# Viral Infections of the Nervous System

7

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## Abbreviations

ADEM, acute disseminated encephalomyelitis; APME, acute postinfectious measles encephalomyelitis; CHIKV, chikungunya virus; CMV, cytomegalovirus; CNS, central nervous system; EBV, Epstein–Barr virus; GCN, cerebellar granule cell neurons; HAART, highly active antiretroviral therapy; HCT, hematopoietic cell transplant; HH6, human herpesvirus- 6; HSE, herpes simplex encephalitis; HSV, herpes simplex virus; IRIS, reconstitution inflammatory syndrome; JCV, JC Virus; JEV, Japanese encephalitis virus; MIBE, measles inclusion body encephalitis; MR, magnetic resonance; MV, measles virus; N.s., nonspecific; PME, primary measles encephalitis; PML, progressive multifocal leukoencephalopathy; PTLD, posttransplant lymphoproliferative disorders; SSPE, subacute sclerosing panencephalitis; TBEV, tick-borne encephalitis virus; VZV, varicella zoster virus; WNV, West Nile virus.

## 7.1 Encephalitis

Encephalitis is an inflammation of the brain parenchyma caused by a specific pathogen or by an antibody-mediated autoimmune mechanism.

Encephalitides with a known etiology account for 30–60 % of the total [1, 2]. Viruses are the most frequent cause of encephalitis in immunocompetent individuals [2], but the clinical phenotype may be nonspecific and similar to the one seen in other forms with an autoimmune pathogenesis. In the early stages of the disease, when an infectious origin is suspected but etiological data are still to be collected, a multidisciplinary collegial assessment of the patient can be very useful, in accordance with the diagnostic and therapeutic work-ups available in literature [3]. Encephalitis caused directly by viruses have, in fact, to be differentiated from those induced by an autoimmune process (referred to as ADEM or post-/parainfectious syndromes), which have a different treatment and carry a different prognosis. Still, there remains a large proportion of cases that cannot be diagnosed on the basis of current knowledge.

The aim of this chapter is to illustrate the information currently available with regard to the main issues in determining the prognosis "quoad vitam" and "quoad valetudinem" of viral encephalitides, and to distinguish clearly, within the same disease, between the forms of immunocompetent and immunocompromised individuals.

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### 7.1.1 Prognosis

Current literature is lacking reliable data regarding the prognosis of viral encephalitides. The few published systematic studies of forms of encephalitis caused by specific pathogens were retrospective and conducted on small samples; as a result, the available data allow only very approximate predictions of survival and functional outcome.

Overall, the prognosis of viral encephalitides depends on three main factors: (1) the neurotropism of the virus, (2) the immune status of the host, and (3) the existence (or otherwise) of an etiological treatment.

### 7.1.2 The Effects of Neurotropism

In the case of viruses with very selective brain neurotropism, such as Herpes Simplex virus (HSV) and Human Herpesvirus- 6 (HH6), the encephalitis presents a rather stereotypic phenotype. Conversely, other viruses, such as varicella zoster virus (VZV) and cytomegalovirus (CMV), whose mechanism of action is linked to either a vasculitis or an ependymal damage, cause multifocal brain and spinal cord lesions whose distribution is unpredictable.

Regardless of the causative agent, the prognosis is linked to the occurrence of two important and mutually independent events: epileptic seizures and myelitis. The event of seizures or status epilepticus during acute infection can significantly affect the patient's chances of survival and the persistence of residual deficits, as well as the quality of life in the long term. All the herpes viruses, but HSV and HH6 in particular, which electively target the temporal lobe and the limbic system (Fig. 7.1), are highly epileptogenic, and the seizures are often drug-resistant. Myelitis is a complication that can impact greatly on functional outcome. Although it is almost always possible, the chances of it occurring are much higher for viruses such as VZV, West Nile (WNV), and enteroviruses. The enteroviruses and WNV, for example, are known to affect the anterior horn cells, causing generally irreversible flaccid and amyotrophic paralysis.

### 7.1.3 The Immune Status of the Host

The patient's immune status is a fundamentally important aspect that must be taken into consideration from the very early stages of the disease, because it will help to indicate the set of aetiologies within which the patient's condition can most likely be framed.

Immunodeficiency occurs in four main clinical situations: HIV infection, cancer, bone marrow and organ transplants, and immunomodulatory therapies. Old age has to be considered a condition of immune depression, per se. In all the aforementioned conditions, the nervous system is particularly vulnerable both to opportunistic infections and to infections that commonly affect immunocompetent individuals.

The relations between immunodeficiency, underlying disease, and neurotropism of viruses are highly complex. Some opportunistic infections are known to occur only in a specific setting of immunosuppression, or in a specific phase of a given disease. Still, in only a few select cases has the experience of recent years been translated into accurate definitions of the risk factors, clinical and biological profiles, survival rates, and functional outcomes associated with a given form. To date, the best defined models are those of HH6 limbic encephalitis in posttransplant patients and progressive multifocal leukoencephalopathy (PML) in HIV infection and treatment with monoclonal antibodies, having a very different prognosis in the two settings.

Regarding the characteristic of the host that can adversely affect prognosis—besides age, a history of cancer and immunosuppressive treatments [4]—the presence of cerebral edema, coma, status epilepticus, thrombocytopenia, and the need for mechanical ventilation have also been reported [4, 5].

### 7.1.4 Antiviral Therapies

The antiviral and antiretroviral treatments introduced over the past two decades have changed the natural course of certain forms of encephalitis,

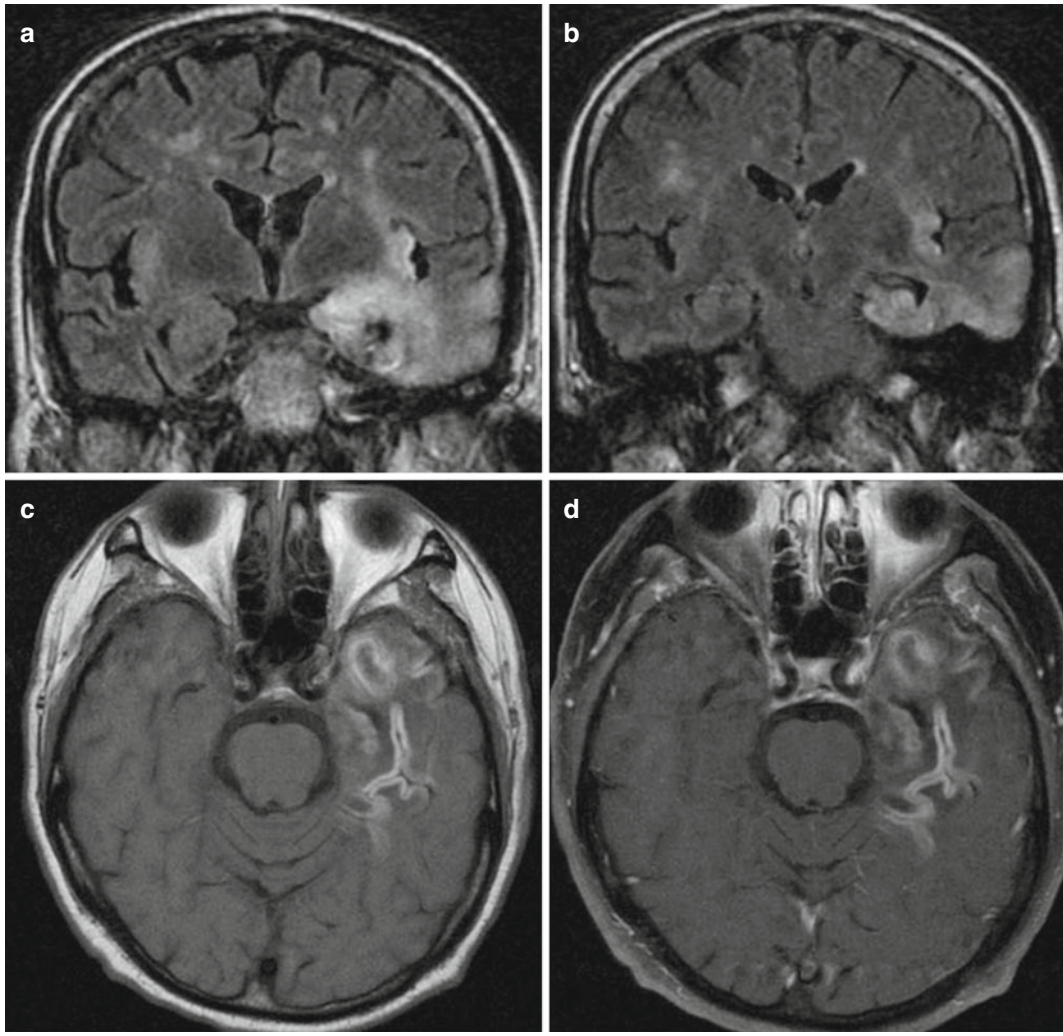


**Fig. 7.1** Herpes simplex encephalitis, subacute stage. Coronal FLAIR images (**a**, **b**) show dishomogeneous hyperintensity in the left temporal medial region and in the left insula. Note the mild enlargement of the temporal horn. In (**c**, **d**), T1-weighted images without (**c**) and with contrast medium (**d**) show cortical hyperintensity due to laminar necrosis, with hemorrhage in the left temporal lobe. No definite enhancement was present.

in particular, herpes simplex encephalitis and all the HIV-related complications. Estimated survival rates have increased significantly, and the frequency of medium- to-long-term complications has fallen. Unfortunately, however, there still exist many forms of encephalitis for which there is no etiological treatment and whose outcome is determined essentially by variables related to the host and by the symptomatic treatment.

## 7.2 Herpesviruses

Herpesviruses are a common cause for severe acute and chronic neurological disease of the central nervous system (CNS), either during primary infection or following reactivation from a latent state. Especially in the immunosuppressed, the infection can take a life-threatening course, and diagnosis can be challenging, due to the presence of atypical clinical and instrumental

findings [6]. Therefore, the early detection of herpesvirus-associated neurological diseases should have high priority.

In immunocompromised hosts, in whom herpesviruses can undergo systemic reactivation, it is of capital importance to perform PCR CSF/serum ratio to distinguish active CNS compartmental viral replication from systemic responses.

In this chapter, we will consider the neurological diseases caused by six neurotropic herpesviruses: herpes simplex virus (HSV), varicella zoster virus (VZV), Epstein–Barr virus (EBV), cytomegalovirus (CMV), and human herpesvirus-6 (HH6).

## 7.3 Herpes Simplex

**Key Facts**

- **Terminology and definition** – Species: *Herpes simplex virus type 1 and 2 (HSV-1 and HSV-2)*; genus: *Simplex virus*; family: *Herpesviridae.*
- **Epidemiology** – HSE is the most common form of sporadic viral encephalitis in the general population. HSVs infect via mucosal surfaces or damaged skin. Primary infection with HSV-1 usually occurs during childhood or adolescence, and is asymptomatic or results in gengivostomatitis. After primary infection, HSV-1 establishes latency in the neurons of the trigeminal ganglion, and can undergo reactivation with oral mucocutaneous shedding.
- **Clinical features** – The most frequent clinical features include fever, headache, aphasia, seizures, and alterations of consciousness, personality, and behavior, mimicking acute psychiatric conditions.
  HSV-2 can also be responsible for a form of benign, recurrent, lymphocytic meningitis (Mollaret's meningitis).
- **Diagnostic markers**
  - **CSF** – inflammatory changes in >95 % of cases.
  - **PCR for HSV-1 DNA** – very sensitive (98 %) and specific (94 %).
  - HSV CSF/serum antibody ratio may be helpful if > 1 week into therapy.
  - **Imaging** – Monolateral or bilateral temporoinsular hyperintensity (MR-FLAIR and T2W images); hemorrhagic foci.
- **Prognosis** – Neurologic sequelae in surviving patients are often severe, including focal deficits, seizures, and neuropsychological changes. Untreated, mortality approaches 70%.
- **Principles of treatment** – Intravenous acyclovir 10 mg/kg every 8 h for 14–21 days. Early recognition of the infection is critical since a delay in therapy is associated with increased morbidity and mortality. In the immunocompromised, HSV resistance to acyclovir is a serious concern, affecting about 5–25% of patients receiving long-term antiviral prophylaxis.

### 7.3.1 Prognosis

#### 7.3.1.1 Mortality and Disability

Although the prognosis for patients with HSE has been dramatically improved by the availability of specific antiviral therapy, neurologic sequelae in surviving patients are often severe, including focal deficits, seizures, and neuropsychological changes. If untreated, mortality approaches 70 %.

The table below summarizes the prognostic factors for HSE.

| Prognostic factors (predictors of poor outcome) |
|---|
| Older age |
| Depressed level of consciousness before the onset of therapy |
| Delay of >2 days between admission to the hospital and initiation of acyclovir |
| Simplified Acute Physiology Score II ≥27 at admission |
| Disorientation |
| Low albumin levels |
| Low sodium levels |
| Abnormal early CT scan |

### Immunocompetent Hosts

In immunocompetent hosts, HSE mortality is estimated between 10 and 25 %, despite adequate treatment; about half of the deaths are attributable directly to encephalitis and another half to infectious complications.

Among survivors, the overall incidence of neurologic sequelae is 30–70 %, ranging from mild/moderate (20–50 %) to severe (10–20 %) [7, 8]. The most common long-term sequelae are represented by memory impairment (69 %), anosmia (65 %), personality and behavioral changes (45 %), dysphasia (41 %), and epilepsy (24 %) [7]. The severity of the amnesia appears to correlate with the presence of bilateral medial limbic (hippocampal) damage and with its severity, detected by MRI.

Overall, only 14–48 % of the patients regain a premorbid level of functioning.

About 87 % of the survivors are eventually readmitted to the hospital due to epilepsy, infections (other than HSE), or neuropsychiatric conditions [9].

### Immunocompromised Hosts

Although HSE is most commonly seen in immunocompetent hosts, cases of HSE in the context of immunosuppression such as HIV infection, cancer, solid organ or bone marrow transplantation have now been reported. In this setting, HSE presents with atypical clinical and instrumental findings, making diagnosis of the condition particularly challenging. This may possibly contribute to the high morbidity and mortality observed in this cohort [6].

*Cancer*

HSE has been reported in individual patients with cancer, with a majority of cases occurring shortly after brain irradiation. Additional sources of immunosuppression include chemotherapies and corticosteroids . However, estimates of the incidence of HSE in people with cancer compared to the general population are not available.

| *References* | *No of cases* | *Mortality* | *Residual Disability* |
|---|---|---|---|
| Graber, 2011 [10] | 31 | 20 (65 %) | Not available |

*HIV infection*

Most cases of HSE in HIV-infected patients date back to the pre-HAART[a] era, occurring in association to CMV encephalitis. In this setting, mortality was extremely high, and diagnosis mainly autoptic. Latest reports indicate a mortality of about one-quarter or less, comparable to that of the general population.

*Solid organ transplantation*

In solid organ transplant recipients, HSV-systemic reactivation may be seen in the first post-transplant month, in the absence of prophylaxis.

Still, HSE rarely occurs; only a few cases after renal transplantation are reported in literature.

*Bone marrow transplantation*

Up to 25 % of patients who undergo allogenic stem cell transplantation suffer from severe neurological complications involving the CNS, frequently infections, which are associated with a poor outcome. The leading causative organisms of CNS infections in patients with malignancies are *Toxoplasma gondii* and fungi; viral infections have less frequently been reported.

| *References* | *No of cases* | *Mortality* | *Residual Disability* |
|---|---|---|---|
| Schmidt-Hieber, 2011 [11] | 4 | 1 (25 %) | 1 (25 %) |
| Wu, 2013 [12] | 5 | 3 (60 %) | 1 (20 %) |

*Monoclonal antibodies*

HSE has rarely been reported in patients receiving monoclonal antibodies for rheumatologic disorders or multiple sclerosis. In this setting, HSE retains a relatively good prognosis.

| | *References* | *No of cases* | *Mortality* | *Residual Disability* |
|---|---|---|---|---|
| TNF-α inhibitors (rheumatologic disorders) | Bradford, 2009 [13] | 3 | 0 | 2 (67 %) |
| Natalizumab (multiple sclerosis) | Fine, 2013 [14] | 11 | 2 (18 %) | 3 (27 %) |

[a]*HAART* highly active antiretroviral therapy

## 7.4 Varicella Zoster

**Key Facts**

- **Terminology and definitions** – Species: *Varicella zoster virus* (VZV) or *Human herpesvirus 3* (HHV-3); genus: *Varicellovirus*; family: *Herpesviridae.*
- **Epidemiology** – Primary infection results in varicella (syn.: chicken pox). Viral transmission occurs by direct contact with skin lesions or by respiratory aerosols from infected individuals. After varicella resolves, VZV becomes latent in the peripheral nervous system and persists throughout the lifetime of the host.
- **Clinical features** – Neurological complications caused by VZV can occur either during primary infection or following reactivation, and can be caused by direct viral invasion or by vasculitis. They all can course with or without cutaneous rash.
  - **Acute cerebellar ataxia** 1/4000 children with varicella, with headache, vomiting, and mild cerebellar dysfunction.
  - **Encephalitis** without vasculopathy can affect both immunocompetent and immunosuppressed patients with nonspecific clinical features.
  - **Large vessel unifocal granulomatous arteritis** usually affects immunocompetent elderly individuals; the typical presentation is headache and hemiplegia occurring in patients with a recent history of herpes zoster ophthalmicus.
  - **Small vessel multifocal vasculopathy** usually occurs in severely immunocompromised patients (AIDS, lymphoproliferative disorders) and consists of subacute multifocal neurological deficits accompanied by headache, fever, mental changes, and seizures.
  - **Postzoster myelitis:** Sensory–motor dysfunction in the same spinal cord segment as in the cutaneous rash. Immunocompromised patients are at increased risk, and the syndrome is well-described in patients with AIDS.
- **Diagnostic markers**
  - **CSF**: moderate inflammatory changes.
  - **PCR for VZV** in acute cerebellar ataxia, encephalitis, and vasculopathies.
  - **VZV CSF/**serum antibody ratio is significantly altered in vasculopathies.
  - **Imaging** – MR usually normal (acute cerebellar ataxia); normal or n.s. supra- or infratentorial T2 hyperintensities in white/gray matter (encephalitis); ischemic infarction with focal stenosis or occlusion of the affected vessel (large vessel arteritis); multifocal brain infarcts (small vessel multifocal vasculopathy).
- **Prognosis** – Potentially lethal in both immunocompetente and immunocompromised patients.

### 7.4.1 Prognosis

#### 7.4.1.1 Principles of Treatment

Therapy of VZV neurological complications has to rely on the context of immunocompetence, the possible putative pathogenesis, and disease severity.

In the context of immunosuppression, therapy with intravenous acyclovir is always recommended.

#### 7.4.1.2 Mortality and Disability

Varicella zoster reactivation in the CNS is associated with a variety of serious and potentially lethal complications in both immunocompetent and immunocompromised individuals. Prognosis depends on age, immunological status of the host, and clinical pattern [15, 16].

*Acute cerebellar ataxia*

Cerebellar ataxia associated with varicella is self-limited and has a favorable prognosis. Mortality is essentially zero, and deaths that occur are usually attributed to the development of nonneurologic complications. Still, a significant number of patients experience residual disability.

| *References* | *No of cases* | *Mortality* | *Residual disability* |
|---|---|---|---|
| Connolly, 1994 [17] | 26 | 0 % | Behavioral abnormalities (31 %); speech abnormalities (19 %) |
| Camacho-Badilla, 2008 [18] | 37 | 0 % | Minor sequelae (54 %) |

*Encephalitis*

During the last decades, the mortality for VZV encephalitis has ranged from 5 to 35 %.
The actual mortality rate is probably around 10–15 %, with good recovery expected in most cases.

| *References* | *No of cases* | *Mortality* | *Residual disability* |
|---|---|---|---|
| De Broucker, 2012 [19] | 20 | 3 (15 %) | Moderate to severe sequelae (41 %): cognitive impairment, sensory–motor deficits, ataxia |

*Large vessel unifocal granulomatous arteritis*

The mortality rate is 20–25 %, with a high incidence of permanent neurologic sequelae among survivors (headache, focal deficits, coma).

*Small vessel multifocal vasculopathy*

Prognosis is usually unfavorable, characterized by high short-term mortality.

*Myelitis*

In immunocompetent hosts, the involvement of the spinal cord is subtle and usually followed by complete recovery. Conversely, in immunocompromised individuals, the infection is often severe, leading to partial or total cord transection with substantial neurologic sequelae, or even death.

### 7.4.1.3 VZV Neurologic Disease in Settings of Immunosuppression

*HIV/AIDS patients*

The larger series reports 34 cases of neurological complications due to VZV [20], including encephalitis (13 cases), myelitis (8 cases), radiculitis (7 cases), and meningitis (6 cases). Neurological manifestations often involved simultaneously several sites in the central and/or peripheral nervous system. Severe symptoms at onset and a lower CD4 cell count were associated with poorer outcome.

| *References* | *No of cases* | *Mortality* | *Residual disability* |
|---|---|---|---|
| De La Blanchardiere, 2000 [20] | 34 | 6 (18 %) | Severe sequelae (29 %), complete recovery (53 %) |

*Bone marrow transplantation*

Although VZV reactivation during the first 24 months from bone marrow transplantation is a common event, VZV meningoencephalitis is a rare complication, often occurring after the suspension of antiviral prophylaxis. Few cases are reported in literature, some with fatal outcome.

| *References* | *No of cases* | *Mortality* | *Residual disability* |
|---|---|---|---|
| Suzuki, 2012 [21] | 1 + 12 | 2 (15 %) | Not available |

*Monoclonal antibodies*

Few cases of CNS complications caused by VZV during treatment with monoclonal antibodies are reported: one fatal case of VZV vasculopathy with Adalimumab [22] and four cases of VZV meningitis with Natalizumab, with favorable outcomes [14].

## 7.5 Epstein–Barr

**Key Facts**

- **Terminology and definitions** – Species: *Epstein–Barr virus* (EBV); genus: *Lymphocryptovirus*; family: *Herpesviridae.*
- **Epidemiology** – EBV is one of the most widespread viruses, infecting over 90 % of human beings in the first decades of life. EBV is most frequently transmitted via saliva. Primary infection is asymptomatic or results in infectious mononucleosis; once the initial lytic infection is brought under control, EBV establishes latency in B cells.
- **Clinical features** – Complications caused by EBV can involve the central or peripheral nervous system and can occur shortly before, during, or after infectious mononucleosis, as well as following acute EBV infection in the absence of symptomatic mononucleosis.
  - **Aseptic meningitis** is the most common complication of primary EBV infection.
  - **Encephalitis** is characterized by nonspecific clinical features ranging from fever and headache, to seizures, personality changes, and coma.
  - **Myelitis** may sometimes accompany encephalitis.
  - EBV has also been associated with AIDS-related CNS lymphomas and posttransplant lymphoproliferative disorders (PTLD). These entities range from reversible lymphoproliferative disorders that recover with the suspension of immunosuppressants, to malignant aggressive lymphomas.
- **Diagnostic markers**
  - **CSF**: lymphocytic pleocytosis and mild elevation in protein levels.
    The value of PCR assessment for EBV infections is uncertain, as EBV DNA is often detected in the CSF in the absence of neurological symptoms.
  - **Imaging**: T2W hyperintensities in cerebral white and/or gray matter on MRI.
- **Prognosis** – Aseptic meningitis has self-limiting course. Enchefalitis has 10-20% mortality rate.

### 7.5.1 Prognosis

#### 7.5.1.1 Principles of Treatment

No specific antiviral therapy is available for the treatment of EBV-related neurologic complications, and therapy is mainly supportive. Corticosteroids may be effective in selected cases.

#### 7.5.1.2 Mortality and Disability

- *Aseptic meningitis:* Self-limiting course; usually resolves without neurologic sequelae.
- *Encephalitis*: Mortality of 10–20 %. Incidence of neurologic sequelae of 20–38 % in immunocompetent hosts.
- Most cases of *myelitis* occur in children and young adults, and eventually resolve without sequelae, although reports of long-term sensory–motor deficits exist.

## 7.6 Cytomegalovirus

**Key Facts**

- **Terminology and definitions** – Species: *Human cytomegalovirus* (CMV); genus: *Cytomegalovirus*; family: *Herpesviridae.*
- **Epidemiology** – Primary infection with CMV usually occurs early in life by direct contact with bodily fluids (saliva, urine, blood, vaginal secretions, or semen) and is asymptomatic or can manifest as infectious mononucleosis. After primary infection, the virus establishes latency and is able to undergo reactivation in the event of immunosuppression.
- **Clinical features** – CMV encephalitis usually presents with nonspecific signs of encephalopathy, such as lethargy, confusion, and seizures. Immunocompromised individuals are at increased risk for potentially fatal disseminated CMV infections that can involve the eye, cochlea, and the CNS. Rarely, CMV can induce myelitis or polymononeuritis.
- **Diagnostic markers**
  - **CSF** analysis and *PCR* for CMV.
  - **Imaging** – MRI reveals subependymal gadolinium enhancement and nonspecific white matter abnormalities on T2W images.
- **Prognosis** – CMV eningoencephalitis carries favorable prognosis in immunocmpetent patients. Prognosis s frequently poor in immunocompromised hosts.

### 7.6.1 Prognosis

#### 7.6.1.1 Medical Therapy

Ganciclovir is the treatment of choice for systemic CMV infection. Second-line antiviral drugs include valganciclovir, cidofovir, and foscarnet.

#### 7.6.1.2 Mortality and Disability

##### Immunocompetent Hosts

CMV meningoencephalitis in immunocompetent hosts is characterized by favorable prognosis: most cases are mild and resolve without sequelae, but even cases characterized by severe neurologic involvement present high rates of complete recovery and very low mortality.

##### Immunocompromised Hosts

In immunocompromised hosts, the prognosis of CMV-induced neurological conditions is frequently poor, depending upon the cause of immunosuppression and the response to antiviral medications. In this cohort, CMV encephalitis is most frequent in HIV/AIDS patients, while it is a rare event in transplant recipients.

*HIV infection*

CMV-associated neurologic conditions among patients with HIV/AIDS have become much less common and less severe in the HAART[a] era (prevalence <2 %). They usually occur in patients with very low CD4 cell counts (<50 cells/μL) and are often accompanied by CMV disease in other sites, such as retina, gastrointestinal tract, and blood. CMV encephalitis can either be diffuse, focal, assume the pattern of ventriculitis, or occur in the form of pseudotumoral mass.

| *References* | *No of cases* | *Mortality* | *Residual disability* |
|---|---|---|---|
| Silva, 2010 [23] | 9 | 3 (33 %) | Not available |

A neuropathology study of HIV-infected patients reported 28 (17 %) cases of CMV encephalitis, most of them with *premortem* diagnosis of HIV dementia, showing that CMV may be an underestimated cause of neurocognitive disorders in the HIV population.

*Bone marrow transplantation*

CMV-related CNS disease after allogenic stem cell transplantation is a late-onset event and usually causes encephalitis in the absence of the other sites of CMV disease. It is associated with umbilical cord blood transplantation, severe and protracted T-cell immunodeficiency, recurrent CMV viremia treated with multiple courses of antiviral therapy, and ganciclovir-resistant CMV infection. In this context, mortality is extremely high, reaching 90 % of cases.

| *References* | *No of cases* | *Mortality* | *Residual disability* |
|---|---|---|---|
| Reddy, 2010 [24] | 2+9 | 10 (90 %) | Not available |

*Solid organ transplantation*

Solid organ transplant recipients are at risk for invasive disease from CMV reactivation, usually occurring during the first year after completion of prophylaxis. Although CMV systemic reactivation is relatively frequent, isolated CNS disease induced by CMV rarely occurs. Prognosis is highly dependent on the general conditions and the presence of end-organ disease.

[a]*HAART* highly active antiretroviral therapy

## 7.7 Human Herpesvirus-6

**Key Facts**

- **Terminology and definitions** – Species: *Human herpesvirus-6* (HHV-6)*;* genus: *Roseolovirus*; family: *Herpesviridae.*
- **Epidemiology** – HHV-6 is ubiquitous and transmitted through respiratory and oral secretions. Primary infection usually occurs within 2 years of age, and in normal infants results in roseola (exanthema subitum). After primary infection, HHV-6 establishes latency in the salivary glands, brain, and white blood cells. Viral reactivation usually occurs in severely immunocompromised states, causing fever, hepatitis, pneumonitis, and occasionally encephalitis.
- **Clinical features** – In immunocompromised hosts, there is a recognized pattern of HHV6 encephalitis targeting the limbic lobes, producing amnesia, neuropsychiatric changes, seizures, and hyponatremia. Nonspecific patterns have also been rarely reported. In immunocompetent hosts, the occurence of HHV6 encephalitis is still debated. The few reported cases in literature might be the result of a diagnostic bias due to the presence of chromosomally integrated viral genome in the host cells, resulting in positive CSF PCR testing.
- **Diagnostic markers**
  - **CSF** – Mild pleocytosis and elevated protein levels.
  - **PCR for HHV-6** has a low positive predictive value (30 %), due to the presence of chromosomally integrated viral genome in about 2 % of the general population. In this scenario, it is of capital importance to value the PCR CSF/serum ratio, to confirm active specific CNS compartmental viral replication.
  - **Imaging** – In immunocompetent hosts, MRI findings are frequently nonspecific. Conversely, in patients with limbic encephalitis, MRI shows bilateral nonenhancing medial temporal lobe hyperintensities in the T2, FLAIR, and DWI.
- **Principles of treatment** – Ganciclovir is currently used as first-line therapy for HHV-6 encephalitis. Other drugs that proved efficacy *in vitro* include forscarnet and cidofovir.
- **Prognosis** – Variable outcome. Complete recovery is frequent.

## 7.7.1 Prognosis

### 7.7.1.1 Mortality and Disability

#### Immunocompetent Hosts

HHV-6 encephalitis is a rare entity in immunocompetent hosts, and there are only few cases reported in literature. Outcome is variable, as complete recovery is frequent, but fatal cases are reported too.

#### Immunocompromised Hosts

Among the immunocompromised, HHV-6 encephalitis is most commonly described in bone marrow transplant recipients; it is a rare event in solid organ transplant recipients and HIV-infected patients.

*Bone marrow transplantation*

HHV-6 reactivates between 2 and 6 weeks after transplantation in 40–50 % of hematopoietic cell transplantation recipients. Younger age, underlying malignancy, allogenic transplants, unrelated or gender-mismatched donors, receipt of anti-T-cell antibodies, and receipt of steroids have all been identified as risk factors for HHV-6 reactivation in the HCT recipients.

| *References* | *No of cases* | *Mortality* | *Residual disability* |
|---|---|---|---|
| Zerr, 2006 [25] | 48 | Overall mortality 39 %;<br>25 % encephalitis,<br>14 % sepsis, organ failure | Lingering neurological compromise (18 %) |
| Seeley, 2007 [26] | 9 | Overall mortality 55 %<br>(sepsis, GVHD, acute renal failure, venoocclusive disease) | Residual cognitive impairment (33 %) |
| Shimazu, 2013 [27] | 11 | Overall mortality 82 %;<br>18 % encephalitis,<br>64 % progression of malignancy, pulmonary disease | All survivors experienced cognitive deficits |

*Solid organ transplantation*

Although systemic HHV-6 reactivation is a frequent event in the early phases after solid organ transplantation, only few cases of HHV-6 encephalitis are reported in literature after liver, lung, heart, or kidney/pancreas transplantation. Prognosis quoad vitam is commonly favorable in this cohort; no data are available on neurologic sequelae.

| *References* | *No of cases* | *Mortality* | *Residual disability* |
|---|---|---|---|
| Vinnard, 2009 [28] | 1 + 5 | 1 (17 %) | Not available |

*HIV infection*

The role of HHV-6 in the pathogenesis of CNS disease in HIV patients remains unclear, as HHV-6 DNA is detected in the CSF of patients with HIV/AIDS and neurological disease in 2–30 % of cases, but CNS disease is finally attributed to other opportunistic pathogens.

Acute HHV-6 infection often presents with a rapidly fatal meningoencephalitis.

| *References* | *No of cases* | *Mortality* | *Residual disability* |
|---|---|---|---|
| Corti, 2011 [29] | 5 | 4 (80 %) | Good clinical recovery in the surviving patient |

## 7.8 Progressive multifocal leukoencephalopathy (PML)

**Key Facts**

- **Terminology and definitions** – species: *JC Virus (JCV)*; genus: *polyomavirus*; family: *Polyomaviridae*.
- **Epidemiology** – Primary infection with JCV occurs early in life through inhalation, and is typically asymptomatic. Tonsillar lymphocytes infected with JCV carry virions to the kidney and bone marrow, which are thought to be the primary sites of latency. Despite the high prevalence of JCV infection in healthy adults, PML almost exclusively develops in immunocompromised individuals (AIDS, treatment with monoclonal antibodies).
- **Clinical features**
  - **Classic PML** – PML typically presents with subacute neurological deficits including altered mental status, motor/sensory/visual deficits, and ataxia. Lesions may occur anywhere in the CNS white matter, although they appear to spare the optic nerves and the spinal cord. The natural clinical course usually spans over weeks or months, resulting in dementia, blindness, paralysis, and finally coma and death.
  - **Inflammatory Progressive Multifocal Leukoencephalopathy (PML/IRIS)** – New onset or clinical worsening of PML has been described in the setting of recovery of the immune system (e.g., HAART); this phenomenon has been called immune reconstitution inflammatory syndrome (IRIS).
  - **JCV Infection of Cerebellar Granule Cell Neurons (GCN)** – Ataxia and cerebellar atrophy can occur in the absence of white matter lesions in the cerebellum.
- **Diagnosis**
  - **CSF** – PCR for JCV on CSF has sensitivity of 50–75 % and specificity of 98–100 %.
  - **Imaging** – Classic PML is characterized by one or more, nonenhancing, confluent, subcortical white matter hyperintensities on T2W/FLAIR images. Conversely, PML/IRIS is defined by enhancing, inflammatory lesions.
  - **Brain biopsy** – Has sensitivity of 64–96 % and specificity of nearly 100 %.
- **Principles of treatment**
  There is no specific antiviral therapy against JCV. Although anecdotal reports of response to various treatments are reported, all controlled studies have failed to show any efficacy of the drugs tested.
- The best treatment for PML is the restoration of the immune system, although it can lead to IRIS. In severe forms of IRIS, the use of steroids may be indicated.
- **Prognosis** – The natural clinical course of classic PML usually spans over weeks or months, resulting in dementia, blindness, paralysis, and finally coma and death.

### 7.8.1 Prognosis

#### 7.8.1.1 Mortality and Disability

PML was originally described in patients with HIV/AIDS with very low CD4+ cell count. In recent years, PML has been increasingly reported in other cohorts, such as patients receiving immunosuppressors for hematologic malignancies, and patients receiving monoclonal antibodies.

*HIV infection*

The advent of HAART[a] has markedly reduced the incidence and the mortality due to PML in the HIV cohort. During the pre-HAART era, death was nearly universal, with an average survival of 2–4 months. Since the introduction of HAART, survival has improved significantly, with a 1-year probability of survival of 50 % or higher, compared with 5 % or lower in patients not receiving HAART. Still, patients surviving PML frequently experience irreversible neurological sequelae. Engsig [30] analyzed the incidence, clinical presentation, and outcome of PML in HIV-infected patients during the HAART era: a CD4 + cell count ≥50 cells/uL at the diagnosis of PML and a diagnosis of PML after 1997 were associated with reduced mortality. Only two patients had IRIS: both patients died at 40 and 59 days after the diagnosis of PML.

| *References* | *No of cases* | *Mortality* | *Residual disability* |
|---|---|---|---|
| Engsig, 2009 [30] | 47 | 74 % | Progression or stability of neurological symptoms (27 %); high degree of restitution or return to premorbid status (73 %) |

*Hematologic malignancies*

The use of new antineoplastic agents, high-dose therapy with hematopoietic stem cell transplantation (HDT/HSCT), and monoclonal antibodies for lymphoproliferative disorders has led to a striking improvement in disease-free survival but also to a higher incidence of opportunistic infections, such as PML. A recent review [31] reports a mortality rate of 90 % in patients diagnosed before 1989 and treated with alkylating agents and/or radiotherapy for an advanced Hodgkin lymphoma, and a mortality rate of about 80 % in patients diagnosed from 1990 to 2004 receiving purine analogs (mortality 90 %) and high-dose therapy with HSCT (mortality 62.5 %) for a B-cell chronic lymphocytic leukemia or an aggressive non-Hodgkin lymphoma.

| *References* | *No of cases* | *Mortality* | *Residual disability* |
|---|---|---|---|
| Garcia-Suarez, 2005 [31] | 46 | 80–95 % | Only 5 patients survived (median survival — 12 months) |

*Solid organ and bone marrow transplantation*

The risk factors, clinical spectrum, and incidence of PML among transplant recipients remain uncertain even though the transplant population is likely at a significant risk of developing PML.

A recent study [32] reported 69 cases of posttransplantation PML described in literature (44 solid organ transplants and 25 bone marrow transplants). Median survival following symptom onset was 6.4 months in solid organ versus 19.5 months in bone marrow recipients. Overall, transplant recipients were exposed to 42 different immunosuppressive drugs and various chemotherapeutic agents or monoclonal antibodies. One fatal case of IRIS is described.

| | *References* | *No of cases* | *Mortality* | *Residual disability* |
|---|---|---|---|---|
| | Mateen, 2011 [32] | 15 + 54 | 84 % | Not available |

*Monoclonal antibodies*

A number of PML cases in patients receiving monoclonal antibodies have been reported and summarized in the following table [33].

| | Rituximab | Natalizumab | Efalizumab |
|---|---|---|---|
| Target | Anti-CD20 | Binds the α-4 integrin | Anti-CD11 |
| Therapeutic indications | Rheumatoid arthritis, NHL[b], CLL[c] | Relapsing–remitting MS[e], Crohn's disease | Plaque psoriasis (withdrawn in 2009) |
| Number of confirmed cases of drug-associated PML (mortality) | 57 (89 %) | 13 (23 %) | 3 (66.6 %) |
| Epidemiological estimate for drug-associated PML | 1 in 4000, in patients with SLE[d] | 1 in 1000 | 1 in 400 in patients who received ≥3 years of therapy |

A recent study [34] analyzed the clinical outcome and the variables connected with survival of the first 35 postmarketing cases of natalizumab-associated PML. At the time of analysis (follow-up 6.8–4.5 months), 25 patients (71 %) had survived. Of the ten patients who died, five probably died of IRIS. Survivors were younger and had lower pre-PML expanded disability status scale scores and a shorter time from symptom onset to diagnosis, compared with individuals with fatal cases. Among survivors with at least 6 months follow-up, disability levels were evenly distributed among mild (16 %), moderate (36 %), and severe (48 %).

[a]HAART Highly active antiretroviral therapy
[b]NHL Non-Hodgkin lymphoma
[c]CLL Chronic lymphocytic leukemia
[d]SLE Systemic lupus erythematosus
[e]MS Multiple sclerosis

## 7.9 Measles

**Key Facts**

- **Terminology and definitions** – Species: *Measles virus (MV)*; genus: *Morbillivirus*; family: *Paramyxoviridae.*
- **Epidemiology** – Measles virus spreads between individuals through aerosolized respiratory droplets and enters the CNS through cerebral endothelial cells or infected monocytes.
  The CNS complications of measles (syn: rubeola) can occur within days of acute measles infection or may be delayed for weeks, months, or even years. While most forms affect immunocompetent hosts, measles inclusion body encephalitis affects mainly immunocompromised children.
- **Clinical features** – Measles can induce encephalitis in at least four different paradigms, each with a different pathogenesis: primary measles encephalitis (PME), acute postinfectious measles encephalomyelitis (APME), measles inclusion body encephalitis (MIBE), and subacute sclerosing panencephalitis (SSPE) [35]. (The main characteristics of measles encephalitides are summarized in Table 7.1).
- **Diagnosis**
  - **CSF** – Mild pleocytosis, normal/elevated proteins, increased gammaglobulins (SSPE). Other useful tools include CSF/serum antibodies ratio (MIBE, APME, SSPE) and RT–PCR for MV on CSF (PME).
  - **Imaging** – Cerebral T2 focal hyperintensities (PME); white matter multifocal T2 hyperintensities in brain and spinal cord (APME); normal at presentation, followed by edema, atrophy, and ventriculomegaly (MIBE); focal leukodystrophy, and diffuse cortical atrophy (SSPE).
  - **EEG** – High-amplitude bursts of periodic slow-wave complexes, accompanied by axial myoclonic spasms (SSPE); diffuse slow waves with disease progression.
- **Prognosis** – The CNS complications of measles are severe often resulting in disability or death.

**Table 7.1** Measles encephalitides

| | PME | APME | MIBE | SSPE |
|---|---|---|---|---|
| Clinical setting | Active measles infection | Recent measles infection, no longer active | Measles infection in immunocompromised children | Measles infection in the first 2 years of life |
| Time of onset after infection/vaccination | During the exanthema | Weeks to months | Within 1 year | From 3 to 20 years |
| Presence/absence of MV | Presence of infectious MV | No MV present | Persistence of infectious MV | Defective MV |
| Clinical signs | Fever, headache, altered mental status, seizures, weakness, rash | Weakness, sensory loss | Altered mental status, seizures, motor deficits, no/mild rash | Behavior changes, progressive dementia, myoclonus |
| Treatment | Antiviral drugs | Corticosteroids, IVIG, and plasmapheresis | Cessation of immunosuppressants (when possible), antiviral drugs | Symptomatic supportive care |

### 7.9.1 Prognosis

#### 7.9.1.1 Mortality and Disability

The CNS complications of measles are often severe, resulting in substantial disability or death. Prognosis varies according to clinical pattern [35].

*Primary measles encephalitis (PME)*
The prognosis for patients with PME is guarded. Of these patients, 10–15 % will die, and an additional 25 % will be left with permanent neurologic sequelae, including seizures and mental retardation.

*Acute Postinfectious Measles Encephalomyelitis (APME)*
Mortality related to APME is estimated around 10–25 %, depending on the age of the reports. Although some experience full recovery, about one-third of survivors are left with lifelong neurological sequelae, including severe retardation, motor impairment, blindness, and hemiparesis.

*Measles Inclusion Body Encephalitis (MIBE)*
MIBE affects mainly immunocompromised children with lymphoblastic leukemia, solid malignancies, HIV infection, or autoimmune diseases. The mortality rate associated with MIBE is approximately 75 %, with death generally occurring within weeks of onset of the illness. Those who survive this illness suffer considerable morbidity from neurologic abnormalities.

| *References* | *No of cases* | *Mortality* | *Residual disability* |
|---|---|---|---|
| Mustafa, 1993 [36] | 2+31 | 85 % | All surviving patients experienced neurologic sequelae, ranging from severe psychomotor retardation to moderate cognitive disability |

*Subacute Sclerosing Panencephalitis (SSPE)*
SSPE is relentlessly progressive, with a fatal outcome in 95 % of affected individuals. The mean survival ranges from 1 to 3 years. In one study by Risk and Haddad [37], 41 % of affected individuals remained alive after 2 years of disease progression. Prashanth [38] has analyzed the clinical profile of 19 patients with a relatively "benign" course, who survived beyond 3 years. Clinical course of these patients included spontaneous stabilization, remissions, and relapses. There was spontaneous stabilization for 6 months to 6 years in 13 patients. Nine patients had temporary remissions in clinical status, which lasted from 6 months to 9 years. Ten patients received disease-modifying agents, without any discernible effects. Prolonged survival from 3 to 13.8 years was documented.

## 7.10 Arboviruses

**Key Facts**

- **Terminology and definitions**
  Arboviruses are transmitted to humans and other vertebrates by hematophagous arthropod vectors such as mosquitoes, biting midges, phlebotomine sand flies, and ticks.
- **Epidemiology** [39] – Japanese encephalitis virus (JEV) in SE Asia, Pacific Rim; West Nile virus (WNV) in North America, Africa, Europe, Asia, and Australia; Tick-borne encephalitis virus (TBEV) in Europe and Russia; Toscana virus in Europe; Chikungunya virus (CHIKV) in Africa, India, and SE Asia.
- **Clinical features**
  Arboviruses cause serious illness in humans, ranging from rash and arthritis to hemorrhagic fever and encephalitis. CNS diseases occur both in immunocompetent and immunocompromised hosts and are usually preceded by variable combinations of fever, headache, body aches, nausea, and vomiting. Encephalopathy and seizures are the most common neurological signs of the ensuing phase additional features include signs of dysfunction of the basal ganglia (dystonia, tremors, or rigidity), cranial nerves, or anterior horn cells (areflexia, flaccidity).
- **Diagnosis**
  - **CSF** – Lymphocytic (JEV) or neutrophil (TBEV) pleocytosis, normal/decreased glucose levels, and elevated protein levels. For etiologic diagnosis: IgM antibodies titers on CSF, and RT–PCR (WN, TBEV, Chikungunya).
  - **Imaging** – T2/FLAIR hyperintense lesions in thalami, basal ganglia, and brain stem.
- **Principles of treatment** – No antiviral drugs have been proven effective in the treatment of arboviral encephalitides in humans.
- **Prognosis** – Mortality rate: JEV = 20–30 %, CNS WNV = 10 %, TBEV = 20–60 % (Far East subtype) 2 % (European), CHKV = 10 %, Toscana virus usually causes benign diseases.

### 7.10.1 Prognosis

#### 7.10.1.1 Mortality and Disability

**Japanese Encephalitis Virus (JEV)**

JEV is the leading cause of viral encephalitis in Asia (35,000–50,000 cases reported annually). JEV encephalitis is a particularly severe disease, with death sometimes occurring quickly after an initial fulminant phase. Overall, 20–30 % of hospitalized patients die, and half the survivors have neuropsychiatric sequelae [16]. Patients destined to recover tend to manifest improvement after 2–4 days of illness. Higher morbidity and mortality are found in individuals younger than 10 years or older than 65 years. Poor prognostic signs include a depressed level of consciousness, decerebrate posturing, increased intracranial pressure, multiple seizures, isolation of the virus from CSF, and low levels of JEV-specific IgM and IgG in CSF and serum.

**West Nile Virus (WNV)**

WNV infection manifests with neuroinvasive disease in <1 % of cases, with a mortality rate of about 10 % in affected patients. Increased age is the most important risk factor for the development of neuroinvasion and death; other risk factors include the presence of deep coma, impaired immunity, failure to produce IgM antibodies, and coexisting illnesses such as hypertension and diabetes mellitus. Survivors of WNV encephalitis often suffer long-term cognitive and neurological impairments, including muscle weakness, insomnia, depression, confusion, headache, and myalgia. A study by Weiss et al. [40] reports 19 cases of CNS involvement: 7 (37 %) recovered fully, 10 patients (53 %) recovered partially, and 2 died (11 %).

**Tick-Borne Encephalitis Virus (TBEV)**

TBE is a disease with a severe acute clinical course and considerable long-term morbidity. Traditionally, the disease caused by the Far East subtype of TBEV is thought to be more severe than that caused by the European subtype, with case-fatality rates of 20–60 %, compared with 1–3 %, respectively [16]. Neurologic sequelae have been identified in about 35–58 % of the patients with TBE, including decreased concentration and memory, emotional lability, aphasia, headache, tremor, and ataxia. Age, severity of illness in the acute stage, and low neutralizing antibodies titers at onset are associated with severe forms of disease, along with early CSF IgM response. Patients with severe disease may present incomplete recovery.

**Chikungunya Virus (CHIKV)**

CHIKV has been implicated in a number of outbreaks of painful polyarthralgia and myalgia in East and Southern Africa and Southeast Asia over the last 50 years. It was during one of the most recent outbreaks (La Réunion, 2005–2006) that the ability of CHIKV to cause encephalitis was first appreciated. In epidemics that have occurred since 2005, mortality associated with CHIKV infection has been described, with a case-fatality rate of about 1 in 1000, with most deaths occurring in neonates, elderly people, and in adults with underlying disorders. The common causes of death were heart failure, multiple organ failure, hepatitis, and encephalitis. The estimated mortality in patients with CHIKV infections of the CNS is around 10 %.

**Toscana Virus**

A recent review [41] summarizes 41 cases of Toscana virus infections of the CNS reported in literature; most patients (92 %) had a benign and self-limiting disease. Recovery is usually complete, and neurologic sequelae are uncommon.

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