Viral Infections of the Central Nervous System

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Abstract

Viral-mediated central nervous system (CNS) disease is a complex spectrum of clinical syndromes that result from viral tropism and individual immune responses and genetic susceptibility of patients. The epidemiology of the pathogens is constantly influenced by the availability, or non-availability, of health care services; preventative strategies; and the process of globalization, with rapid movement of people, animals and products. It is further complicated by natural disasters, wars and changes in lifestyle.

The effects of the neurotropic viruses are discussed against the background of the epidemiology. The pathogenesis is a chain of events with the point of departure when the virus enters the body to spread and reach the different sites of the CNS. The blood-brain barrier and blood-cerebrospinal fluid barrier are then overcome by captivating mechanisms. Once the different viruses have settled at the preferred site or sites, and have sidestepped the initial immune surveillance, the phases of injury commence. The cytopathic effect of the viruses elicits a para- and post-infectious inflammatory response and a vicious circle of continued damage, viral entry and inflammation results in a process not merely of inflammation, but of intense inflammation.

The different clinical syndromes are then identifiable and should be interpreted against their own specific and appropriate epidemiological backgrounds. Clinicians face the challenge of problematic management decisions while awaiting results on gravely ill patients and differential diagnostic considerations have to be taken into account. Establishing a diagnosis is a two-tier process: first it

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R.J. Green (ed.), *Viral Infections in Children, Volume II*,
DOI 10.1007/978-3-319-54093-1_4

requires the integration of cerebrospinal fluid findings, imaging results, electrophysiological studies, serology and ancillary blood tests, for example full blood count, liver function tests and other appropriate microbiological investigations, and then these should be correlated with the clinical condition of the patient. Treatment should be initiated as soon as possible.

General treatment principles for stabilizing and maintaining vital functions are crucial and empiric treatment should be initiated as soon as possible. This usually includes a broad-spectrum antibiotic, such as third-generation cephalosporin and acyclovir. As soon as specific etiologies have been excluded antibiotics can be stopped. The use of acyclovir is discussed. In the last section of the chapter specific characteristics of the neurotropic viral families are summarized.

4.1 Introduction

Children are often admitted with a differential diagnosis of a possible viral-associated central nervous system (CNS) infection. Viruses affect the CNS in many different ways and clinical manifestations may overlap, resulting in a spectrum of syndromes. Sejvar (2014) eloquently summarizes the different alternatives of the viral-mediated disease in the CNS responsible for these syndromes [1]. In the more acute phase patients may present with meningitis, encephalitis, myelitis or combinations if multiple regions are affected e.g. meningoencpehalitis or encephalomyelitis [1–3]. If vasculitis is a prominent component in a specific disease process, patients may present with more focal signs due to areas of infarcts [1]. In the long term, reactivation of a dormant infection with episodic recurrence will be observed, or a relentless chronic neurodegenerative process may occur and cause subacute sclerosing panencephalitis (SSPE) or "slow viruses" [1]. Congenital infections, such as cytomegalovirus (CMV) or rubella, may result in neurodevelopmental disorders with a more chronic nature [1]. The CNS may also be affected secondarily by a viral-induced immune-mediated attack on the CNS, or indirectly, as seen in liver failure-associated encephalopathy due to viral hepatitis or Reye's syndrome, which is precipitated by salicylate treatment in children with influenza or varicella-zoster virus (VZV) infection [1].

However, to confirm a specific diagnosis is challenging, because the clinical presentation as well as the special investigations are often non-specific. The aim of this chapter is to outline the facts which are known and the many conundrums still faced, and to aid clinicians in making informed decisions on the management of their patients. General principles applicable to virus-associated CNS infections are discussed in the first part of the chapter, and specific viruses of interest at the end.

4.2 Case Definitions and Descriptions of Common Syndromes Associated with Viral Infections of the CNS

Although it is often difficult to apply specific case definitions for the various viral-related CNS syndromes pedantically in a clinical setting, such definitions are ultimately important in patient management and research. The definitions are based on the anatomic site or sites affected. Sejvar et al. (2007) publish case definitions for encephalitis, myelitis and acute disseminated encephalomyelitis (ADEM) on behalf of the Brighton Collaboration Encephalitis Working Group [4]. Britton et al. (2015) compare the different definitions for encephalitis, including the Brighton definition, used in five large epidemiological studies [5]. For the purpose of this chapter different definitions have been collated; in essence the key features overlap and represent the main clinical syndromes related to the anatomic site affected. The broader clinical terminology used in the definitions is explained in the section on clinical manifestations.

4.2.1 Encephalitis

Encephalitis is inflammation of the brain tissue with infiltration of inflammatory cell and perivascular cuffing, therefore in essence a histopathological diagnosis [4, 6], but brain biopsies are impractical and not readily available. A clinical approach has thus been followed, and case definitions have been formulated in a number of excellent epidemiological studies, but these definitions vary slightly, for example in the age of the patients and inclusion criteria [4, 7–9].

In practice the definition of encephalitis depends on the presence of clinical signs due to the involvement of the brain tissue itself manifesting as encephalopathy for a period of at least 24 hours and/or specific neurological features with evidence of inflammation [4, 5, 7–9]. The indicators of inflammation are fever, cerebrospinal fluid (CSF) pleocytosis, and electroencephalogram (EEG) and neuroimaging findings consistent with encephalitis [4]. One of the most useful ways to think of infection is “fever for infection”. The clinical signs of encephalitis are usually non specific but not subtle. However, in immune suppressed patients they may be subtle and often also chronic. The encephalopathy is not due to other metabolic causes, toxins, other neurological disorders or systemic infections [5]. It can be caused by a wide variety of etiological factors including viruses, bacteria, parasites, atypical bacteria or immune-mediated processes [5], but the specific etiology is only confirmed in 60% of cases [8]. The disease course can be acute, sub-acute or chronic, and it is determined by the immune status of the patient [10]. Viruses responsible for sub-acute or chronic presentations in immunocompromised patients are measles virus causing inclusion body encephalitis, VZV causing multifocal leukoencephalopathy, CMV, herpes simplex virus (HSV) type 2, human herpes virus (HHV) type 6, enteroviruses, John Cunningham virus and BK virus causing progressive multifocal leukoencephalopathy and human immunodeficiency virus (HIV). In immune

competent patients John Cunningham virus and BK virus can also cause progressive multifocal leukoencephalopathy, whereas measles virus causes SSPE [10].

4.2.2 Meningitis

In contrast to viral encephalitis, the brain tissue is not involved in viral meningitis and the patients do not have an associated encephalopathy or myelitis, but they present with the triad of fever, headache and signs of meningeal irritation [6, 11]. Viral meningitis is also referred to as aseptic meningitis if the bacterial cultures are negative where meningitis has been suspected and no antibiotics were administered before the lumbar puncture (LP) was done [4, 6, 11]. It is often a mild disease, which has a favorable outcome with complete recovery within 7–10 days [4, 6, 11]. Enteroviruses are identified in up to 95% of aseptic meningitis cases [11].

4.2.3 Meningoencephalitis

If both the brain parenchyma and the meninges are affected it is referred to as meningoencephalitis. It is often difficult to assess signs of meningeal irritation in an encephalopathic patient and confirm meningeal involvement [4].

4.2.4 Myelitis

Myelitis implies that inflammation of the spinal cord parenchyma is present, usually in the anterior horn cell [4]. The viruses implicated are enteroviruses, arboviruses, HSV-1, VZV, poliovirus and coxsackie virus-A and B. If both the brain parenchyma and the spinal cord are affected it is called encephalomyelitis [4]. Patients present with acute flaccid paralysis. Transverse myelitis is a post-infectious demyelination, with 20–40% of patients showing evidence of a viral infection [12].

4.2.5 Myelopathy

Myelopathy is the more diffuse and non-specific involvement of the spinal cord caused by human T-cell lymphotropic virus (HTLV) I and II, HIV and in rare occasions by HSV, CMV or enteroviruses [1, 12]. HTLV-I causes tropical spastic paraparesis and HTLV-I-associated myelopathy, and although these usually present later in life, around the fourth and fifth decades, they have been observed in younger patients [1]. The onset of disease is slow but progressive, and associated with backache and typical sparing of the arms [1]. The legs are affected and the clinical signs are stiffness, spasticity, hyperreflexia, dysesthesia and a positive Babinski sign [1]. The posterior columns are often involved with a loss of position and vibration sense [1]. A similar presentation has been observed by a number of South African clinicians (unpublished data), who have seen children with HIV-1 infection present with

spastic diplegia and no bowel or bladder involvement. The magnetic resonance imaging (MRI) findings for the brain and spinal cord are normal. It is unclear whether this may perhaps overlap with HIV-associated vacuolar myelopathy, as these patients also present with spastic paraparesis and weakness exceeding the degree of spasticity, with hyperreflexia, positive Babinski signs, ataxic gait and dysmetria, and both bowel and bladder incontinence are present [12]. The position and vibration senses are also affected [12]. The macroscopic examination of the spinal cord and dura mater is normal but there is loss of myelin in the lateral and posterior columns, with spongy degeneration or microvacuolization of the white matter [12].

4.2.6 Acute Disseminated Encephalomyelitis

Although ADEM is one of the immune-mediated encephalitides, it is referred to regularly in pediatrics and therefore merits being singled out and set into the context of encephalitis. It is a monophasic syndrome with focal or disseminated demyelination and inflammation of the brain parenchyma. It is also regarded as one of the CNS demyelinating conditions, which include transverse myelitis, optic neuritis, acute hemorrhagic leukoencephalitis and multiple sclerosis. It has an immunological basis and is usually preceded by an infection or vaccination [13]. The Encephalitis/ADEM Working Group emphasizes the fact that encephalomyelitis or ADEM that occurs after the administration of an inactivated component or live vaccine is not inevitably the result of the vaccine, but may be just temporarily associated with it [4].

The clinical features overlap significantly with encephalitis, but in essence encephalitis is predominantly a grey matter problem as a result of the cytopathic effect on the cell bodies in the cortex, basal ganglia and thalami, presenting with a change in the sensorium and with seizures, as opposed to ADEM, which is primarily a white matter disease. Features of white matter disease or demyelination are spasticity, optic neuritis and/or atrophy, ataxia, neuropathy, myelopathy and occasionally seizures; the sensorium is affected to a lesser extent [4, 14].

A mild pleocytosis may be present, but oligoclonal bands are less common (less than 7%). MRI is helpful to identify the demyelination of ADEM. In the absence of specific biomarkers of ADEM, diagnostic criteria have been formulated. A diagnosis of ADEM can be confirmed if all five of the following criteria are met [15]:

- It is the first episode of a presumed inflammatory demyelinating disorder resulting in multifocal CNS manifestations
- There is encephalopathy without fever
- An MRI is abnormal, with lesions predominantly in the cerebral white matter. The lesions are large, diffuse and poorly demarcated. In rare cases T1-hypointense lesions may be present in the white matter. The thalami or basal ganglia may also be affected
- The MRI shows no new lesions after 3 months
- There are no other reasonably possible etiologies.

It is extremely important to be diagnosed promptly as aggressive treatment with corticosteroids and other immune modulatory drugs have shown promising results [16]. The first line of treatment includes steroids, intravenous immunoglobulins and/or plasma exchange. Second line therapy is azathioprine, cyclophosphamide, rituximab or other treatments. In some centers, rituximab is used as a first-line treatment [14].

4.2.7 Brain Stem Encephalitis

Brain stem encephalitis, or rhombencephalitis, is the result of para-neoplastic syndromes or bacterial and viral infections. The viruses implicated are enteroviruses (specifically enterovirus-71), flaviviruses, alphaviruses and rabies. Patients present with typical brain stem symptoms including lower cranial nerve palsies, myoclonus, respiratory drive disturbances, autonomic dysfunction and locked-in syndrome [13]. There are MRI changes in the brain stem and basal enhancement with gadolinium contrast [10].

Bickerstaff's encephalitis has a classic triad of symptoms of abnormal mental status, bilateral external ophthalmoplegia and ataxia, and relates to Miller-Fisher syndrome. Collectively, this has been referred to by some clinicians as GQ1b antibody syndrome, because the IgG anti-GQ1b is highly specific for these conditions [14].

4.2.8 Autoimmune Encephalitis

Immune-mediated encephalitides form a broad group of disorders including ADEM, but the recently described group of encephalitides associated with antibodies against the proteins in the synapses and cell surfaces of neurons or with antibodies against intracellular antigens, is specifically referred to as autoimmune encephalitis and is potentially treatable [13, 14, 16]. Demyelinating disorders can present as autoimmune encephalitis, but the two entities can co-occur and must rather be investigated separately than seen as an expansion of the spectrum of a single disease [14].

The constant discoveries of new antibodies over the past decade have revealed novel mechanisms in the pathogenesis of altered memory, cognition, behavior, psychosis, seizures and movement disorders. A detailed discussion of the different antibodies falls beyond the scope of this chapter because many are more frequently associated with disease manifestations in adults. Leypoldt et al. (2015) have reviewed them in great detail [17].

In a multicenter study in England in which the etiology of encephalitis was studied, an immune-mediated etiology was identified in 21% of patients [8]. In the California Encephalitis Project, the frequency of anti-*N*-methyl-*D*-aspartate receptor (anti-NMDAR) encephalitis was four times higher than that of viral-mediated encephalitis and 65% of the patients were younger than 18 years [18]. Although anti-NMDAR encephalitis has been associated with tumors, mostly ovarian teratomas, it is seldom present in children younger than 12 years [16]. To complicate

matters even further, it has also been found that herpes simplex encephalitis (HSE) is able to trigger autoimmune encephalitis through synaptic autoimmunity or choreo-athetosis post-HSE [16, 19].

Autoimmune encephalitis, rather than a primary viral encephalitis, should be considered in a patient presenting with a movement disorder and psychiatric disturbances (psychosis, catatonia and abnormal behavior) [13]. Other associated clinical features may be diverse but may include seizures, language disturbances, a change in the level of consciousness, and autonomic disturbances [16]. Fever may be present during the course of the disease in 50% of cases and there may be a history of prodromal flu-like symptoms with headache [16]. In the reactivation of VZV, skin lesions may or may not be present [16]. In anti-NMDAR encephalitis, rabies might be considered in the differential diagnosis, because the patient may also have severe agitation, hypersalivation and dyskinesia [16].

Standard diagnostic tests are used in correlation with the clinical facts to make a preliminary diagnosis in order to initiate treatment while awaiting more specific confirmatory test results [14]. The CSF reveals a mild pleocytosis, normal glucose and mildly elevated protein [16]. MRI is useful, and specific findings have been related to various antibodies [17]. The MRI in anti-NMDAR encephalitis can be normal in 60% of cases, and the rest may have non-specific findings, best seen on T2/fluid-attenuated inversion recovery (FLAIR) MRI images demonstrating cortical and subcortical changes in the brain and posterior fossa. Transient meningeal enhancement or demyelination have also been observed [16]. The MRI in rabies, by contrast, may show changes in the basal ganglia, thalamus, gray matter of the dorsal brain stem and central regions of the spinal cord [16]. In limbic encephalitis (usually in elderly patients rather than children), uni- or bilateral involvement in the medial aspects of the temporal lobes has been demonstrated on T2/FLAIR images but the diffusion weighted images are normal and there is no meningeal enhancement [16]. The frontal, occipital and parietal lobes of children, when affected, may have more extensive MRI abnormalities [16].

The gold standard for the confirmation of a diagnosis is to prove the presence of the specific antibodies, but the absence of autoantibodies does not exclude the diagnosis [14]. It is important to test for antibodies in the serum as well as in the CSF, because some of the antibodies may be detected only in the CSF. Furthermore, the CSF and serum antibodies can differ, but the clinical presentation usually correlates with the CSF antibodies. In addition, the concentrations of the antibodies in CSF and serum may vary. There are fewer false positive or negative results with the determination of antibodies in CSF, than in serum [14].

4.3 Epidemiology

The epidemiology of CNS viral infections is a constantly changing scene as new viruses emerge and old ones re-emerge. It is complex, and influenced by the interplay between the three constituents of the “epidemiologic triad”, namely the host, the agent and the environment [1]. With modernization and constant population

growth and increase in population density, not only is the transmission of infectious agents between humans easier, but zoonotic transmission is also favored [1]. Within dense urban communities, with social behaviour that involves increased promiscuity, with easier methods of travel, and with exposure to exotic pets, viruses can spread with great ease. With advances in health care such as the use of chemotherapy and immunosuppressive drugs in transplant patients, opportunistic infections emerge. The food industry has become mass-production orientated, and this favors more food-borne outbreaks. The natural evolution of viruses may increase the virulence of the organisms. Natural disasters and war responsible for the breakdown of infrastructure, as well as deliberate biological warfare, all contribute to the emergence, re-emergence and spread of viruses [1].

It is difficult to compare incidences and prevalences, because the case definitions used in different studies vary, and most studies reflect the endemic disease in industrialized countries [1]. Another contributing factor complicating agreement on incidence and prevalence is that encephalitis is, in most countries, not a notifiable disease [20]. Britton et al. (2016) mention incidence ranges of between 2.8 and 10.5 per 100,000 that have been reported in England, Sweden and the USA [21]. The highest rates have been documented in infants less than 1 year of age. Hospital admissions of children due to encephalitis decreased over a period of 11 years in Australia, but the average hospitalization rate was 5/100,000 [21]. There has been a significant decrease in varicella encephalitis, explained by good varicella vaccine coverage [21]. By contrast, an increase in ADEM-related encephalitis has been documented, and ADEM-related encephalitis now accounts for 15–17% of encephalitis-related admissions [21].

4.4 Viral Etiology

There are many viruses associated with CNS infection. Table 4.1 summarizes the global distribution of viruses associated with CNS manifestations [1]. At least eight virus families have been associated with CNS infection, and these include different species from the deoxyribonucleic acid (DNA) virus families *Herpesviridae* and *Polyomaviridae*, as well as from the ribonucleic acid (RNA) virus families *Flaviviridae*, *Paramyxoviridae*, *Picornaviridae*, *Retroviridae*, *Rhabdoviridae* and *Togaviridae* [3]. Table 4.2 summarizes the classification of these most common viruses. In general it is accepted that HSV, VZV and enteroviruses, as a group, are responsible for most of the CNS infections in children [5].

4.5 Pathogenesis

For neurotropic viruses to be able to cause disease in the brain, a chain of events must happen. Swanson and McGavern outline the current understanding of this process clearly [2]. First of all the virus has to enter the host. This can happen through inhalation or ingestion, or through the skin. Viruses such as mumps and

Table 4.1 Global distribution of viruses causing CNS infections and clinical manifestations [1, 10]

Distribution	Virus	Clinical manifestations				
		Encephalitis	Meningitis	Anterior myelitis	Associated with immunosuppression	Other comments
Worldwide	Adenovirus	+	+	+	+	Reye's syndrome
	Cytomegalovirus	+	+		+	Congenital neurodevelopmental disorder, polyradiculitis
	Enteroviruses (many serotypes)	++	+++	++		Large epidemics Enterovirus-70 hemorrhagic conjunctivitis, Enterovirus-71 hand foot and mouth disease, brain stem encephalitis
	Epstein-Barr virus	++	++		+	Brachial plexopathy, Guillain-Barré syndrome, CNS lymphoma
	Herpes simplex virus 1 and 2	+++	+	+		Radiculomyelitis
	Human herpesvirus-6	++			+++	Febrile convulsion
	Human herpes virus-7	++			+++	Febrile convulsion
	Human immunodeficiency virus	Subacute	+		Causes immunosuppression	Dementia, peripheral neuropathy, myelopathy
	Human T-cell lymphotropic virus (HTLV)				Chronic HTLV-1 myelitis	Tropical spastic paraparesis, HTLV-1 associated myelopathy
	Influenza (A, B)					Uncommon associated encephalopathy, Reye's syndrome
	John Cunningham virus				+++	Progressive multifocal leukoencephalopathy
	Lymphocytic choriomeningitis virus	+	+		++	

(continued)

Table 4.1 (continued)

Distribution	Virus	Clinical manifestations				
		Encephalitis	Meningitis	Anterior myelitis	Associated with immunosuppression	Other comments
	Measles virus	+	+			Subacute sclerosing panencephalitis
	Mumps virus	+	++			Parotitis, orchitis, pancreatitis
	Rabies virus	Fatal				Rare in first world, paralytic illness possible
	Rotavirus	+	+			
	Rubella virus	+	+			Congenital rubella syndrome, progressive rubella panencephalitis
	Varicella-zoster virus	+	+	+		Cerebellitis, granulomatous, arteritis. Shingles, postherpetic neuralgia, vasculopathy
Africa	Chikungunya virus	++ Epidemics				Arthritis associated with febrile illness
	Poliovirus	+	+	+++		Eradicated in western world
Americas	Eastern equine encephalitis virus	Epidemics				Encephalitis in horses
	Western equine encephalitis virus	+				Encephalitis in horses
	Venezuelan equine encephalitis virus	Epidemics				Encephalitis in horses
	St. Louis encephalitis virus	++ Epidemics				
North America	La Crosse encephalitis virus	Sporadic seasonal				
	Other California encephalitis viruses	Sporadic seasonal				

	Tick-borne encephalitis virus	+	+			Travel in Eastern Europe, tick bites, upper limb flaccid paralysis
	West Nile virus	+++	+	+		Flaccid paralysis, parkinsonian movement disorder
South America	"New world" (Junin, Machupo, Guanarito, Sabia viruses)	++				Hemorrhagic fever
Asia and Pacific	Chikungunya virus	++ Epidemics				Arthritis associated with febrile illness
	Japanese encephalitis virus	+++	++	++		Flaccid paralysis, parkinsonian movement disorder
	Nipah virus	Epidemics	Unknown			Relapsing neurological disease, transmitted in feces of fruit bats in Malaysia and Bangladesh
	Poliovirus	+	+	+++		Eradicated in western world
	Tick-borne encephalitis virus	+	+			Travel in Eastern Europe Tick bites, Upper limb flaccid paralysis
	West Nile virus (excluding Asia)	+	+	+		
Australia	Hendra virus	+				Severe encephalitis
	Murray Valley encephalitis	+++ Epidemics				
Europe	Tick-borne encephalitis virus	++	++			Eastern Europe, upper limb flaccid paralysis

Adapted from Sejvar (2014) [1] and Kneen et al. (2012) [10]
+ uncommon, ++ occasional, +++ most common

Table 4.2 Classification of most common viruses affecting the central nervous system and their points of entry

Virus family	Species name	BBB	BCSFB
Herpesviridae	Cytomegalovirus	+	+
Double-stranded DNA	Herpes simplex virus-1	+	
	Herpes simplex virus-2	+	
	Human herpes virus-6	+	
	Varicella-zoster virus	+	
Polyomaviridae	John Cunningham virus	+	
Double-stranded DNA			
Flaviviridae	Japanese encephalitis virus	+	
(+) Single-stranded RNA	Tick-borne encephalitis virus	+	
	West Nile virus	+	
Paramyxoviridae	Measles virus	+	
(−) Single-stranded RNA	Mumps virus	+	+
Picornaviridae	Human parechovirus	+	+
(+) Single-stranded RNA	Nonpolio enterovirus	+	+
	Poliovirus	+	
Retroviridae	Human immunodeficiency virus	+	
(+) Single-stranded RNA	Human T-lymphotropic virus-1		
Rhabdoviridae	Rabies virus	+	
(−) Single-stranded RNA			
Togaviridae	Chikungunya virus	+	+
(+) Single-stranded RNA	Eastern equine encephalitis virus	+	

Adapted from Dahm et al. (2016) [3]; *BBB* blood-brain-burrier; *BCSFB* blood cerebrospinal fluid barrier

measles are spread via droplets, and are inhaled to reach the mucous membranes of the upper respiratory tract. The fecal-oral route of ingestion is a way for other viruses, such as enteroviruses, to enter through the alimentary tract. Once at the mucosal membrane, the viruses pass the epithelial barrier and cause infection in the lymphoid tissue of the oropharynx and gut. Insect bites, abrasions and wounds all create a back door through which viruses can enter the body via the skin. Langerhans cells carry arboviruses delivered by insect bites to the adjacent lymph nodes [2].

The second step, for viruses on their way to reach the CNS, is to spread via one of two main routes, blood or peripheral nerves [2, 6]. Viruses either just float to the brain in the bloodstream, or are transported in white blood cells. The "Trojan horses" for Epstein Barr virus are monocytes. HSV-1 and VZV migrate from the keratinocytes to the peripheral sensory neurons to reach the trigeminal ganglion, where they can be latent for years before being reactivated [2]. The dendrites of the olfactory nerve are in direct contact with mucosa in the nose and offer a unique port of entry for HSV-1, Nipah virus, influenza virus and rabies virus [2]. In the case of a dog bite, rabies virus first infects the myocytes, and migration via the peripheral somatic nerves follows [2].

The third step, once in closer proximity to the brain parenchyma, is for the virus to overcome the blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCSFB) protecting the brain [2, 3] by creating physical, metabolic and transport barriers [3]. The BBB is between the lumen of the blood vessels and the brain parenchyma while the BCSFB is between the CSF and apical choroid plexus blood vessels [3]. The permeability of these barriers is regulated by tight junctions and adherence junctions [3]. The tight junctions are complexes of different proteins and adhesion molecules, whereas adherence junctions are transmembrane cadherins (named for calcium dependent adhesion) linked to the cytoskeleton [3]. Most viruses enter through the BBB, whilst coxsackie virus-B3, chikungunya virus, mumps virus and echovirus-30 may also use the BCSFB as their port of entry [3].

There are six different possible mechanisms for viruses to cross the barriers:

- Virus-carrying white blood cells squeeze through between the endothelial cells and deposit the viruses in the brain parenchyma [2]
- Some viruses enter the vascular endothelial cells directly and then cross over into the CSF [2]
- The open pores in the choroid plexus provide for direct entry of viruses into the CNS [2]
- The BBB is not intact in the circumventricular organs, for example the area postrema and lamina terminalis. This forms an ideal site for viruses to enter the CNS [2]
- The CNS lymphatic system as newly described by Louveau et al., in which the meningeal lymphatic vessels act as a reservoir for leukocytes, is a groundbreaking discovery [22] that may play an important role in future explanation of the pathogenesis of CNS infections [22, 23]
- The barriers are disrupted as a direct cytotoxic effect of the pathogen and secondary inflammatory mediators [3].

By step 4, when the viruses have entered the brain, it is very difficult to detect them as a result of their "hiding" in the cells and being almost invulnerable to immune control [6]. The BBB acts as a strong immunological barrier and hampers the migration of leukocytes into the parenchyma, while the BCSF is regarded as a selective gate primarily responsible for immune surveillance in the CNS [3].

Step five is the phase of injury, hallmarked by a cascade of events. It starts with the direct cytopathic effect, and para- and post-infectious inflammatory responses follow [13]. These responses are unique for specific viruses [3], and are influenced by viral tropism [2]. Viral tropism is the specificity that a virus has for a specific cell type of the host. Neurotropic viral tropism is summarized in Table 4.3 [2]. As an example, John Cunningham virus affects the oligodendrocytes [2], and therefore myelin production is compromised and

Table 4.3 Viral tropism in the central nervous system

Region or component of the central nervous system affected	Viruses
Meninges	Human enteroviruses
	Human immunodeficiency virus-1
	Japanese encephalitis virus
	Lymphocytic choriomeningitis virus
	Measles virus
	Mumps virus
	Nipah virus
Cortex	Alphaviruses
	Bunyaviruses
	Herpes simplex virus
	Japanese encephalitis virus
	Measles virus
	St. Louis encephalitis virus
	Tick-borne encephalitis virus
	West Nile virus
Cerebellum	Epstein-Barr virus
	Human enteroviruses
	West Nile virus
	Varicella-zoster virus
Brain stem	Human enteroviruses
	Poliovirus
	Rabies virus
	West Nile virus
Thalamus	Human enteroviruses
	Rabies virus
	West Nile virus
Hippocampus	Human enteroviruses
	Rabies virus
	West Nile virus
Choroid plexus/Ependyma	Cytomegalovirus
	Human enteroviruses
	Lymphocytic choriomeningitis virus
	Mumps virus
Oligodendrocytes	John Cunningham virus
Microglia	Human immunodeficiency virus
Anterior horn of the spinal cord	Human enteroviruses
	Japanese encephalitis virus
	Poliovirus
	Rabies virus
	Tick-borne encephalitis virus
	West Nile virus

Adapted from Swanson and McGavern [2] and Glaser et al. [7]
The viruses are listed in alphabetical order within each region or component

white matter is affected. Viruses that affect the temporal lobe are HSV, VZV, Epstein-Barr virus and HHV-6 [7].

The cytopathic effect of viruses elicits not merely brain inflammation, but intense brain inflammation with breakdown of the BBB, allowing further entrance of viruses; in addition, the repair mechanisms are restricted [2]. Due to the limited blood supply the brain depends more on cell than on humoral-mediated immunity. The interstitium is constantly patrolled by microglia and antigen presentation is weakly developed [2]. Apoptosis follows and the inflammation intensifies [2]. The cascade may further be complicated by autoimmune mediated mechanisms [13].

4.6 Clinical Manifestations

Viral infections of the CNS result in a spectrum of complex neurological syndromes and therefore clinical manifestations must always be interpreted in the context that relates to the specific patient, considering demographics, epidemiology and individual immune status.

4.6.1 Meningeal Irritation

Signs of meningeal irritation include neck stiffness, photophobia and a positive Kernig or Brudzinski sign [6, 11].

4.6.2 Encephalopathy

Encephalopathy is a change in the mental state of a patient characterized by an altered level of consciousness, and may refer to anything on the continuum from lethargy to coma, with alterations in the behavior or personality [4, 5, 9]. It is the result of diffuse cortical involvement [4]. A new-onset psychosis is more likely associated with an autoimmune encephalitis than with a viral infection [7].

4.6.3 Focal Neurological Signs

Focal neurological signs depend on the specific areas of the CNS that may be affected. Focal cortical signs may include, for example, aphasia, alexia or cortical blindness. If the motor area is affected motor weakness may be present, and abnormal sensation is experienced in the case of an affected sensory cortex. Cranial nerve fallout and visual defects are common. Deep tendon reflexes may be either absent or brisk, and primitive reflexes may appear. Cerebellar involvement will manifest as nystagmus, dysmetria, ataxia and dysdiadochokinesia [4].

4.6.4 Raised Intracranial Pressure

It is of utmost importance to diagnose raised intracranial pressure (ICP) clinically. The pressure may be normal in viral meningitis [24], but elevated in encephalitis [25]. Infants may have a bulging fontanel, splayed sutures, sunsetting eyes, vomiting, severe irritability or lethargy that may progress into coma [24]. Older children may have headache, vomiting, cranial nerve IV or VI palsies, a Cushing triad (elevated blood pressure with a slow pulse and respiratory slowing, coma and papilledema) [24]. Papilledema can take days to develop and may be absent in the initial stages. For less experienced clinicians it may be difficult to identify papilledema as a sign of raised ICP. When this is the case it may be helpful to assess the posturing (decorticate or decerebrate), respiratory patterns and pupillary responses [13, 25].

4.6.5 Seizures

Seizures are common in viral encephalitis and are often subtle, but intractable [7]. Such cases may evolve into status epilepticus and even non-convulsive status epilepticus [10]. If a patient presents with a new-onset status epilepticus a viral cause should be considered [7]. Patients with viral encephalitis may have electroclinical dissociation, so that motor activity during the seizure is not visible, and can be detected only with an EEG [10]. Other subtle clinical signs of seizures are a bitten tongue, injuries, and twitching of an eyelid or corner of the mouth [10]. Failure to control the seizures inevitably increases the metabolic activity, resulting in acidosis with vasodilation and increased ICP [13].

4.6.6 Acute Flaccid Paralysis

Flaccid paralysis occurs if the anterior horn cells are affected, and is associated with polio, enterovirus-71 and flaviviruses [10, 12]. Rabies also presents with a rapid ascending weakness [26].

4.6.7 Systemic Involvement

Many viruses cause multi-system involvement, so a careful examination should always be made for possible associated manifestations. This may assist the clinician in the selection of appropriate special investigations.

4.6.7.1 Skin Manifestations

A variety of skin manifestations are associated with neurotropic viruses. A vesicular rash is found with HSV and VZV [27]. Enteroviruses and coxsackie virus may also have an accompanying rash on the palms of the hands, soles of the feet and inside of the mouth [27]. Inflamed oral mucosa, referred to as herpangina, is often associated with coxsackie virus, HSV and adenovirus [27]. A slapped cheek appearance

in association with fever and headache is due to fifth disease, also called erythema infectiosum, caused by human parvovirus B19 [28]. Roseola infantum (sixth disease) has a morbiliform rash and is caused by HHV-6 [29]. An eschar from a tick bite may be hidden in the hairline or groin, between the fingers or toes, or even in the ear canal. Measles has a typical maculopapular rash [10].

4.6.7.2 Cardiac Manifestations

Cardiac manifestations in patient with CNS viral infections can be either primary or secondary phenomena. Primary cardiac involvement is caused by viruses with both neurotropic and cardiotropic features causing myocarditis. These cardiotropic viruses are EV, coxsackie virus, adenovirus, HIV, human parvovirus B19, HHV-6 and Epstein-Barr virus [30]. Hypotension and arrhythmias may be the result of brain stem encephalitis or be a subtle manifestation of seizures.

4.6.7.3 Respiratory Symptoms

Paramyxoviridae and influenza viruses may cause encephalitis preceded by respiratory symptoms [10] This was initially believed only to occur on rare occasions [7], but it has become evident that respiratory viruses are increasingly becoming relevant in the context of CNS-associated infections. Coronavirus, responsible for 20% of common colds, has been linked to fatal encephalitis in a child who was immunocompromised [31].

4.6.7.4 Gastrointestinal Symptoms

Enteroviruses, human parechovirus and rotavirus cause gastrointestinal symptoms and may also affect the CNS. Mumps is often associated with parotitis and abdominal pain due to pancreatitis and orchitis [13]. Patients with CMV and Epstein-Barr virus-associated hepatitis may have elevated liver enzymes [13].

4.6.7.5 Myositis

Myositis is a common symptom in influenza infections [10].

4.7 Differential Diagnostic Considerations

The diagnosis of CNS viral infections and confirmation of a specific etiology is a tedious process often veiled in both clinical and diagnostic uncertainties. Alongside the bed of a gravely ill patient with suspected CNS infections where the clinician is awaiting confirmatory results, it is inevitable that other differential diagnoses should be considered and excluded. The background information, history and clinical examination are crucial. The key questions necessary to draft a list of possible etiologies are [10]:

- What is the age of the patient?
- Where does the patient live?
- Is the child vaccinated?
- Is the child immunocompromised?
- Are other children affected?

- Is there a travel history or any possible exposure to ticks and mosquitoes?
- Which sites of the CNS are involved? [10]

Table 4.1 summarizes the viruses present in different geographical areas and the clinical manifestations associated with them [1, 10], and may guide clinicians towards possible etiologies.

In a child with an encephalopathy four groups of conditions should be excluded, namely infections outside the CNS, toxins, autoimmune and metabolic disorders [10]. Persistent metabolic acidosis may be a clue to an underlying metabolic disorder, because respiratory acidosis is the consequence of hypoventilation associated with a decrease in the level of consciousness [13]. Encephalopathy associated with a movement disorder is uncommon in uncomplicated viral encephalitis. Where it is present, autoimmune encephalitis, ADEM, streptococcal infection or mycoplasma infections should be considered.

The differential diagnoses for a lymphocytic pleocytosis in the CSF or aseptic meningitis are partially treated meningitis, tuberculous meningitis, HIV encephalopathy or – often overlooked – neighborhood syndrome frequently associated with mastoiditis. A lymphocytosis in the blood supports a viral etiology [13].

When there is cranial nerve involvement in a patient with encephalopathy, HSE, tuberculous meningitis, raised ICP, Bickerstaff (brain stem) encephalitis or Miller Fischer syndrome should be considered.

Hydrocephalus is not associated with encephalitis, but rather a complication with meningitis caused by other bacteria, tuberculous, fungi or cryptococcus [7].

4.8 Diagnostic Procedures and Special Investigations

Brain biopsies have been the gold standard for confirming viral encephalitis, but they are invasive and unfeasible in most centers. Various other investigations have thus been developed for use in the first tier of investigations. A stereotactic brain biopsy has a place only if a diagnosis remains unable to be confirmed after a week and other alternatives have been considered, and then only provided it is performed by an experienced neurosurgeon [10].

To make an accurate diagnosis, the interpretation and integration of different test results should be done with caution, as there is no single solution that addresses all possibilities, and every modality has its limitations. Furthermore, interpretation of test results should always be correlated with the patient's clinical condition, and CSF analyses, done in the acute phase, should be paired with those done in the convalescent phase [20].

4.8.1 Lumbar Puncture

It is relatively easy to collect CSF, but always exclude any contraindications before it is performed. These contraindications are summarized by Kneen et al. and Boyles

et al. [10, 32]. The first group of contraindications, which necessitates imaging before an LP, includes the following:

- A change in the level of consciousness, or coma. There is no consensus on the depth of the coma, but the British Guidelines recommend that prior imaging is indicated if the Glasgow coma scale is less than 13 or fluctuates more than 2 [10]
- The presence of papilledema. Clinicians should bear in mind that papilledema may take time to develop, and will not be observed in the initial clinical assessment [32]
- Relative bradycardia in the presence of hypertension or abnormal doll's eye movements [10]
- New-onset focal neurological deficits including unequal, dilated or poorly responsive pupils [10, 32]. If the level of consciousness is normal, isolated cranial nerve palsies are, however, not regarded as a contraindication to performing an LP [32]
- Inexplicable seizures. These should first be stabilized [32] and stabilization should be followed by imaging
- Patients with ventriculoperitoneal shunts in situ [32]
- Immunocompromised patients [10].

If a computed tomography (CT) scan reveals midline shifts or narrow basal cisterns associated with space-occupying lesions or brain edema it is dangerous to perform an LP as it may precipitate brain stem and/or tonsillar herniation [10]. It is very important to remember that CT scanning cannot be used to rule out raised ICP; this remains a clinical diagnosis [10].

Other contraindications to LP include:

- Underlying coagulation disorders with unexplained bleeding from mucous membranes, a petechial rash, expanding purpura or other features associated with disseminated intravascular coagulopathy [32]. Although a platelet count $<100 \times 10^9$/L is used as a cut-off point, an LP may still be possible after careful consideration if the platelet count is 50×10^9/L [10]
- Sepsis in the area of the LP site
- Hemodynamic instability with shock and respiratory insufficiency [10, 32].

If an LP cannot be performed, the patient must be reviewed every 24 hours and then the LP must be performed as soon as the contraindications are cleared [10]. If the analyses of the CSF obtained with the first LP are non-diagnostic, the LP should be repeated 24–28 hours later [10].

4.8.2 Cerebrospinal Fluid

The analyses of CSF include assessment of the opening pressures, the biochemistry, the different cell types and the microbiology [10]. The normal opening pressure is 10–20 cm H_2O, but this can be normal or mildly elevated in viral encephalitis [10].

4.8.2.1 Biochemistry

The brain is protected by the BBB and therefore the CSF is merely an ultrafiltrate of plasma filtrates across the BBB, containing water, electrolytes, glucose and protein – mostly albumin because of its low molecular weight. The protein concentration of the CSF is very low in comparison to that of the serum. Under normal conditions albumin is 50% of the total protein in the serum, but the major protein in CSF. Immunoglobulins may be present in the CSF of normal individuals with an intact BBB, in which case the immunoglobulin G (IgG):total CSF protein is in the order of two thirds of the serum IgG:total protein. The CSF protein concentration increases either when the BBB is damaged or when intrathecal IgG production occurs. Various indices help in determining whether the BBB is intact and in ascertaining the contribution of intrathecal IgG synthesis. It is important that serum and CSF are sent to be analyzed simultaneously [33].

High resolution electrophoresis and isoelectric focusing are techniques to determine protein bands in specimens. Normal individuals will have no bands in the CSF that do not correspond to bands present in the serum. If there is intrathecal IgG production then additional bands will be detected in the CSF, and if two or more different bands are present these are known as oligoclonal bands. If the BBB is damaged it may help create additional bands. To distinguish between intrathecal IgG production and the contribution from IgG in serum that might have leaked across the BBB, four indices are helpful provided that the tap is not traumatic: the albumin index (Q_{Alb}), IgG index, IgG synthesis rate and local IgG synthesis [33].

Albumin is not produced intrathecally and therefore the ratio of CSF to serum albumin concentration, or Q_{Alb}, is constant in healthy individuals, and less than 9.0. When the BBB is damaged albumin leaks into the CSF and the albumin concentration increases. The Q_{Alb} reflects the degree of damage: if it is more than 100 then there is almost total breakdown of the BBB [33].

The IgG index or quotient (Q_{IgG}) is the CSF:serum IgG ratio, and can be elevated with either intrathecal IgG production or BBB damage; the Q_{Alb} is normal in the case of the former and elevated in the case of the latter.

The IgG synthesis rate is a formula for calculating the amount of intrathecally produced IgG by correcting for differences in molecular weights, daily CSF production and possible serum IgG in the event of the BBB being damaged. The reference range is −9.9–3.3 mg/day, but false elevated levels may occur if the BBB is damaged [33].

Local IgG synthesis calculation is valuable because the diagnostic sensitivity is high and the false positive rate is low. It is used to determine the minimum amount of local synthesis in the CNS. Any value above the upper limit of normal (0.0 mg/dL) in conjunction with an elevated Q_{IgG} is strongly suggestive of increased intrathecal IgG synthesis [33].

The biochemical analyses of the CSF also include lactate and glucose in addition to the determination of protein. The glucose has to be compared to a plasma glucose which should be taken before the LP [10]. For viral-related CNS infections the protein is normal or mildly elevated (<0.95 g/L), the glucose ratio normal or decreased

(normal = >0.4–0.5), and the lactate normal. Albuminocytologic dissociation (elevated protein and normal CSF cell count) is a strong marker for acute and chronic demyelinating polyneuropathies, but may be detected only after at least 1 week of illness [34].

4.8.2.2 Cell Types

There are immune cells in the CSF of healthy persons, but in limited numbers [3]. The majority of the cells are $CD3^+$ memory T cells, $CD4^+$ and $CD8^+$ cells. The group of B-cells, natural killer cells, dendritic cells, mast cells, monocytes and polymorphonuclear granulocytes is in the minority and makes up not more than 20–30% of the immune cells [3]. CSF leukocytosis is an indicator of an inflammatory process [4, 7, 9], but the composition of cells changes constantly during the disease progress and is also influenced by the primary site of infection [3]. An increased number of leukocytes is more likely in viral meningitis than in encephalitis [3]. If the primary site is the meninges the number of leukocytes in the CSF is increased, with polymorphonuclear granulocytes the dominant cell type early in the disease, followed later on by monocytes and lymphocytes [4, 10]. In encephalitis the CSF may be normal in up to two thirds of cases [3]. Sejvar et al. define CSF pleocytosis as >15 cells/mm^3 in babies less than 2 months of age and >5 cells/mm^3 in older infants and children [4]. However the CSF may also be completely acellular, and this has been associated with VZV, Epstein-Barr virus and CMV infections. It is also often observed in immunocompromised patients [10].

Red blood cells (RBC) are elevated in approximately 50% of HSE cases [10]. The differential diagnoses for an elevated RBC include a traumatic tap or subarachnoidal hemorrhage. In the case of a traumatic tap, corrections should be made for the protein and cell counts [10]. Although more complicated formulae adjusting for anemia and peripheral leukocytosis are available online at http://reference.medscape.com/calculator/csf-protein-concentration-correction, a simplified way to correct for the influence of a traumatic tap is to subtract one white blood cell for every 700 RBC/mm^3 and 1.1 mg/dL protein for every 1000 RBC/mm^3 [35, 36].

4.8.2.3 Microbiology

Microscopy, culture and sensitivity for bacteria should be performed on all CSF samples. Antigen detection may also be helpful [10]. Testing for *Mycobacterium tuberculosis* should always be considered in endemic areas and in immunocompromised patients [10]. Specific virological studies on CSF depend mainly on epidemiology. It is advisable to keep and store an extra CSF sample if further specific investigations are indicated [10, 20]. Viral cultures nowadays play an inferior role in the identification of the viruses, because they are costly and have a low yield [20]. They are still used to serotype enteroviruses [20].

Polymerase chain reaction (PCR) has changed diagnostic virology because it can detect low copy numbers and has a high sensitivity in the detection of viruses, but the diagnostic window has not been clearly described for viruses other than HSV [37]. Despite this a CSF specimen for HSV-1, HSV-2, VZV and enteroviruses should be sent for PCR for patients with suspected viral CNS infection, as it will

identify 90% of known viral causes. A HSV PCR is often negative for the first 3 days after the onset of the disease [32], and then remains positive for the next 7–10 days even if acyclovir treatment has been started [10]. The probability of getting a positive PCR is thus reduced if the sample is taken early (that is, within 3 days) or late (after 14 days) in the course of the disease [37]. It may be worthwhile to defer the initial LP for two reasons: if there is a contraindication for the LP due to severe cerebral edema, and to give time for the edema to subside and the PCR to have a better diagnostic yield. There is a correlation between viral replication, degree of clinical severity and the possibility of a positive PCR.

Furthermore, a positive PCR result should be interpreted with caution, because three different scenarios should be considered: firstly a primary infection, secondly the reactivation of a latent infection, and thirdly concomitant infection that may stimulate reactivation of a latent virus [20]. The fact that more than one type of virus can be in the brain simultaneously, and that there can be an interplay between them, complicates matters further [20]. False positive and negative results are always an issue of concern, and therefore it is important to standardize the molecular diagnostic tests. This is illustrated clearly in a study that examined nine different European reference laboratories and found concordant results in only 28–32% of specimens tested for HSV by PCR, whereas real-time PCR has 94% specificity and almost 100% sensitivity [38].

The selection of additional microbiological investigations is directed by the clinical features, travel history and local epidemiology [10]. Virus cultures or PCR on samples from other sites are useful in specific cases. Rectal and throat swabs should be investigated for enteroviruses in all cases of encephalitis [10]. For respiratory viruses, a PCR on throat swabs or sputum is indicated if a patient has had a recent respiratory infection [10].

4.8.2.4 Cytokines, Chemokines and Associated Mediators

There is a constant drive to explore novel ways to assist in the diagnosis of encephalitis and to differentiate between infectious, immune-mediated and unknown etiologies. Although a detailed discussion of the diagnostic value and role of mediators in CNS infections falls beyond the scope of this chapter, it has been shown that the cytokine and associated mediator profiles particularly, differ in the CSF of patients with an underlying infection and of those with an immune-mediated pathology [39].

Cytokines are polypeptide messengers and important regulators in a variety of biological processes, but particularly of importance in proinflammatory and anti-inflammatory processes [3]. Four groups of cytokines have been identified. The first group (interleukin (IL)-1, IL-5, IL-6 and IL-8) is involved in innate immunity, the second group (IL-1, IL-4 and transforming growth factor (TGF)-ß) orchestrates inflammatory processes, the third group (IL-2 and IL-4) is responsible for the activation and proliferation of lymphocytes and the fourth group (IL-1, IL-3, IL-5, IL-6) is involved in leukocyte growth [3]. Chemokines are specific cytokines involved in the attraction or trafficking of other cells. There are four subgroups, CXC, CC, XC and CX3C [3].

4.8.3 Serology

Although serology, in practice, refers to the antibodies in the blood, in the context of CNS viral infections the CSF antibodies are also measured and interlinked with the serological diagnosis of viral infections. Serology in general is of limited value unless serial samples are analyzed and serum and CSF results are compared. Antibody production is a dynamic process. It takes 10–14 days for antibodies to become positive initially, and then antibodies steadily rise to peak production and remain positive for years in latent infections [10, 20].

There are certain specific scenarios where serology is beneficial. The presence of Immunoglobulin M (IgM) in CSF is an indication of an intrathecal antiviral immune response and is more useful in RNA viruses, such as flaviviruses, which are usually primary infections and not merely reactivations of DNA virus-associated disease [10]. The serological investigations for Epstein-Barr virus or arboviruses are useful if any of these are suspected as the cause of CNS infection [10]. In the case of Eastern equine encephalitis, serum antibody testing is most helpful, as the disease can be detected within 6 days of onset, and increases fourfold in just 4 days [40]. As seroconversion is a dynamic process, serial specimens should be analyzed and the results should be paired with the CSF results [20]. The interpretation of CSF serology is discussed in Sect. 4.8.2.1.

4.8.4 Imaging

Acutely ill patients with the possibility of a CNS infection are usually imaged to exclude other possible causes or complications, but the limitations of imaging should always be kept in mind. A recent study by Granerod et al. shows that there is a “subjective component to scan interpretation”. The matter is further complicated by the fact that imaging data are also influenced by the timing of the scan and the specific imaging techniques. These factors directly influence the value of imaging among diagnostic criteria for encephalitis, other than HSE, based on radiological abnormalities. Further research in this area is required [41].

4.8.4.1 Computed Tomography of the Brain

It is common practice to perform a CT brain scan before an LP is performed if there is any doubt about relative contraindications. An LP should not be performed if there is overwhelming brain edema with swelling, or any midline shifts or space-occupying lesions [32]. A normal CT brain scan is, however, not a guarantee that the ICP is normal [32]. In the case of HSE, a first CT scan may also be normal, with abnormalities detected only in a follow-up scan [10].

4.8.4.2 Magnetic Resonance Imaging

Under ideal circumstances an MRI scan should be performed on all patients with suspected encephalitis within 24–48 hours after admission to hospital [10]. For specific details, refer to the different sections on clinical syndromes of viruses.

4.8.5 Electroencephalogram

An EEG is not routinely done on all patients with suspected encephalitis, but is useful to confirm encephalopathy and to exclude possible psychiatric conditions as an alternative reason for associated behavioral changes [10]. It is also important to detect seizure activity in subtle or non-convulsive seizures [10], because seizure activity has a significant effect on the development of brain edema and worsens coma. A recent study by Mohammad et al. shows that an early EEG is a non-specific marker for encephalitis and has a high sensitivity, as 86% of patients in the study had abnormalities on their first EEG [42].

The general characteristic EEG features of encephalopathy are slowing and focal or generalized epileptiform features [25]. More specific patterns have also been described. Periodic lateralized epileptiform discharges have been regarded as pathognomonic for HSE, but it may also occur in patients with SSPE [10]. An early reactive EEG background and extreme spindles have been associated with anti-NDMAR encephalitis [42].

EEG has some prognostic value in encephalitis. A normal EEG in patients with suspected encephalitis is associated with a low relative risk for death [43], but a non-reactive background in an EEG performed early in the disease predicts abnormal outcome [42].

4.8.6 Additional Investigations

It is advised that HIV must be excluded in every patient with encephalitis for a number of reasons. Patients may present with acute meningoencephalitis during the primary HIV-1 infection or longstanding encephalopathy. HIV predisposes the patient to other rarer CNS infections, such as CMV, and the incidence of common CNS infections is higher in HIV-infected patients [10]. Other additional investigations are selectively requested on the basis of specific systemic involvement.

4.9 Treatment

4.9.1 General Measures

Ensure that the patient is hemodynamically stable and treat hypoglycemia, which is often present in viral encephalitis, instantly [13]. Treat seizures and raised ICP according to standard protocols [13], but because the pathogenesis of raised ICP, associated with viral encephalitis, is different to that of other contexts, further studies are essential to investigate the efficacy of specifically edema-lowering modalities [44]. Observe for autonomic instability. While results are pending treatment should be administered without delay and should include broad-spectrum antibiotics, often a third-generation cephalosporin and acyclovir [13].

The role of steroids as adjuvant therapy for HSE is still controversial, and steroids should thus not be administered routinely [10]. Results are currently awaited from a multicenter, multinational, double-blind placebo-controlled European study known as the German Trial of Acyclovir and Corticosteroids in HSE [45].

4.9.2 Antiviral Treatment

Empirical treatment with intravenous acyclovir should be started sooner rather than later, and within 6 hours of hospital admission, if viral encephalitis is strongly suspected [10]. This is usually combined with a third-generation cephalosporin for possible bacterial meningitis. There are two treatment categories. In neonates a higher dosage of acyclovir, 20 mg/kg per dose 8 hourly, is administered and if HSE is confirmed it is continued for a period of 21 days [46, 47]. In children of 28 days to 16 years, acyclovir should be started at 10 mg/kg 8 hourly IVI and continued for 14–21 days if HSE is confirmed, and then the LP should be repeated to confirm that the CSF PCR is negative for HSV [10, 46]. If the PCR is positive in the repeat LP, acyclovir should be continued and PCR should be performed weekly until it becomes negative [10]. The dose should be reduced for patients with renal impairment [10].

The next question to be answered is when the acyclovir can be stopped if the patient with the suspected encephalitis has a negative HSV PCR. If the patient is immunocompetent it can be stopped as soon as another diagnosis has been confirmed, or when the HSV PCR has been negative on two LPs, performed 24–48 hours apart and there are no HSV-associated characteristics on the MRI at least 72 hours after the onset of the disease [10]. In a case where the LP has been deferred for some reason, acyclovir has been started empirically and the patient has subsequently improved, the acyclovir can be stopped if the level of consciousness is normal, both the HSV PCR and the MRI performed 72 hours after symptom onset are normal, and the CSF white blood cell count is less than 5×10^6/L [10].

An alternative, simplified regime for HSE involves administering acyclovir intravenously at 10–15 mg/kg per dose 8 hourly for 21 days [6]. It has also been suggested that all patients should have a CSF HSV PCR negative to confirm that treatment can be stopped [47]. Some patients have benefitted from a second course of acyclovir, which supports the hypothesis that the virus has not been completely inactivated and it may be related if a shorter course of acyclovir has been given [48]. Suppressive acyclovir treatment for a period of 6 months has been associated with less damage and fewer episodes of recurrence [6]. It is most likely that patients with post-infectious encephalopathy will benefit from steroid therapy rather than acyclovir [49].

Oral acyclovir cannot be used for HSE, because it does not reach adequate levels in the CSF. Valacyclovir has been used orally in children after 10–14 days of intravenous acyclovir when venous access became problematic, but it is not registered for use in children and further research is required [10].

In the case of VZV encephalitis the dose is higher, namely 15 mg/kg 8 hourly for 14 days in all age groups. Treatment should be continued if the patient is immunocompromised [10]. VZV cerebellitis does not require treatment, because it is a self-limiting disease resolving within 3 weeks [10], but if vasculopathy is present corticosteroids are indicated [10].

Enterovirus encephalitis is not routinely treated, but intravenous immunoglobulin has been used in patients with chronic enterovirus meningitis or severe enterovirus-71 infection [10]. Treatment protocols for CMV encephalitis have not been well established, but ganciclovir, foscarnet and cidofovir have been studied in open-label studies [10].

4.9.3 Treatment of Autoimmune Encephalitis

Evidence for specific protocols is still lacking, but aggressive treatment in the acute phase includes intravenous steroids, plasma exchange or immunoglobulins. Such treatments are then followed up with oral steroid and corticosteroid sparing drugs, for example azathioprine and cyclophosphamide [10, 13].

4.9.4 Novel Therapies

There is a constant search for novel drugs in the treatment of viral-related CNS infections and a detailed discussion falls beyond the scope of this chapter, but there are a few interesting ideas that deserve mention. Nucleotidyltransferase superfamily enzyme inhibitors have been identified as a potential novel treatment for HSV infections and suppress the replication of the virus [50]. Significant advances in gene editing have been made and include three possible strategies in antiviral drug development: zinc-finger nucleases, transcription activator-like effector nucleases and clustered regulatory interspaced short palindromic repeat-associated nine systems [51].

4.10 Complications and Prognosis

The complications and prognosis vary in the different clinical syndromes of CNS infections due to viruses [52]. The mortality rates for encephalitis vary between five and 15% [52]. The morbidity for encephalitis in adults has been reported as 20% [52].

In the acute phase status epilepticus, coma, thrombocytopenia, hyponatremia as a result of inappropriate secretion of antidiuretic hormone, and cerebral edema are serious complications. Cerebral edema is the result of direct viral infection, for which enteroviruses are known, or for seizure activity. Both the seizure activity and accompanying hypoxia in untreated convulsive status epilepticus may contribute to the maintenance of a vicious cycle of continued cell damage.

A number of studies identify prognostic factors in the acute phase. Cerebral edema, status epilepticus and thrombocytopenia were associated with in-hospital mortality [52]. Additional poor prognostic factors are a lower level of consciousness on admission, hypothermia and elevated CSF protein [52]. The presence of glial and neuroaxonal protein in CSF are indicative of inflammation and neuronal damage and are potential biomarkers to determine prognosis [52]. Lower quality-of-life scores have been found in patients who had abnormal MRI findings or were admitted with seizures that resulted in epilepsy [53]. A normal EEG has been associated with survival [52].

Long-term outcomes are not always very well described or quantified, but an Israeli study found attention deficit hyperactivity disorder and behavioral disorders each to be present in 50% of individuals, with 10% of patients showing residual motor deficits. It has also been documented that cognition was affected [52]. Other long-term sequelae are spasticity, epilepsy, movement disorders and feeding difficulties [13]. A systematic review and meta-analysis by Khandaker et al. concluded that almost 50% of children show incomplete recovery, and the sequelae are developmental delay, behavioral disturbances and other neurological complications, including seizures [54]. Patients treated for anti-NDMAR encephalitis in the acute phase generally have good outcomes, but 50% may experience complications from chronic use of immunotherapy [55]. It has been shown that there is a relationship between patients readmitted after the acute illness and the development of neurological sequelae, as well as between the later onset of epilepsy in patients with neurological sequelae [56].

4.11 Prevention

The first and foremost preventative strategy is to avoid exposure. Hygiene is important in such avoidance. Protection against vectors includes the wearing of protective clothing, control of breeding sites and use of insect repellents [57, 58], although insect repellants are not always effective anymore. Insects become insensitive to insecticides, and climate variability and change in vegetation influence the survival of arthropods [58].

The second important strategy in the prevention of CNS viral infections is vaccination. There are vaccines available for mumps, measles, rubella, influenza, Japanese encephalitis virus, rabies and tick-born encephalitis virus [5]. A group of researchers has however found that the current vaccine against Japanese encephalitis virus may not protect against a the new emerging G5 strain of the virus [59]. A new vaccine against enterovirus 70 and 71 has been proven successful [6]. The biggest threat to successful prevention through vaccination is low vaccination coverage due to religious beliefs, mistrust and inadequate vaccination programs as a result of many different reasons [58].

The majority of vaccines are against communicable diseases and very few exist for use against arboviruses [58]. In response to this problem scientists are investigating different innovative strategies. Most of these are aimed at preventing the

virus from completing its life-cycle in the vector, ultimately preventing transmission to humans. These vaccines are called transmission blocking vaccines [58]. One example is dengue virus vaccine. The proteins required in the mosquito for the attachment of the virion to target cells in its midgut, are used in the vaccine as antigens. When a mosquito feeds on a vaccinated human, the antibodies are ingested and subsequently impair the virion attachment in the mosquito, interrupting the completion of its life cycle. This blocks any further transmission by preventing infection of the vector. This type of vaccine is referred to as an "altruistic" vaccine because, while it may not protect the person who has been vaccinated from infection, it prevents the disease from spreading to other members of the community [58]. Significant advances have been made in development of transmission blocking vaccines to control viral vector-borne disease, but further research is still required [58].

4.12 Specific Viruses

Specific characteristics and manifestations of the different viral families and relevant species are highlighted in this section.

4.12.1 Herpesviridae

The family *Herpesviridae* is a large family of double-stranded DNA viruses. The species commonly associated with CNS viral-related diseases are CMV, Epstein-Barr virus, HSV-1, HSV-2, HHV-6 and HHV-7 and VZV [3]. It must be noted that the test specificity for differentiating between the lymphotropic herpes viruses (Epstein-Barr virus, CMV, HHV-6) and neurotropic viruses (HSV, VZV), varies and is much better for the latter [60].

4.12.1.1 Herpes Simplex Virus

Herpes simplex viruses, including type 1 and 2 are the most common causes of sporadic encephalitis in children and one of the few treatable causes [8, 61, 62]. Schleede et al. report in their multicenter study that HSV-1 accounts for 97% of the HSE cases they studied and HSV-2 caused only 3% [62]. The morbidity and mortality are severe and the mortality rates vary from 11 to 19% [8]. Neonates are more affected by HSV-2, but HSV-1 is the predominate type in non-neonates [46, 62]. Males are more readily affected than females [63].

The virus migrates along the trigeminal or olfactory nerve to the brain and causes HSE predominantly affecting the temporal and frontal lobes of the brain. It results in focal neurological signs. HSV may remain latent in the dorsal roots of the sensory ganglia throughout life [3]. Two thirds of HSE case are not during the primary infection, but due to reactivation or reinfection [64].

The central chemokine receptors (CCR2, CCR5 and CXCR3) and related ligands (CCL2 and CCL5) are the main role players in the pathogenesis of HSV-1 infection

in humans [3]. The ligand CCL5 is presented by T-cells and macrophages which are important in leukocyte migration. In an experimental model for HSV-1 and autoimmune encephalitis, the interaction between CCL5 and CCR5 has played an important role in the recruitment of T-cells into the CNS [3, 65]. The chemokines CCL2, CCL5, CCL9 and CCL10 were elevated in the trigeminal ganglia and brain stems of $CCR5^{-/-}$ mice infected with HSV-1. The consequence was an increased viral load, followed by an increased $CD4^{+}$and $CD8^{+}$ infiltration in the respected areas [3, 66]. Interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) are elevated in the CSF of patients with HSE and may contribute to demyelination [67].

The clinical presentation of children with HSE varies; de Tiège et al. summarize eloquently the spectrum of disease [63]. It can present with acute onset of fever, encephalopathy, seizures and focal signs, but sub-acute and milder forms have also been described [63]. The fever may be absent initially [63]. Opercular syndrome, hallmarked by dysarthria, dysphagia and oro-facial palsy, may also manifest [63]. In the California Encephalitis Project, two age groups in which HSE peaks were identified [68]. The first group includes younger children, from 6 months to 4 years, and the second peaked in the age group 10–18 years [68]. Lethargy, fever, confusion and seizures are the most common manifestations, but seizures are observed more commonly in the younger age group, and the difference is statistically significant [68]. In contrast to adults, children who develop encephalitis with primary HSV infection may be affected by herpes labialis [10]. Deaths observed in this project were all in children older than 13 years, but this point was not statistically significant [68].

Patients who have had HSE may find it recurs [69]. Such relapses may happen early, within weeks after the disease, or later, after months or years [70]. Relapse rates of up to 24% have been reported [62]. The reactivation of the virus is triggered by the release of corticosteroids under stressful conditions responsible for activating the c-Jun N-terminal kinases pathway. The methylation/phosphorylation switch is then switched on and viral gene expression can proceed [71]. Patients present with a variety of neurological symptoms, of which abnormal movement is the most common, present in 56% of patients studied by Schleede et al. Other important clinical manifestations are lethargy, seizures, hemiparesis and cranial nerve palsies [62]. Patients may have a negative HSV PCR during these episodes [69].

The CSF may be normal in up to 5% of patients, but protein may be elevated and continue to rise even after treatment has been started [46]. It may even stay elevated after the treatment is stopped [46]. In the California Encephalitis Project, only 47% of children with HSE had elevated protein in the CSF, while 95% of them had pleocytosis with a median of 47 cells/mm^3, and the median RBC count was only three cells/mm^3 [68]. De Tiège et al. note also that polymorphonuclear cells may predominate early in the disease process, and the disease may then be mistaken for bacterial infection [63]. The RBC may be elevated, reflecting underlying necrosis [63]. Glucose in the CSF may be normal or slightly decreased; 13% of patients in the Schleede et al. study had values <2.8 mmol/L [62].

The gold standard for diagnosis remains an HSV PCR [46, 72]. The PCR may be negative initially, but become positive if the LP is repeated 2–4 days later, with a median of 6 days after the onset of symptoms [68]. Multiple hypotheses have been

suggested to explain the false negative PCR. One of the reasons may be a very low viral load in the CSF at the onset of the disease [69]. A link between a negative PCR and low CSF protein and white cell count has also been described [69].

Fluid from vesicles may be sent for PCR if it is present in a primary HSV infection, but most cases of HSE and VZV encephalitis do not have skin lesions [20]. It is also true that a peri-oral vesicle does not mean the patient has associated encephalitis as well.

Serology is often not helpful to confirm a diagnosis in the initial stage, because it can take up to 2 weeks for HSV IgM to be produced intrathecally [73]. HSV IgG can be detected in the CSF 10–14 days after the onset of illness, then rises to peak at around 30 days and may be detectable for years after the disease [10].

Imaging, including CT and MRI scans, is helpful in the diagnosis. MRI is more sensitive, and 95% of patients in the California Encephalitis Project had abnormal MRI findings [68], but MRI findings may nevertheless be normal [62, 68]. Although temporal lobe involvement was present in 86% of patients, 59% had extra temporal lobe abnormalities either in association with temporal lobe abnormalities or in isolation [68]. T2-weighted images may demonstrate signal changes right at the onset, followed by diffusion-weighted changes visible 3 days after the onset of symptoms [62, 68]. Contrast enhancement in MRI becomes positive over a period of 4–90 days after the onset of symptoms. T1-weighted changes develop during the course of the illness and can be normal, high or low. Necrotic lesions develop later, at 2 weeks, after the onset of symptoms [62]. Neonatal MRI images differ from those of older children. The parietal lobes, occipital lobes and insula may be affected more frequently than the temporal lobes [62]. Diffuse white matter lesions occur in patients with relapse HSE [62].

The diagnosis is also supported by EEG. The most common finding in the California Encephalitis Project was the presence of multifocal or diffuse slowing in 53% of patients. Periodic lateralized epileptiform discharges were present in 13% of the cases, and focal epileptiform discharges were identified in 13% of patients [68].

Prompt treatment limits morbidity and mortality, but if HSE is left untreated the mortality rate is 70%, and only 2.5% of patients may recover completely [6, 61]. For a more detailed discussion of treatment refer to Sect. 4.9.2. It is documented that immunotherapy is 100% beneficial in the treatment of autoimmune post-HSE [74].

4.12.1.2 Varicella-Zoster Virus

A highly contagious virus, VZV presents with fever and a vesicular exanthema [1]. Two different disease patterns are recognized, namely chickenpox during the primary infection and shingles or herpes zoster during reactivation [75]. The rash may precede the CNS infection, but it may be completely absent or even appear later [10]. The CNS is involved in one to three in 10,000 clinical cases, and it manifests as encephalitis, vasculopathy or post-infectious immune-mediated cerebellar ataxia [1, 10]. The latter is often benign and self-limiting, but hydrocephalus may develop if the cerebellum is extensively swollen [10]. Around one third of arterial strokes in children can be associated with VZV; from 1 week up to 48 months after the rash,

patients present with acute-onset, but permanent, hemiparesis [10]. Other clinical features include transient facial weakness, chorea, seizures, and visual and speech disturbances [10]. The VZV PCR may be positive in only 30% of cases, but VZV IgG antibodies are positive in as many as 90% of cases. It is recommended that both assays are done [9]. The CSF IgG levels must be compared to serum VZV IgG to confirm intrathecal synthesis [10].

4.12.1.3 Cytomegalovirus

CMV is the HHV with the largest genome and affects mainly immunocompromised patients, with an expanded range of clinical manifestations including encephalitis, meningitis, extensive transverse myelitis and polyradiculomyelitis. The outcome is highly variable. The major sites of the brain that are affected are the basal ganglia, brain stem and diencephalon. Although astrocytes are commonly infected, almost all the other cell types in the CNS can be involved. Congenital CMV infection causes severe cerebral palsy, cognitive impairment and sensorineural deafness [75]. CMV can be treated with acyclovir, but the effectiveness in CNS complications is unclear.

4.12.1.4 Human Herpes Virus-6

There are two species of HHV-6, A and B, and these are important pathogens in both immunocompetent and immunocompromised patients [76], and are common in the general population, with 90% of the population already seroconverted at the age of 1 year [77]. These viruses have, in addition to lymphotropic and neurotropic features, the ability to be integrated into the telomeric regions of the chromosomes of the host and subsequently to be transmitted vertically with a Mendelian pattern of inheritance, via infected organs in organ transplantations, and transplacentally [76]. Babies with congenitally-acquired HHV-6 may exhibit an inability to control exogenous HHV-6 and may suffer from neurological symptoms [76].

There are three stages of disease manifestation. The primary infection is a febrile illness in infants, with fussiness and rhinorrhea and the possibility of encephalitis. The second stage is in children and adults, with roseola infantum (sixth disease), a common disease in childhood. The virus replicates in the salivary glands, is spread via saliva, and becomes latent in the monocytes and lymphocytes. In addition to meningitis and encephalitis, other diseases associated with HHV-6 are multiple sclerosis, temporal lobe epilepsy and status epilepsy. The third stage is due to re-infection or reactivation of the virus in immunocompromised patients [77].

The role of HHV-6 in the pathogenesis of seizure is currently being actively researched. Mohammadpour Touserkani et al. have conducted a meta-analyses and systematic review on this topic, and although there are interesting findings on potential mechanisms involving HHV-6, microglial cells, oligodendrocytes and the immune regulatory effect of astrocytes, further studies to validate the relationship are required [77]. It is however clear that HHV-6 may be present in 19% of children with febrile seizures and that some children with febrile-associated status epilepsy are infected with HHV-6 [77].

HHV-6 poses some difficulties to diagnose, because the viral DNA integrates into the host DNA and consequently high levels of HHV-6 DNA are detected in CSF, blood and plasma [78]. Treatment during the primary infection is not indicated, but ganciclovir and foscarnet may be used firstly, and cidofovir secondly, in reactivation of HHV-6 CNS infections [76, 79]. Another consideration to bear in mind is the fact that the unnecessary use of antibiotics and cortisone in a small child with fever and a skin rash may aggravate viral replication. *In-vitro* experiments have shown that amoxicillin, carbamazepine and valproate activate HHV-6 and cortisone my increase the viral load in CSF [76].

4.12.1.5 Epstein-Barr Virus

CNS infection due to Epstein-Barr virus accounts for less than 5% of primary Epstein-Barr virus infections [75]. Epstein-Barr virus causes encephalitis and encephalomyelitis in teenagers in the absence of the typical infective mononucleosis features, but it may also occur shortly before, or after, infective mononucleosis [75]. Infections in the CNS may also be due to reactivation or post-infectious immune-mediated responses [75]. Visual hallucinations may be a specific characteristic in association with other signs of encephalitis [10]. The outcome varies, and patients with isolated gray or white matter lesions recover well, but almost half of patients in whom the thalami are affected will have residual effects, and the highest mortality is among patients with brain stem involvement [75].

4.12.2 Polyomaviridae

John Cunningham virus is a double-stranded DNA virus from the family Polyomaviridae [3]. Infection during childhood is very common and usually asymptomatic [1]. It is postulated that the virus may persist as a latent infection in the kidneys or mononuclear cells, and then reactivate if the patient becomes immune suppressed [1]. The cerebral white matter is seriously affected, with patchy and confluent demyelination [1]. Other clinical manifestations include rapid neurocognitive deterioration, focal neurological signs, visual field defects and ataxia [1]. Patients may die within 6 months after the onset of the disease [1]. The diagnosis can be confirmed with CSF PCR or a brain biopsy [1].

4.12.3 Flaviviridae

Flaviviridae are single-stranded RNA viruses of which tick-borne encephalitis virus, Japanese encephalitis virus, Zika virus and West Nile virus (WNV) are responsible for severe CNS infections [3]. These viruses are transmitted through tick or mosquito bites and are therefore also referred to as arboviruses. The term "arbovirus" is an acronym for "**AR**thropod-**BO**rne" virus, including not only flaviviruses, but also other viruses, like chikungunya virus, from the family Togaviridae [58].

Outbreaks of WNV are increasing in Europe and North America, and a range of animal models have been studied to explain the pathogenesis. Although a range of cytokines and chemokines that are involved have been identified many questions remain unanswered, but the specific role played by IL-1ß in the attraction of immune cells and regulation of WNV-induced inflammation is unique, and deserves mention [3]. Only a small portion of patients infected with WNV are symptomatic; 20% develop a self-limiting flu-like disease and less than 1% develop neuroinvasive disease [80]. The clinical manifestations are meningitis, myelitis, encephalitis or an overlap syndrome, and they are worse in immunocompromised patients [80]. The use of WNV PCR for diagnostic purposes is limited, because the viremia is short and precedes the clinical features; therefore serology is the preferred diagnostic modality [80].

Although dengue viruses types one to four cause mainly arthralgia, hemorrhagic disease and a skin rash, they can occasionally cause CNS infection [10]. In most arboviruses serological testing is preferred, because the clinical symptoms follow only later, after the viremic peak [9].

CNS infection due to tick-borne encephalitis virus is common in Asia and Europe. Tick-borne encephalitis virus can be contracted not only through tick bites, but also through the ingestion of unpasteurized cow's or goat's milk from infected livestock [75]. The incubation period is only 3–5 days when ingested via the gut, but is 7–14 days after a tick bite. The majority of infections are asymptomatic or, at most, associated with flu-like symptoms, and the disease course can be mono- or biphasic. Meningitis, meningoencephalitis or meningoencephalomyelitis, as well as cardiac arrhythmia and autonomic instability, may occur. The Siberian subtype is associated with chronic manifestations that affect cognitive function, hearing, vision and balance, and that may also cause psychiatric disturbances or flaccid paralysis [75].

4.12.4 Paramyxoviridae

Mumps virus and measles virus are well known single-stranded RNA viruses from the Paramyxoviridae family that are encountered in children [3]. Other members of this group that may potentially affect the CNS are hendra virus and Nipah virus [75].

4.12.4.1 Measles Virus

Despite the availability of a very effective vaccine against measles, it still accounts for significant morbidity and mortality. The highest mortality is among girls, but boys are more readily affected by SSPE [81].

The infection presents with a skin rash and simultaneously the $CD8^+$ T cell-mediated clearance and adaptive immune response appear. Measles RNA persists after the virus has been cleared, and can be detected in blood, saliva, urine and lymphoid tissue for months [81]. The virus can spread across the synapses once in the neurons and accumulate mutations, and the infection then becomes chronic [81]. CXCL10 and CCL5 were identified as important role players in a mouse model, but the pathogenesis may further be influenced by the different CNS cell types, such as

astrocytes or microglia, involved [3]. Severe immunosuppression is present in the later stages of the disease [75].

Measles can affect the CNS in four different ways, namely primary measles encephalitis, postmeasles encephalitis, measles inclusion body encephalitis (MIBE) and SSPE [3]. MIBE is a late manifestation, 3–6 months after the acute episode of measles, in immunocompromised patients [75].

The disease mechanism for MIBE and SSPE is similar, affecting both the neurons and the oligodendrocytes in the frontal, occipital and parietal cortices and the thalami, pons and medulla [75]. It results in severe perivascular infiltrates, neuronal degeneration and gliosis [75].

It is unclear why the measles virus persists in patients developing SSPE years after an initial uneventful measles rash. Children who develop SSPE are usually between 5 and 15 years old, with males more affected than females [1]. Measles before the age of 18 months poses the greatest risk for developing SSPE [1]. The onset is unannounced, and hallmarked by behavioral changes, neurocognitive decline and movement disorders [1]. It is often associated with myoclonus, and the EEG pattern is fairly typical. The disease rapidly progresses to a vegetative state, and affected patients may die within months, and up to 3 years after the onset of the disease [1].

Apart from SSPE, measles virus RNA has been linked to range of other conditions namely multiple sclerosis, Paget's disease, otosclerosis, chronic active hepatitis, achalasia and Chron's disease [81].

4.12.4.2 Mumps Virus

It is astonishing, but little is known about the pathogenesis of mumps [75]. The classical picture is that of bilateral parotitis after 7–21 days' incubation, but in 30% of these cases CNS infection may occur [75]. Mumps encephalitis is characterized by perivascular demyelination in the cerebrum, cerebellum, brain stem and spinal cord. The basal ganglia may also be affected [75]. In children with mumps meningitis, in contrast to other causes of meningitis, there is an increase of IL-8, IL-10, IL-12, IL-13 and IFN-ɣ [3]. Mumps encephalitis is confirmed with a PCR on the CSF, and serum or saliva antibodies can provide supportive evidence [10].

4.12.5 Picornaviridae

The Picornaviridae are a family of RNA viruses that include human enteroviruses and human parechovirus, responsible for CNS infections and sepsis-like illness in children [82].

4.12.5.1 Enteroviruses

The nomenclature may appear confusing to non-virologists. There are four species of enterovirus, enterovirus-A to enterovirus-D [82]. Polio virus is an enterovirus-C species with three different serotypes, but a number of coxsackie-A viruses also belong to enterovirus-C. The nonpolio enteroviruses are enterovirus-A (including enterovirus-71 and several coxsackie-A viruses), enterovirus-B (including coxsackie virus-B

and all echoviruses) and enterovirus-D [75]. The recently described enterovirus-D68 has been associated with significant mortality and morbidity [82]. Enterovirus-A71, coxsackie virus-A9 and coxsackie virus-B are responsible for most of the CNS infections worldwide, and are associated with high morbidity and mortality [3, 82].

The clinical manifestations vary, including meningitis, encephalitis and meningoencephalitis [3]. Most of the experimental work done to determine the pathogenesis of nonpolio enterovirus CNS infection is done with coxsackie virus-B3. A key element in the cell migration across the BCSFB into the CSF is CCL12, a monocyte attractant. B-cells are also involved in the "Trojan horse" mechanism. In addition, the coxsackie virus-B3 infects neural stem cells and thus a viral presence persists [3]. There is a very low yield of positive enterovirus PCR in the CSF, but there is often a higher yield in throat swabs and stool specimens. The virus can often persist in the stools for weeks after a gastro-intestinal infection, therefore it is recommended that not only CSF but also peripheral sites are tested [9].

Before vaccination the poliovirus was the most common cause of anterior myelitis, responsible for the syndrome of poliomyelitis. It was regarded as epidemic in the developed world and endemic in the developing world, mostly affecting children between 6 months and 2 years [1]. Since 1974, enormous emphasis, initiated by the World Health Organization, has been placed on the eradication of vaccine-preventable diseases, including poliomyelitis. Although poliovirus has been controlled to a great extent worldwide, there have been outbreaks reported in Tajikistan, the Republic of the Congo and elsewhere [1]. Two poliovirus vaccines are available, oral (OPV) and intramuscular (IPV). In polio-endemic countries the WHO recommends a birth OPV dose, followed by a primary series of 3 OPV doses and at least one IPV dose. The primary series is administered from the age of 6 week, at 4 week intervals. The clinical presentation is fairly easy to identify, as patients present with typical lower motor neuron symptoms comprising asymmetrical flaccid paralysis, areflexia, fasciculations and wasting, while sensation remains intact and sphincter functions are not usually affected [12]. It is interesting that the weakness seldom progresses after the febrile illness has subsided [12].

4.12.5.2 Human Parechovirus

The usual presentations of human parechovirus are upper respiratory and gastrointestinal tract infections. In children younger than 3 months old, feeding problems and irritability are clinical signs of CNS involvement and which is usually associated with fever. Extensive subcortical white matter involvement has been observed in neonatal encephalitis, with meningothelial and vascular smooth muscles affected as proposed underlying mechanism for the fatal leukoencephalopathy. The exact pathogenesis of human parechovirus has not yet been explained [75].

4.12.6 Retroviridae

Both HTLV-1 and HIV are able to affect the CNS in numerous ways [3]. The CNS manifestations associated with HIV are often collectively referred to as

HIV-associated neurocognitive disorders [3]. During the primary infection a dual attack takes place; both the BBB is disrupted and the CNS is invaded via the "Trojan horse" mechanism for the viruses to migrate within the leukocytes to areas out of the reach of antiretroviral drugs. The virus can persist and replicate, causing long-term chronic disease [3] with a continuous process of monocyte migration, enhanced CCR2 expression on the HIV monocytes, increased levels of CCL2 in CSF, and subsequent migration of $CD14^+$ and $CD16^+$ monocytes into the CNS [3]. It is mandatory to test every patient presenting with suspected viral encephalitis for HIV [10]. A detailed discussion of HIV falls beyond the scope of this chapter.

4.12.7 Rhabdoviridae

Rabies is transmitted not only by infected dog or bat bites, but also through inhalation of droplets, infected donor organs [80] and open wounds if they are licked by a dog infected with rabies [2]. Rabies should always be considered in any child with a rapid progressive encephalitis [80]. As the incubation period can vary from weeks up to 1 year, with an average of 2 months, it may be difficult to link the disease to a specific contact with either bats or infected animals [75]. The prodromal stage is non-specific, with fever, malaise, headache, nausea with vomiting and the more characteristic feature of paresthesia or pain at the point of entry [80]. The disease course is rapid: more specific symptoms, including hypersalivation, agitation, hydrophobia and significant neck stiffness, develop to be followed by coma and subsequently death within 1–2 weeks [80]. The diagnosis relies on serum and CSF serology, but immunohistochemistry on skin may be helpful [80]. Post-exposure management is important and includes wound treatment, vaccination and immunoglobulin [21] as well as prophylaxis of contacts to minimize the risk of secondary transmission [80]. Death is almost 100% preventable if adequate post-exposure prophylaxis is applied [26].

4.12.8 Togaviridae

The chikungunya virus is a single-stranded RNA virus from the genus *Alphavirus,* with three different genotypes. The genotypes are associated with the region of origin: West Africa, East/Central/South Africa and Asia [3]. Several epidemics of this virus have been reported [3]. The CNS is not always affected, and its involvement has been documented in only 16.3% of patients, of which 55.1% presented with encephalitis. The chikungunya virus gains access to the CNS through the olfactory nerve. Although data form a mouse model indicated the upregulation of CCL2, IL-6 and TNF-α, the anti-inflammatory response of IL-4 and the immunosuppressive effect of IL-10, the understanding of the neuropathogenesis in chikungunya virus is still unclear [3].

4.12.9 Other

Both rotavirus, from the family Reoviridae and respiratory syncytial virus from the family Pneumoviridae, have been associated with encephalitis, but there is a controversy about their effect on the CNS [21]. Other rarer causes are adenovirus, erythrovirus B19, lymphocytic choriomeningitis virus, rubella virus and influenza viruses.

Influenza viruses are from the family Orthomyxoviridae, and have a wide range of clinical presentations that vary from very mild encephalitis to ADEM, posterior reversible encephalopathy syndrome, malignant brain edema syndrome and acute necrotizing encephalopathy [10]. Acute necrotizing encephalopathy is associated with influenza A and occurs in young Japanese children. There is a genetic predisposition and an autosomal dominant mutation has been identified. Patients have severe encephalopathy, with involvement of the thalami, brain stem and white matter [10]. The H1N1 influenza virus may cause encephalopathy, focal neurological signs, aphasia and EEG abnormalities [10].

4.13 Conclusion

A variety of viruses from different families, together with viral tropism, successively manifest in an extended spectrum of complex clinical syndromes influenced by the individual immune response of the host and the constantly changing environment, which is affected by globalization, natural disasters, war, availability and influence of health care services and increased population density. Although the outcome of viral encephalitis varies, the morbidity and mortality are significant. Prompt treatment with antiviral treatment may alter the outcome and is usually started empirically when viral encephalitis is suspected, but it is effective for HSV and, to a lesser extent, VZV. Aggressive treatment with immune modulating drugs has been successful in autoimmune-mediated encephalitides. The value of routine use of steroids in viral encephalitis is not clear. Prevention is an important aspect of virus management and the drive to develop new vaccines is ongoing and important. A viral etiology should always be considered in a severely ill child with CNS manifestations.

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