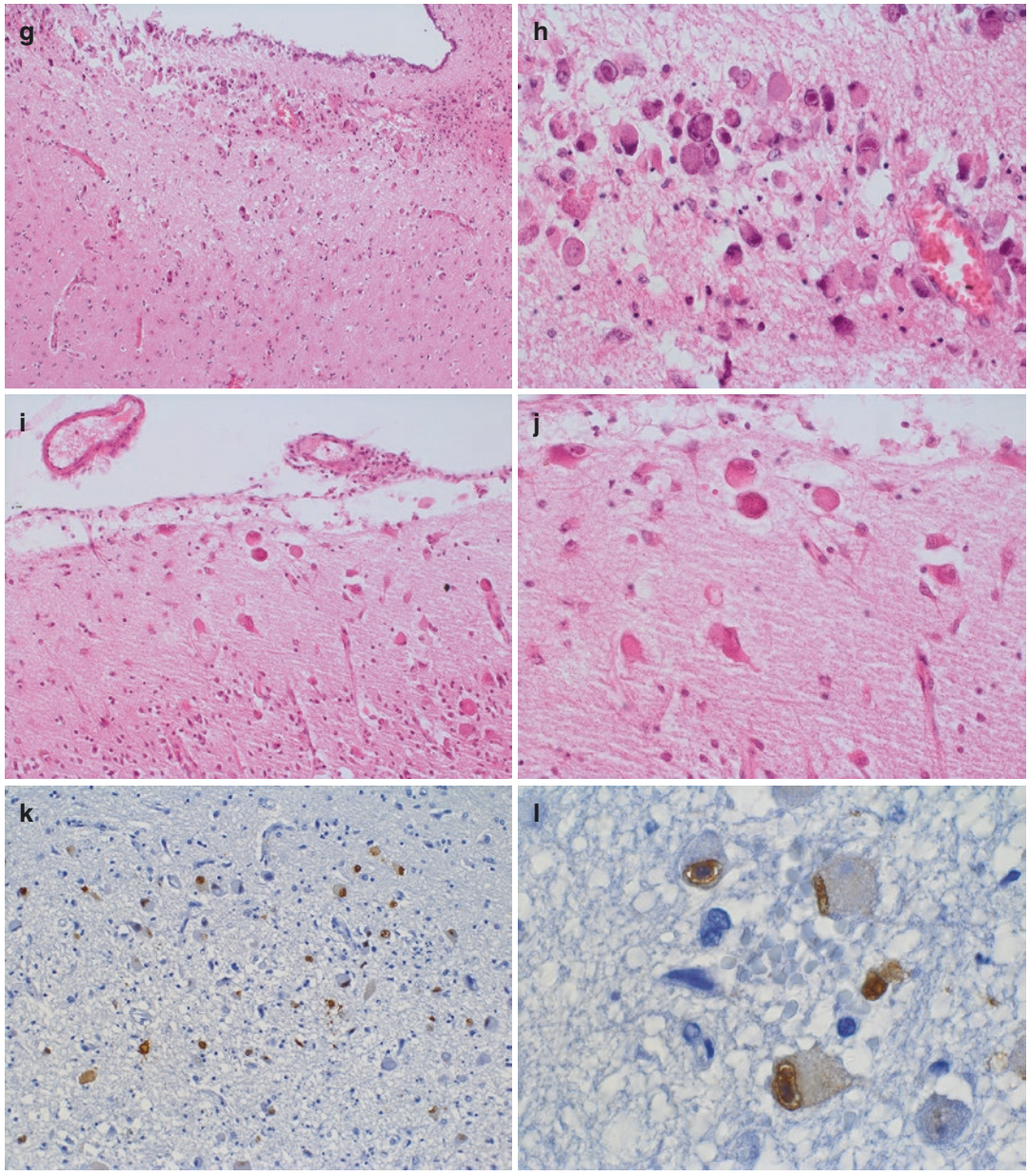


Fig. 26.8 Cytomegalovirus (CMV) infection (**a**–**n**). Cells with inclusion bodies (**a**–**j**) (stain: H&E); cytomegalic cell with inclusion body (**k**–**n**) (stain: immunohistochemistry for CMV)



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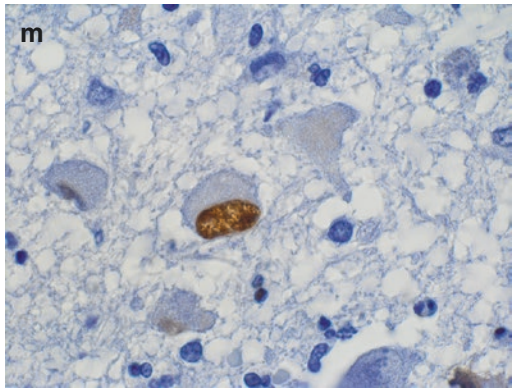

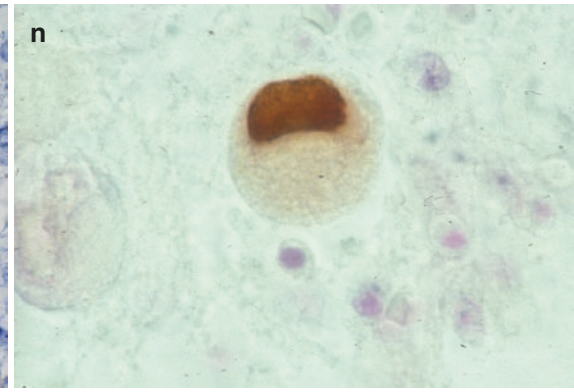

Fig. 26.8 (continued)

  - 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.

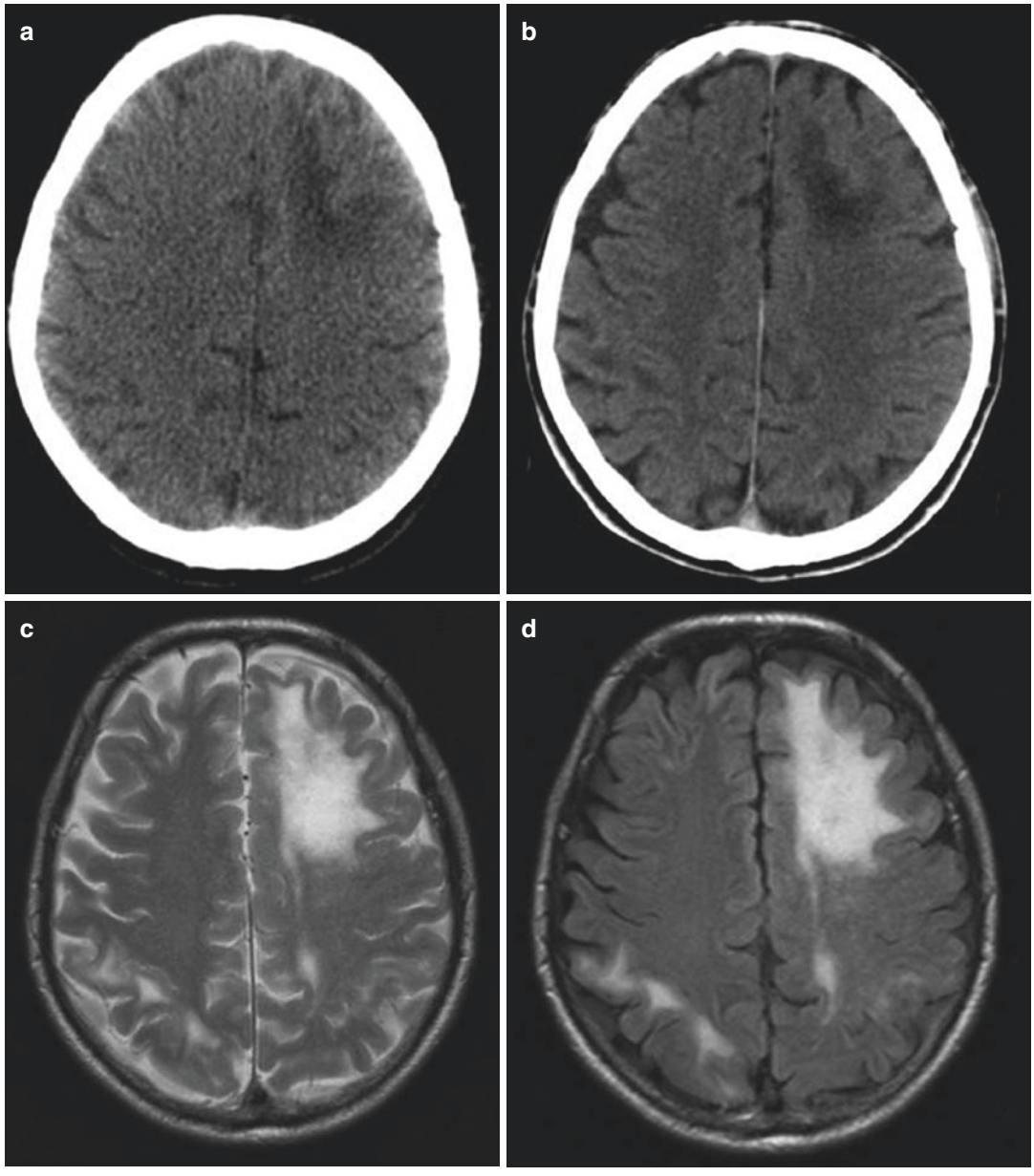

Fig. 26.9 Progressive multifocal leukoencephalopathy (PML). CT non-contrast (**a**), CT contrast (**b**), T2 (**c**), FLAIR (**d**), T1 (**e**), T1 contrast (**f**), DWI (**g**), ADC (**h**)

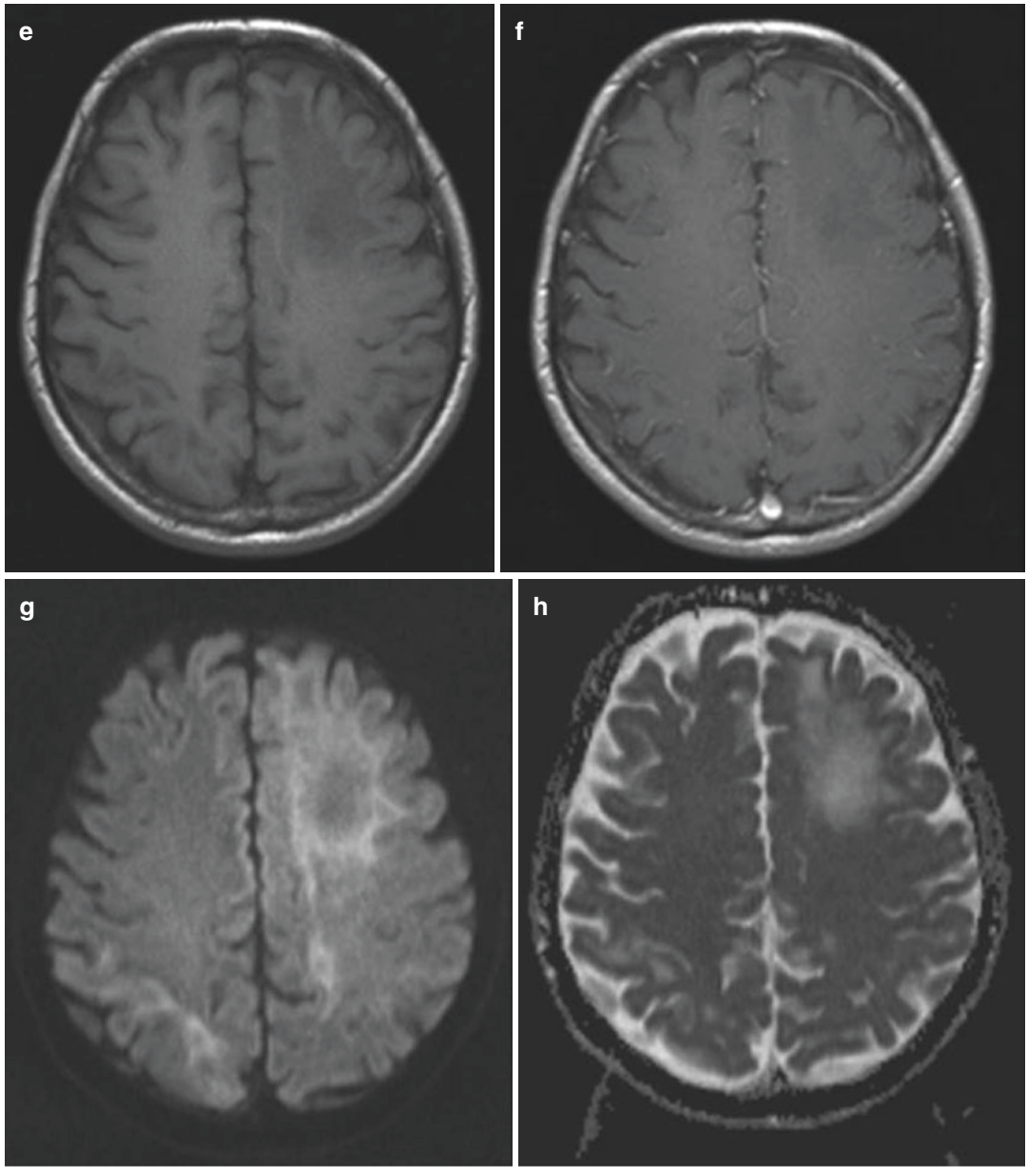

Fig. 26.9 (continued)

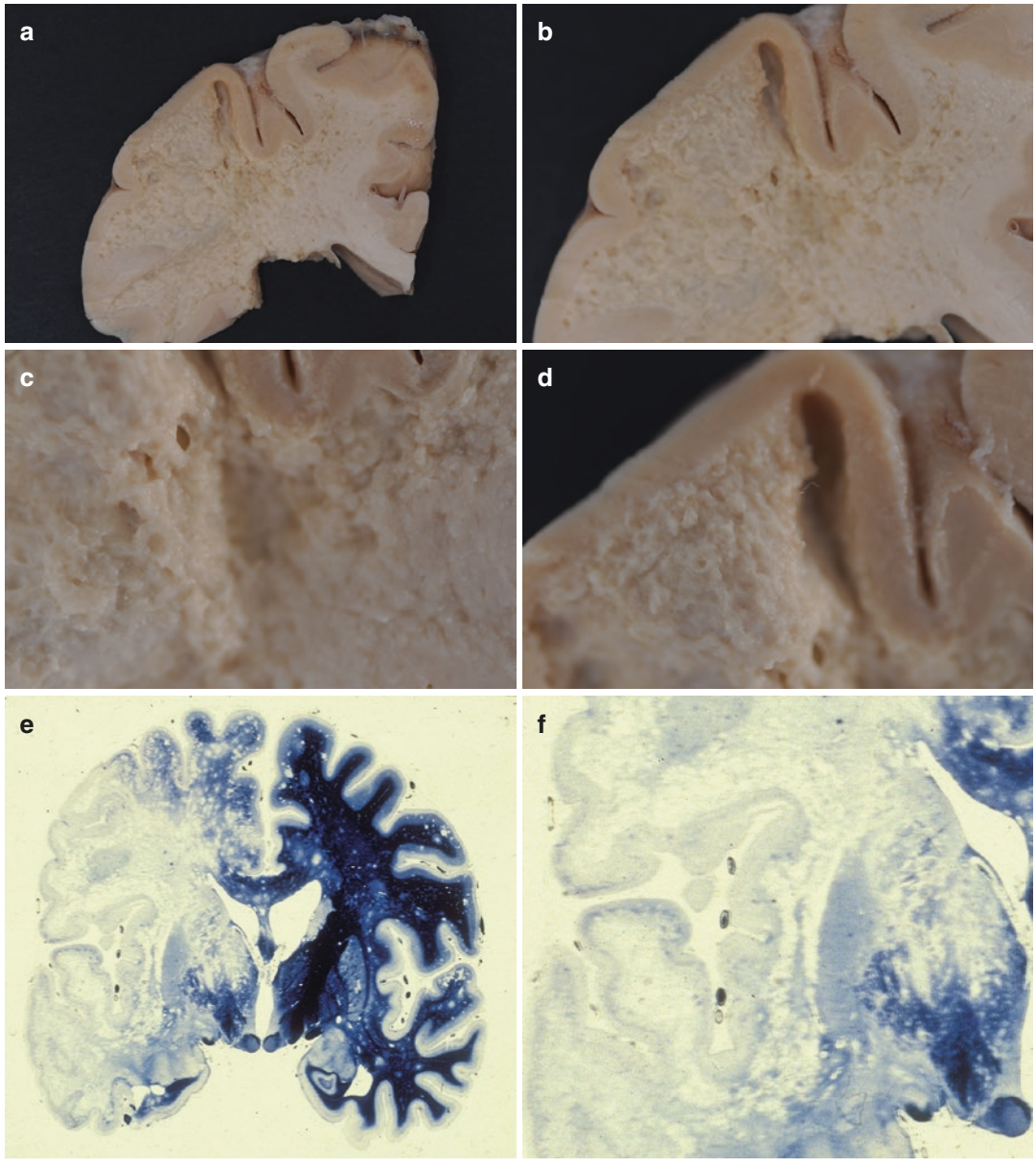

Fig. 26.10 Progressive multifocal leukoencephalopathy: macroscopically, the white matter shows a moth-eaten appearance (**a**–**d**). The myelin of the left hemisphere is completely lost (stain: Woelcke's myelin stain) (**e**, **f**). Histology shows degeneration of myelin accompanied by the presence 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

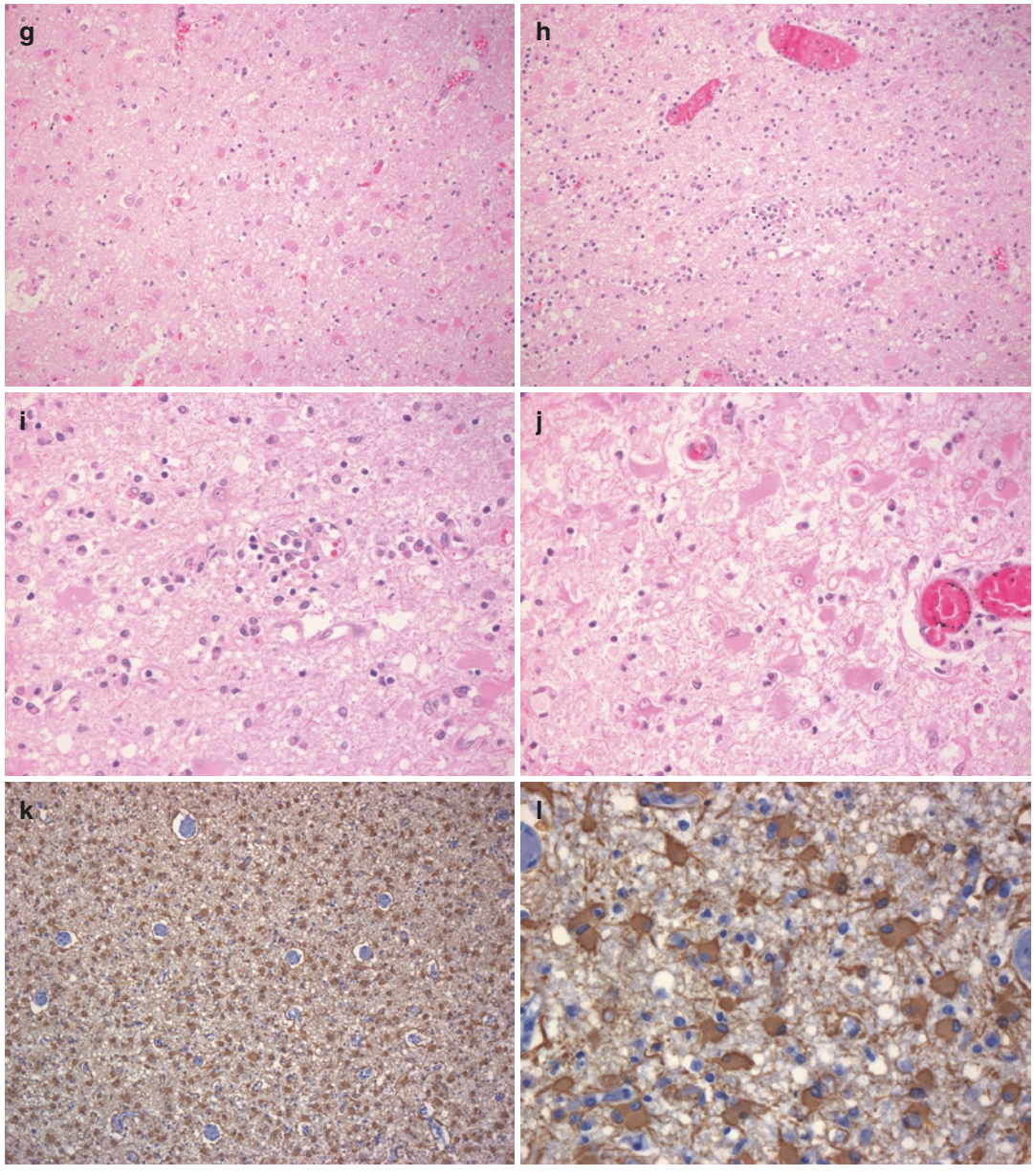

Fig. 26.10 (continued)

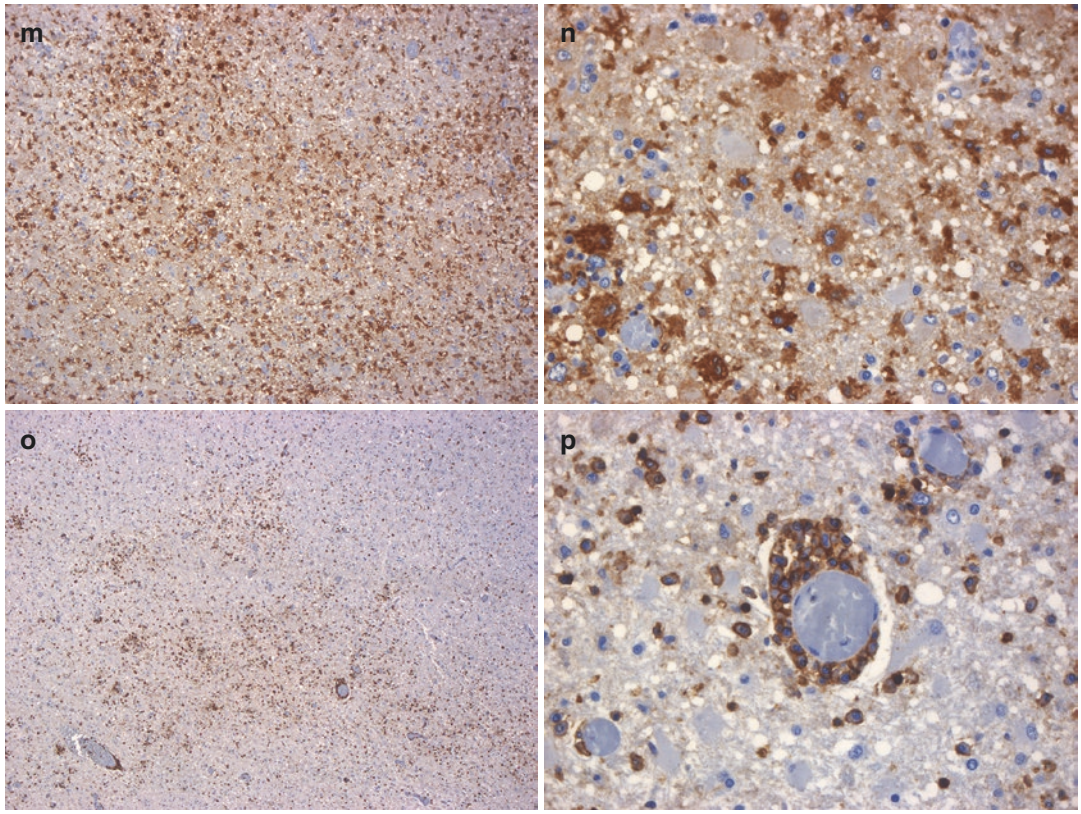

Fig. 26.10 (continued)

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 Nauropathology

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

Table 26.16 Drug-induced cases of PML (Bauer et al. 2015) reproduced with kind permission by Springer Nature

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
Leflunomid	Autoimmune disease
Methotrexate	Cancer/autoimmune disease
Mycophenolate	Transplantation/autoimmune disease
Natalizumab	Autoimmune disease
Rituximab	Cancer/autoimmune disease
Tacrolimus	Transplantation

  - 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.

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. • Lesions predominantly affect the deep and subcortical white matter and can expand into the cortical gray matter. • Intracortical lesions are present. • Spinal cord and optic nerves are spared.	• Lesion distribution is similar to PML.	• Lesions can be found in white and gray matter, but are often found in a periventricular position. • Unlike in PML, lesions can be found in spinal cord and optic nerves.
Neuropathological features		
• Demyelinating lesions reveal oligodendrocytes with enlarged nucleus and cytoplasm. The nucleus may show inclusion bodies. • Oligodendrocytes are mostly found on the border of the lesion. • Subpial lesions are absent. • Remyelination is absent. • Within the demyelinated lesions, large (the so-called bizarre) astrocytes are found. • Lesions contain low to moderate numbers of T-cells. • few B-cells • few plasma cells • Activated microglial cells and macrophages are present in high numbers.	• Like PML, lesions contain infected cells, especially on the border. • In small samples (biopsies) however, infected cells may be low in numbers or may be absent. • Subpial lesions are absent. • Remyelination is absent. • Like in PML, lesions contain bizarre astrocytes. • Lesions contain extremely high numbers of T-cells and B-cells. • Numbers of microglia and macrophages do not differ with PML.	• Unlike in PML, lesions are perivenous and show finger-like extensions (i.e., Dawson fingers). • Subpial lesions are present and are specific for MS. • Lesions can show variable remyelination. • Lesions can show activated astrocytes and/or astrogliosis. • Extremely large bizarre astrocytes are absent. • Lesions contain moderate to high numbers of T-cells. • Low numbers of B-cell • Low numbers of plasma cells • Numbers of (foamy) macrophages do not differ from PML or PML–IRIS.
MRI features		
• Usually larger than 3 cm • Lesions always start in subcortical regions, probably related to a high blood flow. • Borders are sharp towards the GM and ill-defined towards the WM. • In first scans of 28% of patients, lesions extend in deep GM. • 23–57% of (HIV-associated) cases have contrast-enhancing lesions. • T1 lesions are mostly hypointense. • Diffusion-weighted images are always hyperintense. • Punctate T2-hyperintense lesions can be found in the immediate vicinity of the main lesion.	• Usually larger than 3 cm • Lesions always start in subcortical regions, probably related to a high blood flow. • Borders are sharp towards the GM and ill-defined towards the WM. • In first scans of 71% of patients, lesions extend in deep GM. • 86% of PML–IRIS cases have contrast-enhancing lesions. • T1 lesions may have hyperintense rims. • Diffusion-weighted images are always hyperintense. • Punctate T2-hyperintense lesions can be found in the immediate vicinity of the main lesion.	• All MRI features seen in PML and/or PML–IRIS also can be seen in MS. • However, MS lesions usually are and stay smaller in size than in PML or PML–IRIS. • Homogeneous or open-ring enhancing lesions are present in MS but not observed in PML.

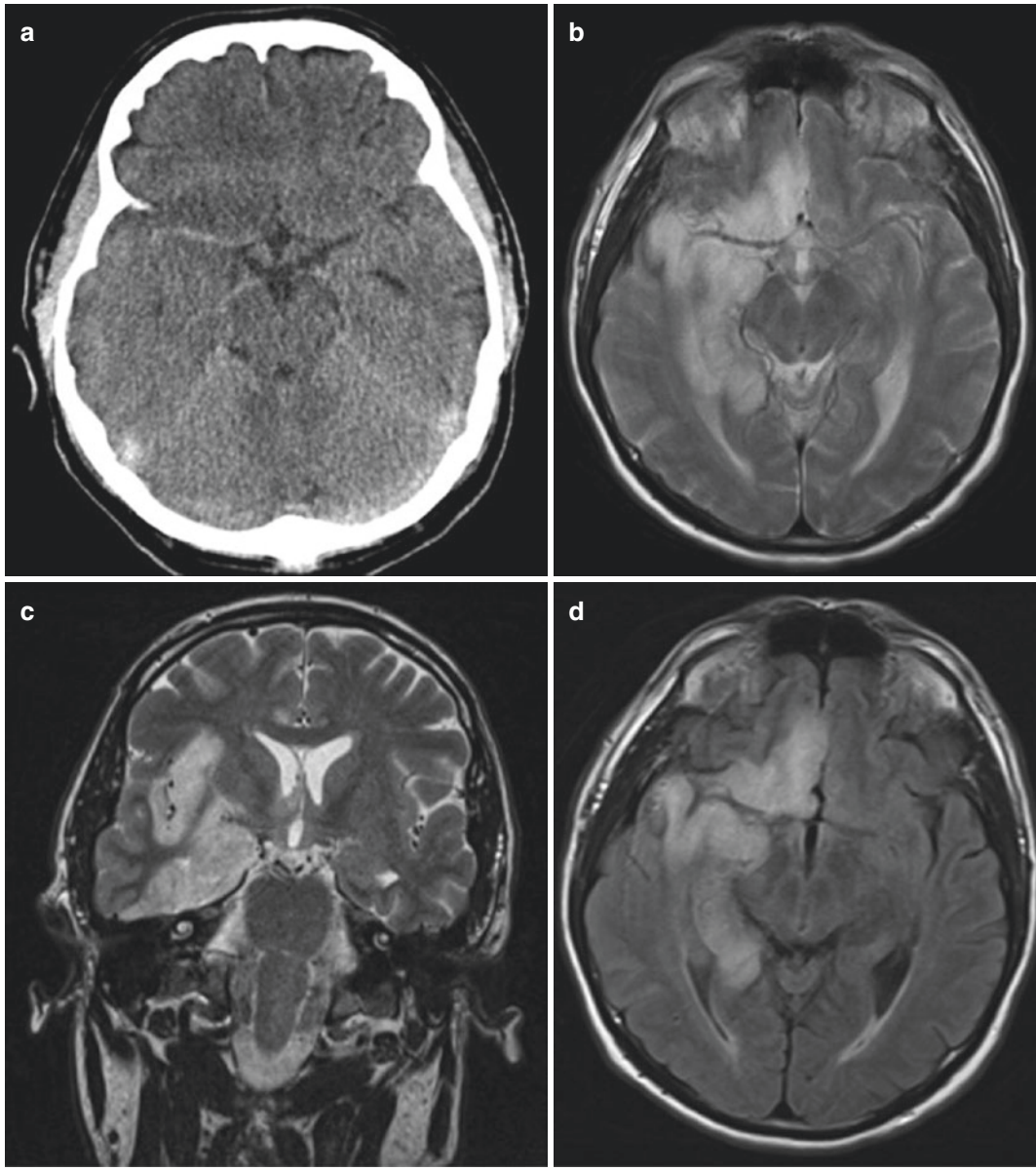

Fig. 26.11 Herpes encephalitis with characteristic involvement of right limbic system, temporal and basal frontal lobe, restricted diffusion and weak enhancement; CT non-contrast (**a**), T2 ax/cor (**b**, **c**), FLAIR (**d**), T1 (**e**), T1 contrast (**f**), DWI (**g**), ADC (**h**)

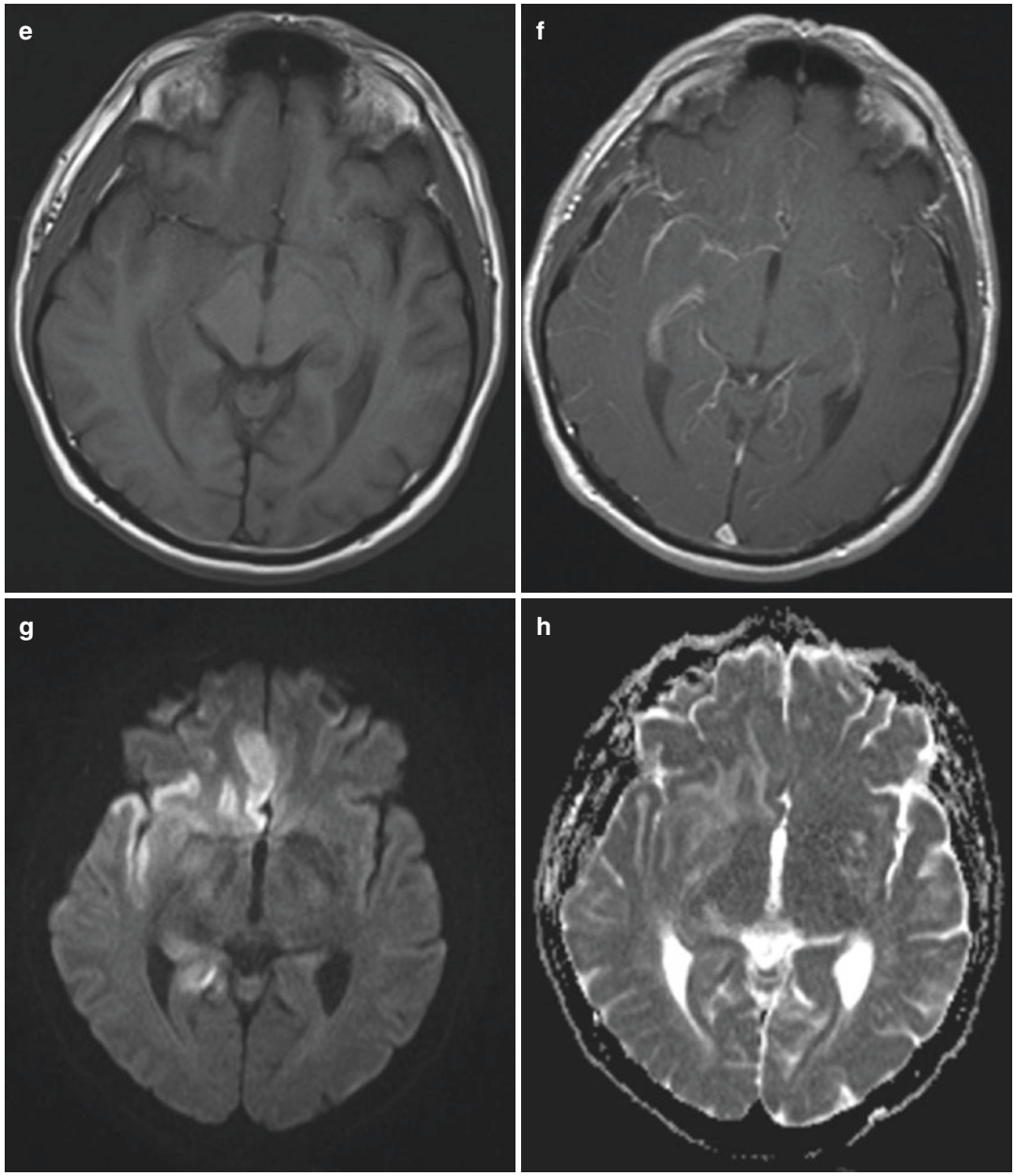

Fig. 26.11 (continued)

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

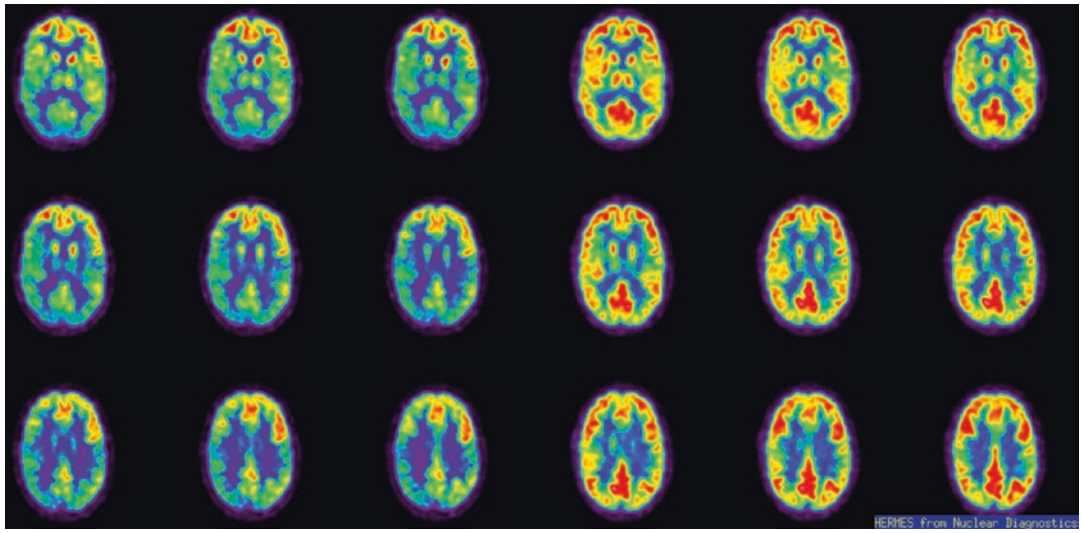

Fig. 26.12 Herpes encephalitis: decreased FDG uptake (left 3 rows) in a patient during the recovery phase of Herpes simplex encephalitis and regular FDG uptake after recovery (right 3 rows)

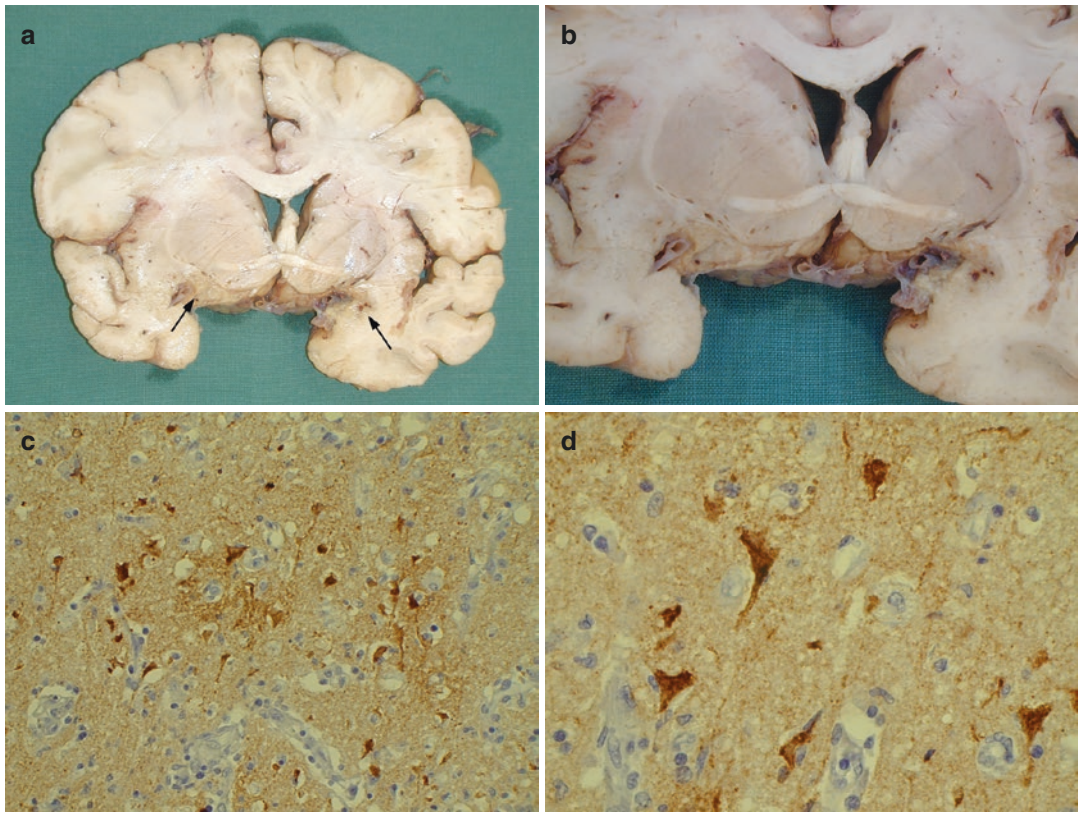

Fig. 26.13 Herpes encephalitis: macroscopically, necrosis is seen in both temporal lobes (arrow) (**a**, **b**). The virus is demonstrated by immunohistochemistry mainly in neurons (**c**, **d**)

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
    - immunosuppression

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

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. • Caribbean • South America
Western equine encephalitis	• Basal ganglia • Thalamus • Brain stem	<5%		• Western and Midwestern USA
St. Louis encephalitis	• Midbrain • Thalamus	<5%	25% of survivors have persistent neurologic disability.	• The USA • Central America • South America
Japanese encephalitis	• Thalamus • Substantia nigra • Brain stem • Spinal cord	Up to 50%	High percentage of survivors have persistent neurologic disability.	• Southeast Asia • Bangladesh • Pakistan
West Nile virus	• Thalamus • Cerebellum • Substantia nigra • Pons • Medulla oblongata • Spinal cord	3–15%	50–75% of survivors have residual neurologic disability.	• Africa • Eastern Europe • West Asia • Middle East • North America
Tick-borne encephalitis		1–10%	Small percentage develop chronic encephalitis with intractable epilepsy and progressive paralysis (Russian spring-summer encephalitis).	

- 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 (Fig. 26.15)
- decreased FDG uptake

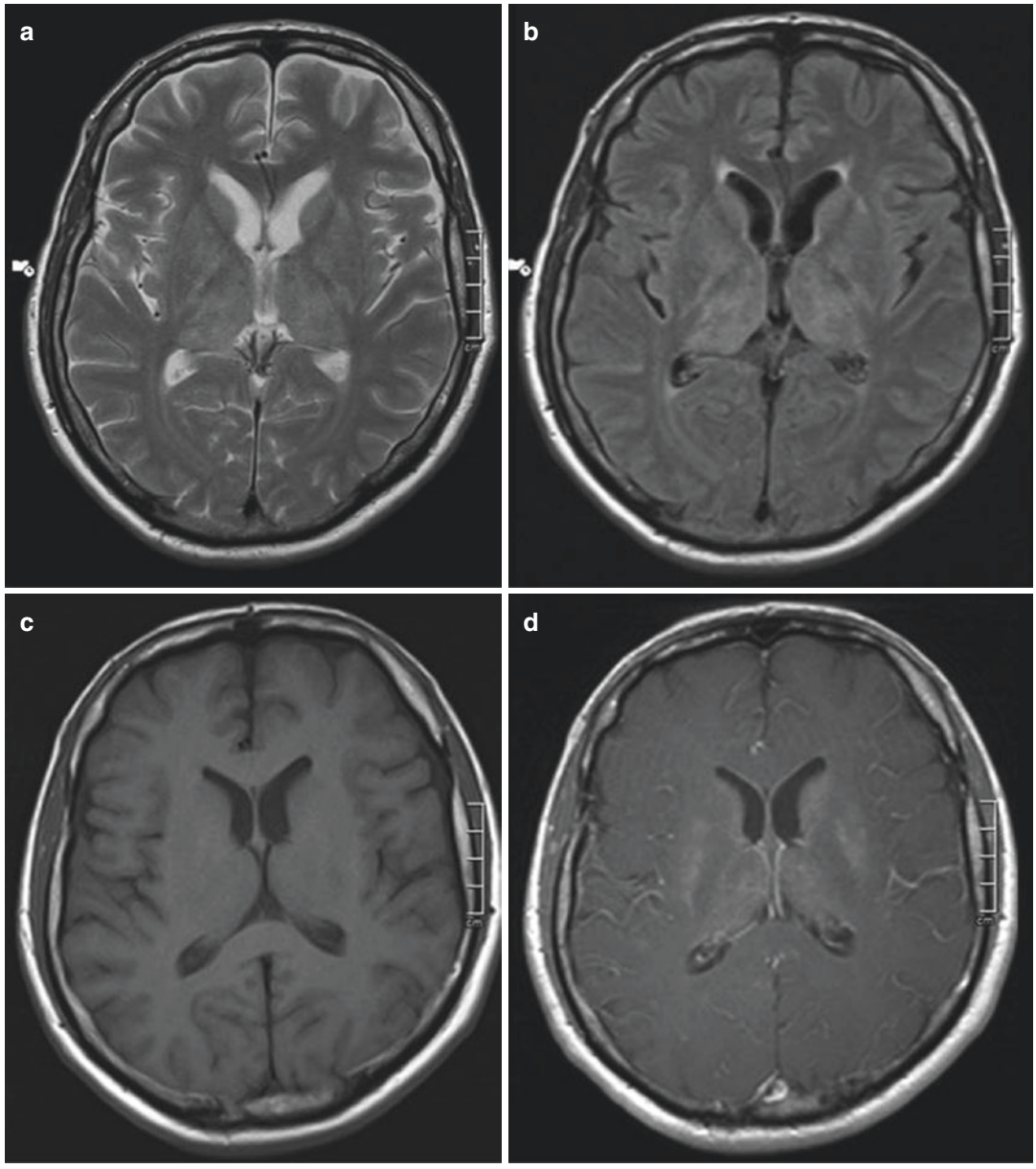

Fig. 26.14 Tick-borne encephalitis with T2-hyperintensity and mild enhancement of thalami and basal ganglia. T2 (**a**), FLAIR (**b**), T1 (**c**), T1 contrast (**d**), DWI (**e**), ADC (**f**)

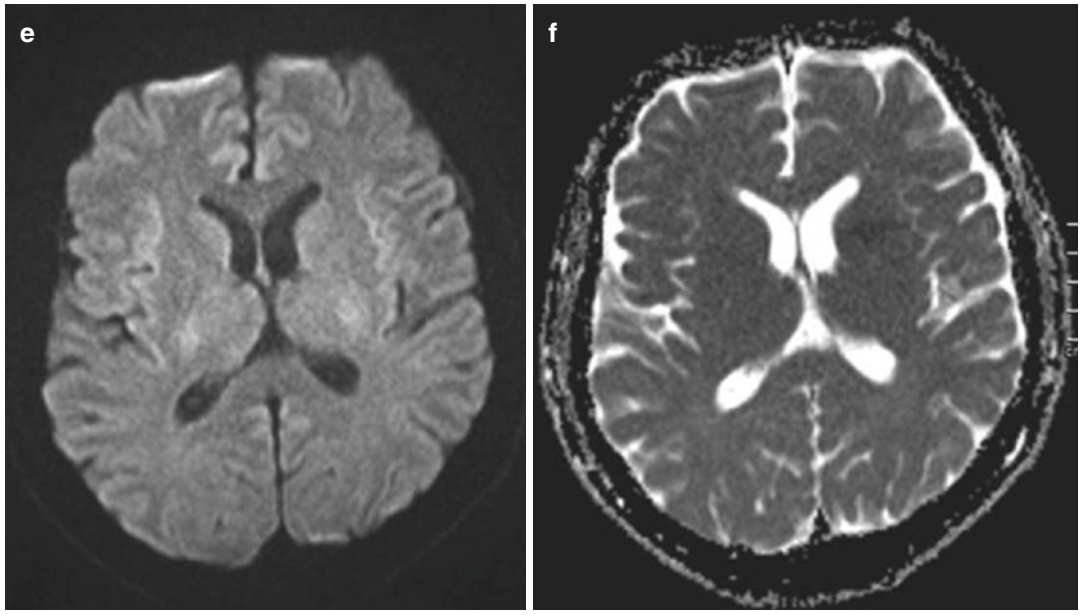

Fig. 26.14 (continued)

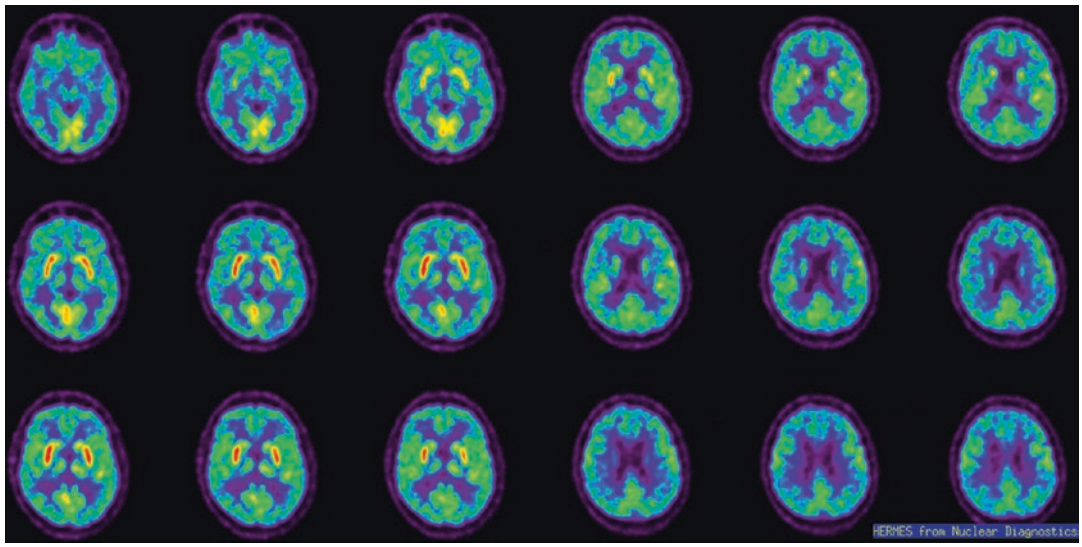

Fig. 26.15 Tick-borne encephalitis: totally decreased FDG uptake in cerebral cortex

26.13.4 Neuropathology Findings

Macroscopic Features
- moderate to sever 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

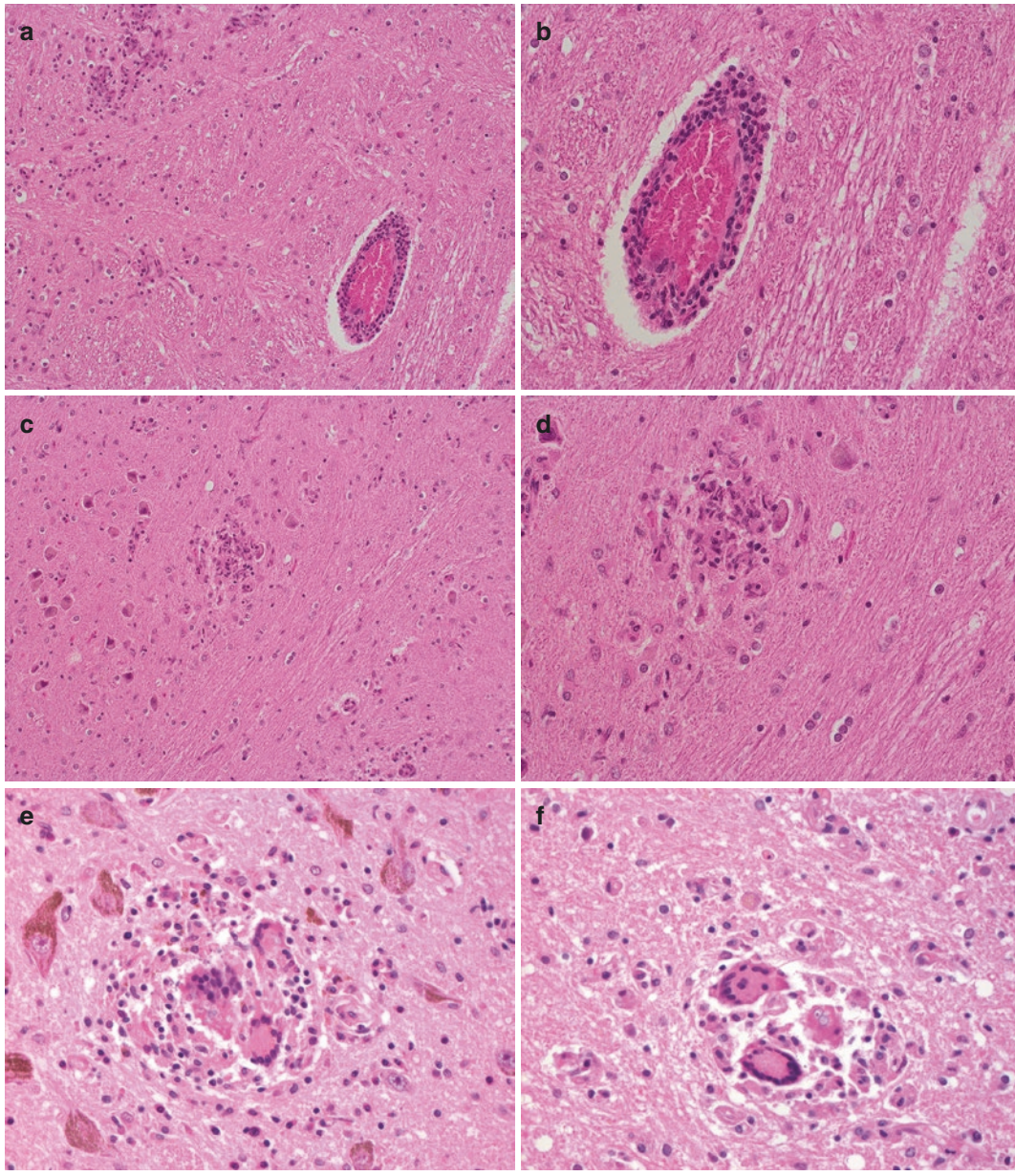

Fig. 26.16 Tick-borne encephalitis: histological examination reveals perivascular lymphocytic infiltrates (**a**, **b**) and the presence of gliomesenchymal nodules (**c**, **d**) which may contain multinucleated giant cells (**e**, **f**). The perivascular infiltrates are mainly made up of CD3-positive 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

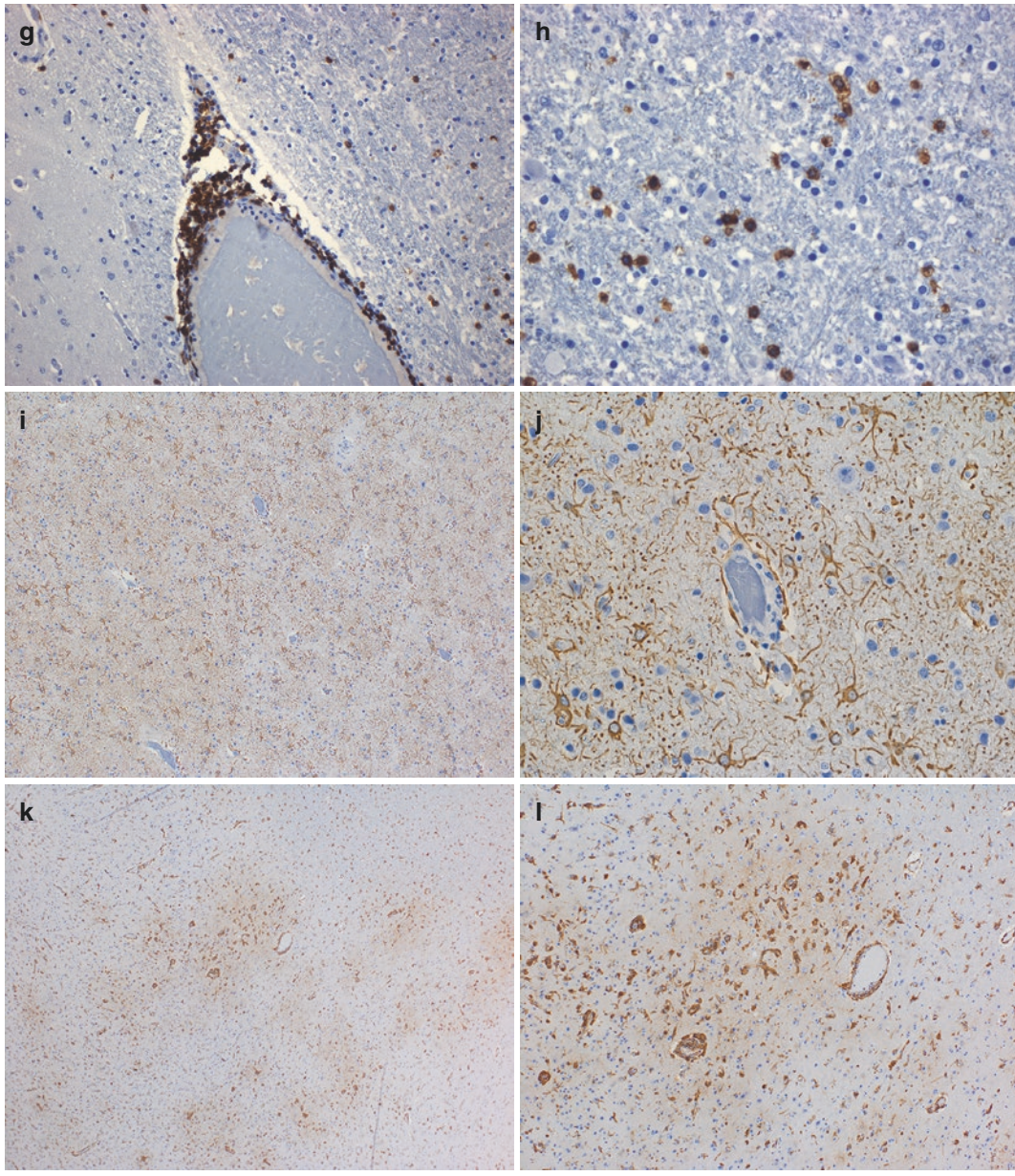

Fig. 26.16 (continued)

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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