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section 24 Neurological disorders 6082 are needed to assess their efficacy in patients with bacterial menin- gitis. There is still an urgent need for new treatment options and refinement of emergency and neurocritical care. Trials are needed to assess treatment modalities such as intracranial pressure man- agement and specific monoclonal antibodies. However, the greatest effect on the burden of illness due to bacterial meningitis is likely to be achieved through widespread use of vaccinations. FURTHER READING British Medical Research Council (1948). Streptomycin treatment of tuberculous meningitis. Br Med J, i, 582–97. Brouwer MC, et al. (2012). Dilemmas in the diagnosis of acute community-acquired bacterial meningitis. Lancet, 380, 1684–92. Dastur DK, et al. (1995). Pathology and pathogenetic mechanisms in neurotuberculosis. Radiol Clin North Am, 33, 733–52. Heemskerk D, et al. (2016). Intensified anti-tuberculosis therapy of adults with tuberculous meningitis. N Eng J Med 374, 124–34. Klugman KP, et al. (2003). A trial of a 9-valent pneumococcal conju- gate vaccine in children with and those without HIV infection. N Engl J Med, 349, 1341–8. McIntyre PB, et al. (2012). Effect of vaccines on bacterial meningitis worldwide. Lancet, 380, 1703–11. Molyneux E, Riordan FA, Walsh A (2006). Acute bacterial meningitis in children presenting to the Royal Liverpool Children’s Hospital, Liverpool, UK and the Queen Elizabeth Central Hospital in Blantyre, Malawi: a world of difference. Ann Trop Paediatr, 26, 29–37. Mook-Kanamori BB, et al. (2011). Pathogenesis and pathophysiology of pneumococcal meningitis.

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distant sites, but polymerase chain re- action technology is now used routinely for diagnosis of viral central nervous system infection. Treatment Aciclovir is effective in treating herpes simplex encephalitis, but there is no effective specific treatment for most viral infections

24.11.2 Viral infections 6083 of the central nervous system. The focus is therefore on sup- portive care. Prevention Prophylactic vaccination is available against poliomyelitis, Japanese encephalitis, tick-borne encephalitis, mumps, measles, rubella, and rabies. Postexposure rabies vaccination is effective in preventing ra- bies encephalitis. Hyperimmune immunoglobulin has been used for prophylaxis of measles, herpes zoster virus, rabies, and some other infections in high-risk groups. Other neurological disorders in which viruses may play a role These include (1) Reye's syndrome—an acute encephalopathy with liver impairment affecting children aged 2–16 years, associated with use of salicylates and a preceding viral illness. (2) Progressive ru- bella panencephalitis and subacute sclerosing panencephalitis — typically occur several years after the initial illness with rubella virus and measles virus, respectively, and are characterized by intellec- tual impairment and behavioural change. (3) Progressive multifocal leucoencephalopathy—caused by papovaviruses, most often in the immunocompromized; onset is usually with progressive evidence of a focal lesion of one cerebral hemisphere, before gradual develop- ment of more widespread signs; there is no effective treatment apart from restoration of immune function. (4) Guillain–Barré syndrome is a post- or parainfectious condition which can follow Epstein– Barr virus, cytomegalovirus, and other viral infections, including the mosquito-borne Zika virus. Introduction Viruses invade and damage the central nervous system in two ways: directly, by infecting the leptomeninges, brain, and spinal cord; and, indirectly, by inducing an immunological reaction re- sulting in para- and postinfectious diseases. In both cases, the terms 'meningitis', 'encephalitis', and 'myelitis' are used alone or in com- bination. Meningitis implies inflammation of the meninges without alteration of consciousness, convulsions, or the production of focal neurological abnormalities; in encephalitis there is impairment of cerebral function, usually with an altered state of consciousness and often with convulsions and focal neurological signs; myelitis indi- cates involvement of the spinal cord resulting in varying degrees of limb weakness with or without sensory disturbance. Retroviral dis- eases of the central nervous system and prions are dealt with else- where (Chapter 8.5.23 and Chapter 24.11.5). Aetiology There is considerable geographical and seasonal variation in the kinds of viruses causing meningitis, encephalitis, and myelitis. Vulnerability varies with age and immunocompetence. Some of the most important causes are zoonotic viruses (i.e. they circulate natur- ally among animals, occasionally spilling over into humans). Often arthropods, such as insect or ticks, are the means of transmission, making them arboviruses (arthropod-borne viruses). Meningitis Enteroviruses are responsible for most cases of viral meningitis glo- bally, where a virus is identified. Almost all serotypes have been implicated both in sporadic cases, and in outbreaks. The second commonest causes of viral meningitis are the herpes simplex virus (HSV) type 2, and varicella zoster virus (VZV). Adenoviruses and Epstein–Barr virus (EBV) are also important causes found glo- bally, as are mumps and measles, although their incidence depends on the extent of vaccination. The importance of arthropod-borne viruses (arboviruses) varies according to geographical location, season, and for some, the extent of vaccinations; although several of these viruses are named for the dramatic encephalitis they cause; they also important causes of meningitis. Tick-borne encephalitis virus occurs across large swathes of northern Europe and Asia; the mosquito-borne Toscana virus is important in Italy in the summer months. In the Americas the flaviviruses (West Nile, and St Louis encephalitis virus) and the alphaviruses (Eastern and Western equine

encephalitis viruses) cause meningitis, as do bunyaviruses, such as California (La Crosse) encephalitis viruses. Throughout the tropics dengue, though better known as a cause of rash and haemor- rhage, also causes meningitis. In many cases of presumed viral meningitis, a pathogen is never identified. The term aseptic meningitis is often used to describe the syndrome of meningitis with lymphocyte predominance, whether or not a virus is identified. Myelitis Poliovirus was considered previously the major cause of viral acute flaccid paralysis globally, but has now been eliminated from much of the world. It remains a problem in a handful of coun- tries in the African and eastern Mediterranean regions, with only two countries in the world still having endemic disease at the end of 2015. Enterovirus 71 is now the leading cause of acute flaccid paralysis. In 2014 a worrying increase in acute flaccid paralysis was seen in the United States which coincided with an outbreak of enterovirus 68. Other enteroviruses, such as coxsackie viruses A and B, and echoviruses have all been implicated as causes of flaccid paralysis. Flaviviruses which attack the anterior horn cells of the spinal cord can also cause a polio-like paralysis, including Japanese encephalitis virus, West Nile virus, Tick-borne enceph- alitis virus, and Zika virus. Other potential viral causes of myelitis include rabies virus, VZV, EBV, and herpesvirus simiae (B virus). HSV-2 can cause lumbosacral myeloradiculitis. HTLV-1 causes a spastic paraparesis often called tropical spastic paraparesis (TSP) or HTLV-1-associated myelopathy (HAM). Encephalitis Viral causes of encephalitis vary from country to country. Japanese encephalitis virus is the major cause in Asia. It is estimated that there are around 68 000 cases of Japanese encephalitis annually, with approximately 17 000 deaths. Dengue viruses have also been implicated as a cause of encephalitis in both south-east Asia and Latin America. Rabies remains an important cause of fatal enceph- alomyelitis, especially in the Asian subcontinent and Africa (see Chapter 8.5.10). In 1999 an outbreak of an encephalitic illness among pig farm and abattoir workers in Singapore and Malaysia heralded the arrival of

 Nipah virus as an important cause of central nervous system (CNS) infection. It has also caused outbreaks in Singapore, Bangladesh, and India. The closely related Hendra virus, which also causes encephal- itis in horses and occasionally humans, has not been seen outside of Australia (see Chapter 8.5.7). In North America and other Western countries HSV is the most common cause of sporadic viral encephalitis. Herpetic encephalitis accounted for 74–81% of cases of encephalitis in the United States where a pathogen was found. In the United Kingdom it has an es- timated incidence of 2.3 per million population each year; HSV- 1 accounts for 95% of cases, whereas HSV-2 causes encephalitis mainly in neonates and those who are immunosuppressed. Since 1999 when West Nile virus was first identified in New York, it has spread to become the third most common cause of viral en- cephalitis in the United States. It has been known to cause enceph- alitis in Africa and the Middle East, as well as southern and Eastern Europe. Zika virus, which has spread in recent years, and is best known as a cause of congenital defects and Guillain-Barre syn- drome, can also cause encephalitis. In the United Kingdom, HSV-1 is also the most frequently diag- nosed cause of viral encephalitis. Other causes include varicella zoster virus, enteroviruses, EBV, and HHV-6. Louping ill is the only indigenous arthropod (tick)-borne encephalitis in the United Kingdom but rarely causes disease in humans. Parechovirus is emerging as an important cause of encephalitis in young children, especially those under 3 months of age. In northern Europe and the former Soviet Union, tick-borne en- cephalitis virus is endemic. In many developing countries rabies is also an important cause of encephalitis. Other regional causes are Rift Valley fever virus in Africa and the Middle East, arenaviruses (Junin, Guanarito, Sabiá, Lassa, and Machupo) in Latin America and Africa, Marburg and Ebola viruses in Africa,

Colorado tick fever virus in North America, and Murray Valley encephalitis and Hendra viruses in Australia. Zika virus, which from 2015 caused large out- breaks in South America also appears to cause encephalitis. Postinfectious encephalomyelitis most commonly follows measles, vaccinia, varicella, rubella, mumps, and influenza. Guillain–Barré syndrome, a sensorimotor polyneuropathy (see Chapter 24.16), has been associated with infections by EBV, cytomegalovirus (CMV), coxsackievirus B, VZV, and recently Zika virus. The decreasingly used nervous tissue vaccines for rabies may give rise to postvaccinal encephalomyelitis, whereas immunization against influenza, rabies, hepatitis B, measles, and poliomyelitis have all been complicated by Guillain–Barré syndrome. Immunocompromized patients are particularly vulnerable to some viral infections. Those with depressed cell-mediated immunity may de- velop VZV encephalitis, and CMV may cause a subacute encephalitis in patients with advanced HIV disease. JC virus also causes neurological damage in the form of progressive multifocal leucoencephalopathy in immunodeficient patients, especially those with advanced HIV or pa- tients on immunosuppressive drugs, such as natulizimab, used in the treatment of multiple sclerosis. This is described in more detail later in this chapter. In children or adults with hypogammaglobulinaemia, enteroviruses, including live-attenuated polio vaccine, may produce a progressive and fatal meningoencephalitis. An acute meningoenceph- alitis can be part of primary HIV infection; the virus may also cause subacute chronic encephalopathies and dementia in patients with AIDS (see Chapter 8.5.23). HHV-6B causes encephalitis in young children following stem cell transplantation. It is most common in Japan. Epidemiology Many viral infections of the CNS occur in seasonal peaks or as epidemics, for example, enteroviral disease and Japanese enceph- alitis; others, such as herpes simplex virus encephalitis, are spor- adic. Epidemics of Japanese encephalitis (see Chapter 8.5.14) occur in the summer or rainy season in northern India, Nepal, northern Thailand, Vietnam, Korea, Taiwan, and China. However, in southern Vietnam, Indonesia, Malaysia, southern India, and the Philippines the disease can occur the year round, although the peak occurs at the start of the rainy season. This variation in the incidence of dis- ease is an important consideration when recommending immun-ization. In endemic areas Japanese encephalitis is mostly a disease of children, but as the disease spreads to new regions, or if non- immune travellers visit endemic regions, adults are also affected. The major vector, Culex tritaeniorhynchus mosquito, is infected by feeding on the bird or mammal reservoir species. West Nile virus is a mosquito-borne flavivirus closely related to Japanese encephal- itis, that occurs in both epidemics and sporadically across Africa, southern Europe, and the Americas. Tick-borne encephalitis (see Chapter 8.5.14) occurs in spring and early summer when the ticks are most active, but can also be ac- quired by drinking the unpasteurized products of infected dairy ani- mals, especially goat’s milk. Mumps encephalitis is most common in the late winter or early spring, whereas enterovirus infections occur most often in the summer and early autumn. Rodent-related encephalitides, such as the arenaviruses, occur typically when the rodent population is at its peak, either in the fields (Machupo and Junin viruses) or around the home (lymphocytic choriomeningitis virus). Rift Valley fever, survives periods of cold weather, during which the invertebrate–vertebrate cycle is suspended by the virus ‘overwintering’ in its arthropod vectors (e.g. in the bottom of dried- up ponds) or hibernating invertebrate reservoirs. Rabies occurs sporadically or in microepidemics (see Chapter 8.5.10). Infections by many neurotropic viruses are most frequent and severe in children and older people. Herpes simplex encephal- itis affects all age groups but shows peaks of incidence in those aged between 5 and 30 years and those over 50 years, it is normally due to HSV-1. When HSV-2 invades the CNS, it is most likely to cause a nonfatal meningitis in adults, but can produce a severe encephalitis in neonates. Enteroviruses and parechoviruses can also cause severe encephalitis and sepsis-like syndromes in young babies.

Among the mosquito-borne epidemic encephalitides, California encephalitis, and Japanese encephalitis are most common in children, St Louis and West Nile encephalitis occur more commonly in older people, whereas Eastern and Western equine encephalitis affect both very young and older people. Postinfectious encephalitis is most frequent in children, because it complicates the common childhood exanthematous viral infec- tions; it can take the form of acute disseminated encephalomy- elitis (ADEM). Emerging viral infections of the CNS Almost all of the new and emerging pathogens are viruses, and many have neurological sequelae. Nipah virus encephalitis is a zoo- nosis infecting pigs and flying foxes (Pteropus spp). The closely re- lated Hendra virus has caused a few cases of equine and human encephalitis, with a human fatality in Brisbane, Australia in 2008 (see

24.11.2 Viral infections 6085 Chapter 8.5.7). Zika virus, a flavivirus, has caused a significant out- break in South and Central America in 2015/2016. There has been an associated increase in the number of cases of microcephaly, although the exact causal relationship remains to be established. Currently there is no treatment or vaccine. Usutu, another flavivirus, has been isolated in birds in Austria and has caused a handful of human cases in Europe. Ebolavirus has been associated with several neurological presentations, including cases of meningitis and encephalitis. Pathogenesis Having entered the body via the skin, mucous membranes, respira- tory or gastrointestinal most viruses multiply in the blood stream be- fore crossing the blood brain barrier to enter the CNS. Rabies virus is different, however, and enters peripheral nerves through acetyl- choline and other receptors and travels to the CNS in axoplasm, employing the microtubular dynein motor system. HSV is throught to travel up the trigeminal nerve and lay dormant in the trigeminal ganglion. Viruses inoculated through the skin include those trans- mitted by arthropods, as well as rabies virus. Arthropod-borne vir- uses are presumed to replicate in local lymph nodes, then the vascular endothelium, and macrophages, in order to sustain viraemia (detect- able virus in the blood). Rabies virus may multiply locally in the cyto- plasm of muscle cells before entering peripheral nerves. Viruses that enter through the respiratory tract (e.g. measles, mumps, varicella) or gut (enteroviruses) multiply in local lymphoid tissue before entering the bloodstream. Viraemia is a feature of most viral infections, yet invasion of the CNS is rare in most cases. The explanation for this is not known, but the CNS has several intrinsic physical barriers to infectious agents, including viruses. These include the blood–brain barrier with its ‘tight junctions’, virus-resistant cells, and the absence of lymphatic drainage. In the case of rabies, HSV and VZV, the virus enters the CNS through the peripheral nerves. Although the sub- arachnoid space surrounding the olfactory nerves projects through the cribriform plate and is directly beneath the nasal mucosa, this route of infection seems to be extremely rare in humans and has been proven only in a few cases of inhaled rabies virus infection and herpes simplex encephalitis. Viruses have accidentally been inoculated dir- ectly into the CNS by infected corneal transplant grafts (rabies). Herpes simplex encephalitis may complicate primary HSV infection in children and young adults, but in most cases of herpes simplex en- cephalitis the cause is thought to be reactivation of latent virus (HSV-

1. in the trigeminal nerve, autonomic nerve roots, or brain. HSV-2 and VZV can also cause neurological disease, either as a result of pri- mary infection or reactivation following latency. In the case of VZV, disease can also occur following vaccination. Different neural cells are selectively vulnerable to invasion by dif- ferent neurotropic viruses. Examples are the predilection of polio- viruses for lower motor neurons of the anterior horns of the spinal cord, and of rabies for neurons of the limbic system and cerebellar Purkinje cells.

HSV-1 primarily causes infection of the brain paren- chyma (encephalitis) and HSV-2 is normally associated with men- ingeal infection. The pathological effects of viral infections on the CNS include: • destruction and phagocytosis of neurons (neuronophagia) as a result of either viral invasion itself or immune lysis • demyelination • inflammatory oedema with the compressive effects of raised intracranial pressure • vascular lesions, in some cases In rabies, a universally fatal encephalitis, neuronolysis is relatively mild. However, the virus may interfere with neurotransmission at central and peripheral synapses. It also produces severe systemic effects, following its centrifugal spread (e.g. myocarditis and car- diac arrhythmias) and focal effects on vasomotor and respiratory centres in the brainstem and in the temporal lobes and amygdala (see Chapter 8.5.10). The host's immune responses to viruses play a crucial role in combating infection. They may be directed against either the virus particle or the virus-infected cell, and may be humoral or cell me- diated. An important local immune response at infected surfaces is provided by IgA antibody, which is present in secretions in the gut, saliva, and respiratory tract. This is important, for example, in the early stages of poliovirus infection where the antibody neutralizes the virus by combining with viral surface proteins. The systemic viral infection may also be limited by means of circulating IgG and IgM antibodies, which can neutralize the virus in a variety of dif- ferent ways. Immune responses may also occur locally within the CNS, where local synthesis of immunoglobulins in response to virus infection, sometimes in an oligoclonal pattern, may be evident. Such antibody elevations may be of considerable diagnostic value. Sometimes the immune responses to the viruses themselves may result in immunopathological processes leading to disease. This may occur in several different ways, such as through the deposition in blood vessels of immune complexes formed between an antiviral antibody and viral antigen. In other cases, such as lymphocytic choriomeningitis virus infection, the induction of virus-specific cytotoxic T lymphocytes is itself responsible for the production of encephalitis. In Japanese encephalitis there is evidence of cytokine mediated apoptosis of noninfected cells. Pathology Meningitis Viral meningitis is mostly a nonfatal disease and, as a result, less is known about the pathology. The basal leptomeninges, ependyma, and choroid plexus are infiltrated with mononuclear cells, but the parenchyma is normal. In mumps meningitis there may be exfoli- ation of ependymal cells. HSV-2 meningitis often occurs following reactivation. HSV-2 preferentially lies latent in the sacral ganglia, as opposed to HSV-1 which preferentially has latency in the trigeminal ganglia. This dif- ference may account for the fact the HSV-2 predominantly causes meningitis and HSV-1, encephalitis. HSV-2 is primarily transmitted sexually and is much more common in women than men, hence HSV-2 meningitis also predominantly occurs in women. Enteroviruses predominantly cause meningitis in older children and young adults, but can also lead to a polio-like illness (especially EV71 and EV68) and encephalitis which can be fatal in young chil- dren. Enteroviral meningitis normally occurs following a primary infection, acquired via the faeco-oral route, and probably occurs

 following haematogenous spread. Enterovirus can be detected in the blood in some cases. VZV meningitis can, and often does, occur in the absence of a rash—either following primary infection or reactivation. It often oc- curs in older adults, possibly as a result of immunosenescence that is also associated with an increased risk of shingles in that age group. Cerebellar ataxia is an uncommon complication following primary VZV infection in children.

Poliomyelitis In poliomyelitis the virus is distributed widely throughout the brain and spinal cord, possibly even in nonparalytic cases, but usually the only cells to suffer chromatolysis and phagocytosis are motor neurons in the anterior horns of the spinal cord, medulla, and grey matter of the precentral gyrus. Encephalitis Most viral encephalitides are characterized by infiltration of the meninges and perivascular cuffing (in the Virchow–Robin spaces) in the cortex and underlying white matter, by lymphocytes, plasma cells, histiocytes, and some neutrophils. There is also proliferation of microglia with the formation of glial nodules. Neuronolysis and demyelination are variable in their degree and location. Infected neurons may show characteristic inclusion bodies in their nuclei (measles, HSV and adenoviruses) or cytoplasm (Negri's bodies in rabies). Microhaemorrhages and foci of necrosis may be found. Herpes simplex encephalitis Characteristic features of herpes simplex encephalitis are cerebral oedema and a severe haemorrhagic, necrotizing encephalitis. The disease is often asymmetrically localized to the inferior and medial parts of the temporal lobe, the insula, and the orbital part of the frontal lobe. Histological sections show eosinophilic Cowdry type A intranuclear inclusions with margination of chromatin in neurons, oligodendrocytes and astrocytes, inflammatory and haemorrhagic perivascular reactions, but no demyelination. Cowdry type A in- clusions are also found in VZV and CMV encephalitis. The unique cerebral localization of herpes simplex encephalitis has not been sat- isfactorily explained, but is probably the result of viral spread along specific neural pathways rather than a differential susceptibility of particular cell populations. A popular idea is that HSV spreads along olfactory pathways to the base of the brain and temporal lobes, but it is also possible that virus may spread from the trigeminal ganglia through sensory fibres innervating the dura near these regions. This latter mechanism is consistent with the discovery of latent HSV-1 in the trigeminal, superior cervical and vagal ganglia in a high pro- portion of normal individuals, irrespective of whether they have a history of mucocutaneous herpes infections ('cold sores'). Latent HSV-1 might be reactivated by a variety of stimuli, such as sun- light, fever, trauma, and stress; however, the actual mechanisms underlying its latency and reactivation in the nervous system are not yet fully understood. If herpes simplex encephalitis is caused by the reactivation of latent virus, its rarity, despite ubiquitous asymptom- atic infection in humans, is hard to explain. Japanese encephalitis Microscopic appearances are typical of other viral encephalitides: there is oedema, congestion, focal haemorrhages of the brain and meninges, perivascular cuffing, neuronophagia, and glial nodules of the brain parenchyma. There may also be punched out necrotic lesions giving a 'Swiss cheese' appearance, which is characteristic of Japanese encephalitis. Neuronolysis and neuronophagia are un- usually widespread in the thalamus, basal ganglia, brainstem, cere- bellum (where there is marked destruction of Purkinje's cells) and the spinal cord. Viral antigen is localized to neurons, especially in the brainstem, thalamus, and basal ganglia. West Nile virus encephalitis Pathological changes include varying degrees of neuronal necrosis in the grey matter, with infiltrates of microglia and polymorpho- nuclear leucocytes, perivascular cuffing, neuronal degeneration, and neuronophagia. Viral antigens have been demonstrated in neurons and in areas of necrosis. No antigen has been detected in other major organs, including lung, liver, spleen, and kidney. The major patho- logical lesions are seen in the brainstem and spinal cord. Nipah virus encephalitis Pathological studies on the brains of fatal cases demonstrated that the endothelium of small blood vessels in the CNS was par- ticularly susceptible to infection. This led to disseminated endo- thelial damage and syncytium formation, vasculitis, thrombosis, ischaemia, and microinfarction. There was also evidence of neur- onal infection by the virus that may have contributed to neuro- logical dysfunction. Enterovirus 71 There is severe perivascular cuffing, parenchymal inflammation, and neuronophagia in the spinal cord, brainstem, and diencephalon,

and in focal areas in the cerebellum and cerebrum. Although no viral inclusions have been detected, immunohistochemistry showed viral antigen in the neuronal cytoplasm. Inflammation was often more extensive than neuronal infection, suggesting that other indirect fac- tors may be involved in tissue damage in addition to the effects of direct viral invasion. Clinical features Meningitis Symptoms include fever, headache, photophobia, and a stiff neck, but no symptoms are pathognomonic and symptoms alone cannot differentiate between bacterial and viral meningitis or indeed be- tween meningitis and other illnesses mimicking meningitis (e.g. upper respiratory tract infections and simple viral illnesses such as influenza), hence the need for lumbar puncture if there is any suspicion. Other nonspecific symptoms such as nausea, anorexia, vomiting, abdominal pain, myalgia, and sore throat are common, particularly in enteroviral meningitis. Myalgia is particularly se- vere with coxsackievirus B infections. As in acute bacterial men- ingitis, infants with viral meningitis usually present with vague irritability and a tense fontanelle, and young children with fever and irritability or lethargy. Conjunctival injection, pharyngitis, and cervical lymphadenopathy may be found. Macular or pe- techial exanthems or enanthemas are seen with coxsackievirus A and B and echovirus infections (especially echovirus 9). Vesicles

24.11.2 Viral infections 6087 on the hands, feet, and mouth occur with coxsackievirus A16 and enterovirus 71 infections. By definition, the level of consciousness is normal in viral meningitis. If there is a reduction in conscious level or change in personality then alternative diagnoses should be considered such as viral encephalitis or bacterial meningitis. A prodromal influenza-like illness, followed by a brief remission of symptoms, is typical of lymphocytic choriomeningitis viral in- fection or tick-borne encephalitis, but in most cases of viral men- ingitis symptoms start suddenly. Occasionally genital or rectal vesicles associated with HSV-2 or VZV skin lesions may occur. Other extraneurological features that may indicate a specific cause include: swelling in the parotid region (mumps, and occasionally coxsackie, lymphocytic choriomeningitis, and EBV), orchitis (mumps and lymphocytic choriomeningitis virus) and arthritis (lymphocytic choriomeningitis virus). Recurrent lymphocytic meningitis Most cases of recurrent viral meningitis are due to HSV-2, al- though there have been case reports of recurrences with most viruses. Recurrent lymphocytic meningitis is often called by the eponymous term Mollaret’s meningitis, although in the original described condition the predominant cells in the cerebrospinal fluid (CSF) were polymorphs. In Mollaret’s meningitis there is complete spontaneous recovery and symptom-free intervals lasting from a few days to years. Large monocytes (Mollaret’s) cells are occasionally seen. Other causes of recurrent meningitis include Behçet’s syndrome, CSF leak, Vogt–Koyanagi–Harada syndrome, sarcoidosis, and sys- temic lupus erythematosus. Myelitis Polioviruses (see Chapter 8.5.8) are acquired by droplet spread from the respiratory tract or by the faecal–oral route. A ‘minor illness’, coinciding with viraemia, is a nonspecific episode of influenza-like symptoms—fever, headache, sore throat, malaise, and mild gastrointestinal symptoms—which resolves in a few days. Most of those infected have no further symptoms but, in a minority, a ‘major illness’ follows, sometimes after a few days’ re- mission of symptoms. The features of muscle pain, spasms, and sensory disturbances may precede or accompany the development of lower motor neuron (flaccid) paralysis. Some may also have fea- tures of meningeal irritation such as neck stiffness, photophobia, or encephalitis. Any combination of motor unit deficits may be seen. Respiratory and bulbar paralysis is life-threatening. The most common causes of death are aspiration and airway obstruction, re- sulting from bulbar paralysis and paralysis of respiratory muscles. Disturbances of respiratory and cardiac rhythm, thought to be the result of damage to medullary vasomotor and respiratory centres, are extremely uncommon. Other complications include impaired control of body temperature and blood pressure,

gastrointestinal haemorrhage, aspiration pneumonia, and paralysis of the bladder and bowel. Other enteroviruses that cause myelitis demonstrate a similar clinical picture; EV71 is the most important of these. A small single centre study of children with acute flaccid paralysis thought to be due to EV68 had proximal and asymmetric flaccid limb weakness. Most children in this series had involvement of the upper limbs and cranial nerve dysfunction which is dissimilar to poliovirus infections. HTLV-1 causes a spastic paraparesis characterized by weak- ness of the lower limbs, associated gait disturbance, and urinary bladder dysfunction. Around 50% of cases may have a sensory disturbance. Encephalitis Most patients with viral encephalitis present with the symptoms of fever, headache, seizures, lethargy, and personality or behavioural changes. In children irritability may be an important symptom. Focal neurology is present in approximately a third of patients. Herpes simplex encephalitis As well as the usual clinical features of severe viral encephalitis, pa- tients with herpes simplex encephalitis have symptoms related to the focal nature of the encephalitis (frontal and temporal cortex and limbic system) (Fig. 24.11.2.1). These include behavioural abnor- malities, olfactory and gustatory hallucinations, anosmia, amnesia, expressive aphasia, and temporal lobe seizures. Most deaths occur within the first 2 weeks. Measles encephalitis Measles virus can cause encephalitis in several different ways. It can cause primary measles encephalitis which occurs at the same time as the rash. This occurs in about 1 in a 1000 people who have measles. There is also an immune mediated encephalitis that oc- curs in the immediate period after an acute measles infection. This postmeasles encephalitis is associated with brain swelling and should be treated with steroids. Measles inclusion body en- cephalitis occurs mostly in immunodeficient children within one year of infection or vaccination, and finally subacute sclerosing panencephalitis (SSPE) can occur several years after the acute mea- sles infection. There are characteristic electroencephalographic (EEG) changes in SSPE (Fig. 24.11.2.2) and very high levels of measles IgG are found in the CSF. The risk of SSPE seems to be greater if measles is contracted at an early age. Japanese encephalitis (See Chapter 8.5.14.) After an incubation period of 7–14 days, patients develop non- specific prodromal symptoms (fever, headache, malaise, and nausea) lasting 2 to 3 days. Neurological symptoms begin with a deteriorating level of consciousness, and often generalized con- vulsions, especially in children, which may lead to status epilep- ticus. Parkinsonian and extrapyramidal features occur frequently and choreoathetoid movement disorders or severe dystonias can last for many months (Fig. 24.11.2.3). The case fatality rate is 20% in those admitted to hospital. Most deaths occur in the first 7–10 days from respiratory failure, aspiration pneumonias, intra- cranial hypertension, or uncontrolled seizures. Up to 50% of sur- vivors suffer from intellectual impairment, psychiatric problems, persistent epilepsy, or a vegetative state (Fig. 24.11.2.4a) with spastic quadraparesis or evidence of basal ganglia involvement (Fig. 24.11.2.5), such as dystonia of the limbs and trunk, rigidity, and tremor (Fig. 24.11.2.4b). Nipah virus encephalitis (See Chapter 8.5.7.)

(b) (a) Fig. 24.11.2.1 (a, b) Magnetic resonance (MR) scans of herpes simplex encephalitis in two Vietnamese patients showing the characteristic bilateral and extensive damage particularly to the temporal lobes but often extending to other parts of the cerebral cortex. Fig. 24.11.2.2 EEG changes in subacute sclerosing panencephalitis showing periodic complexes approximately one every 3 seconds.

 The main clinical features of Nipah virus encephalitis are fever, headache, dizziness, reduced consciousness, and prominent brainstem dysfunction. Distinctive signs included myoclonus, areflexia, hypotonia, hypertension, and tachycardia, suggesting

extensive brainstem and spinal cord involvement. MRI during the acute illness shows widespread focal lesions in subcortical and deep white matter and, to a lesser extent, in grey matter on T2-weighted sequences (Fig. 24.11.2.6). Long-term sequelae are common. West Nile virus encephalitis West Nile virus infections can present either as a simple febrile illness—West Nile fever—meningitis or encephalitis. Encephalitis is the rarest of these but the most severe. In endemic areas, infection with West Nile virus is usually asymptomatic or associated with a mild flu-like illness. When the virus is introduced into a naïve population as it was in the United States of America in 2001, the incidence of encephal- itis rises particularly in older people. An erythematous rash of the neck, trunk and limbs is present in 20% of cases. Extrapyramidal symptoms are common. Muscle weakness, areflexia, and diffuse flaccid paralysis in association with an axonal polyneuropathy are also reported. Tick-borne encephalitis (See Chapter 8.5.14.) A feverish illness accompanied by myalgia, headache and fa- tigue develops 4–28 days after the tick bite. Between 1 and 33 days later, about one-third of the patients will develop meningitis, meningoencephalomyelitis, myelitis, or meningoradiculitis. Enterovirus 71 As the goal of poliomyelitis eradication appears more achiev-able, another enterovirus is emerging as a significant cause of acute neurological disease in Asia. EV71 was first recognized in 1969 and is responsible for a variety of clinical manifestations, including: hand, foot, and mouth disease; aseptic meningitis; meningoencephalitis; and acute flaccid paralysis. In contrast to other enteroviruses, the encephalitis associated with EV71 nor-mally affects the brainstem and is associated with cardiovascular instability—possibly due to neurogenic pulmonary oedema. Myoclonic jerks are also more common in EV71 encephalitis. (a) (b) (c) (e) (d) Fig. 24.11.2.3 Japanese encephalitis in Anuradhapura, Sri Lanka. (a) Comatose female patient showing symmetrical chorioathetotic movements of the upper limbs. (b) Comatose child showing dystonic movements of the upper and lower limbs. (c) Convalescent child, conscious but with residual dystonia of all four limbs. (d) Convalescent child with floppy head and involuntary movements of all four limbs. (e) Convalescent boy with residual weakness of the neck flexors. Courtesy of Dr D T D J Abeysekera.

section 24 Neurological disorders 6090 Most patients with neurological infection due to EV71 will also have features of hand, foot, and mouth disease—a common mani- festation of EV71. Postinfectious encephalomyelitis Encephalomyelitis also occurs as a rare complication of other fe-brile illnesses. Sudden convulsions, coma, fever, or pareses appear 10–14 days after infection with varicella, rubella, mumps, or influ- enza. In the case of varicella and rubella, encephalitic symptoms develop 2–12 days after the rash has appeared, and in mumps before or after parotid swelling. Involuntary movements, cranial nerve le- sions (VII and III), pupillary abnormalities, nystagmus, ataxia, and upper motor neuron signs are common. Imaging usually shows an acute disseminated encephalomyelitis with demyelinating lesions in the white matter. A similar syndrome also occurs very rarely as a complication of immunisation. (a) (b) Fig. 24.11.2.6 MRI of two patients with Nipah virus encephalitis. Acute Nipah virus encephalitis in a 57-year-old pig farmer showing multiple focal lesions in the grey–white matter junction. These are areas of infarction secondary to vasculitis. (a) courtesy of Drs B J Abdullah and Sazilah Sarj, Kuala Lumpur, Malaysia. (a) (b) Fig. 24.11.2.4 (a) Vietnamese patient in a vegetative state after Japanese encephalitis. (b) Thai patient with severe neurological sequelae after Japanese encephalitis. (a) copyright DA Warrell; (b) courtesy of the late Professor Prida Phuapradit. Fig. 24.11.2.5 MRI evidence of inflammation in the basal ganglia, cerebellar peduncles, and substantia nigra in Japanese encephalitis.

24.11.2 Viral infections 6091 Diagnosis Clinical and epidemiological features such as the season, known current epidemics, the patient’s age, occupation, animal con- tacts, and countries or areas visited recently may give some clues to the specific aetiology. However, in most cases laboratory tests and/or imaging will be needed to confirm the diagnosis. A spe- cific diagnosis may be suggested by distinctive clinical features of the illness such as hydrophobia in rabies and temporal lobe features in herpes simplex encephalitis, or features of the asso- ciated infection (e.g. mumps parotitis, measles rash, skin and mucosal lesions of herpesviruses and gastrointestinal symptoms associated with enteroviral infections), but often these features are not present. Laboratory investigations The aim of any investigations should be to confirm the syndromic diagnosis and to demonstrate a specific aetiological agent (par- ticularly important for the potentially treatable herpesvirus in- fections) or to exclude potentially treatable nonviral causes of meningitis or encephalomyelitis (Table 24.11.2.1). The most important investigation is examination of the cerebrospinal fluid. Contraindications to lumbar puncture are the same as for acute bacterial meningitis (see Chapters 24.3.1 and 24.11.01). If there are lateralizing neurological signs or evidence of brain shift, a CT or MRI scan should be performed to exclude an intracranial mass lesion before contemplating a lumbar puncture. Initial CSF investigations The opening pressure is useful as a pointer to certain diagnoses. It is likely to be normal in viral meningitis, but is increased in encephalitis where there is intense cerebral oedema. Pleocytosis ranges from tens to thousands of cells per microlitre. Lymphocytes and other mononuclear cells normally predominate. The cerebro- spinal fluid contains erythrocytes or is xanthochromic in haem- orrhagic encephalitides, such as herpes simplex encephalitis or VZV meningitis, which is often accompanied by a vasculopathy. Protein concentration is usually increased in the range of 50– 150 mg/dl with an increasing proportion of IgG as the disease progresses. Leakage of serum IgG into the cerebrospinal fluid and intrathecal IgG synthesis, indicated by a monoclonal band, are responsible. A blood glucose should be taken at the same time Table 24.11.2.1 Causes of aseptic meningitis,a with or without encephalitis or myelitis, other than viruses and postinfectious/ postvaccinal syndromes Cause Diagnostic clinical feature or investigation Bacteria Acute bacterial meningitis (partially treated) Blood cultures CSF PCR (either specific target e.g. Neisseria meningitidis or Streptococcus pneumoniae or 16S ribosomal DNA PCR), Antigen detection (CIE, LA) Intracranial/spinal abscess or empyema (parameningeal infections) Blood cultures Physical examination (exclude otitis media, trauma, dermoid sinus, and so on), radiographs, CT/MRI, myelogram Brucella spp. CSF culture on serum-dextrose agar, blood culture, serology, PCR Cat-scratch disease bacillus Warthin–Starry stain of skin and lymph nodes, skin test Mycobacteria CSF microscopy, culture; Mantoux test, chest radiograph, PCR Mycoplasma spp. CSF and serum IgM (IFA) Spirochaetes Leptospira spp. Serology Relapsing fevers Blood smear, mouse inoculation Lyme disease Serology (EIA, IFA), culture, CSF IgG (EIA IFT) Syphilis Serology (FTA-abs test) serum and CSF Spirillum minus Microscopy of wound or lymph node aspirates, mouse inoculation Rickettsiae (Rocky Mountain spotted fever, murine, epidemic, scrub typhus) Serology (Weil–Felix), skin biopsy IFT (RMSF) Fungi Blastomyces spp. CSF culture, EIA, demonstration at other sites, lung, skin, biopsy Candida spp. CSF culture (repeated) Coccidioides spp. CSF CFT, culture, microscopy Cryptococcus spp. CSF India ink, LA—beware false positive with surface condensate on agar Histoplasma spp. CSF culture (repeated), demonstration at other sites, blood smear (buffy coat) serum, urine, CSF antigen detection (RIA) (continued)

 as the CSF the lumbar puncture to allow comparison. The CSF to blood glucose ratio is usually normal or mildly decreased in viral brain infections. Lower

levels are occasionally reported, es- pecially in mumps and lymphocytic choriomeningitis virus in- fections. Cerebrospinal fluid examination may be normal if it is performed very early in the illness, or there may be a predom- inantly neutrophil pleocytosis (e.g. in early in enteroviral men- ingitis or herpes simplex encephalitis); occasionally the glucose concentration is low. Virology Full laboratory resources allow a specific virus to be implicated in 60–70% of cases of lymphocytic meningitis and in 20–60% of patients with encephalitis (Table 24.11.2.2). Polymerase chain reaction on cerebrospinal fluid (CSF PCR) is now the mainstay of diagnosis for most viral causes of meningitis or encephalitis. Multiplex PCR has allowed the possibility to test for multiple pathogens at once—this has proven to be cost effective and improve sensitivity. PCR is limited in many cases by the low viral load in the CSF. Identification of virus from a distant site is useful and suggestive, although not definitive of causation, in enteroviral disease (throat and stool samples by PCR). For some viruses detec- tion in the CSF is not diagnostic, for example, EBV and CMV may be found merely as a result of inflammation but may not necessarily be the cause of the illness. Specific viral IgM can be detected in serum for mumps, EBV, CMV, or measles, or using an IgM capture technique in the cerebrospinal fluid for Japanese encephalitis virus. This method is being used increasingly to detect IgM to other vir- uses. Serological evidence of disease does not necessarily confirm the cause of the neurological illness, as some peripheral infections can have prolonged periods of IgM positivity (e.g. West Nile virus). IgM may remain positive for up to one year and hence in areas of high endemicity may not be that useful. Seroconversion between acute and convalescent samples taken 2–4 weeks apart or detecting higher IgM antibody levels in CSF than in blood can provide stronger evidence of causality. Avidity testing has also proven useful Cause Diagnostic clinical feature or investigation Protozoa Amoeba (Acanthamoeba spp., Naegleria spp., Balamuthia spp.) CSF microscopy (fresh wet preparation + India ink), culture Malaria (cerebral) Blood smears Toxoplasma spp. (Immunocompromized patients—AIDS) CSF animal inoculation, serology, brain biopsy Trypanosomiasis (African and South American) Blood smear (buffy coat), lymph node aspirate, CSF microscopy, and IgM, serology, xenodiagnosis Helminths Angiostrongylus cantonensis CSF larvae, eosinophilia Cysticercosis CT/MRI, radiographs, examination for subcutaneous cysts, CSF CFT, histology Gnathostoma spinigerum Cutaneous migratory swelling, CSF eosinophilia Hydatid disease Casoni test, serology, CT/MR scan, radiographs Paragonimus spp. CSF ova, eosinophils, serology, CT/MR scan or skull radiograph, histology Schistosomiasis Low transverse myelitis, ova in urine or stool, CT/MRI, CSF eosinophilia, myelogram, histology Sparganosis Histology, CT/MR scan Strongyloides stercoralis (Immunocompromized patients) larvae, ova in stool, duodenal fluid, and so on Other Behçet’s syndrome Clinical syndrome Carcinomas, cysts, leukaemias, lymphomas CSF cytology, evidence of condition elsewhere Chemical Recent lumbar puncture, spinal anaesthesia, myelography, isotope cisternography Drugs Nonsteroidal anti-inflammatory agents, immunomodulators, antimicrobials (e.g. trimethoprim) Kawasaki’s disease Clinical features, echocardiography, coronary angiography, and so on Lead encephalopathy Blood lead, blood smear, urinary coproporphyrins Sarcoidosis Histology, Kveim’s test, Mantoux test, serum Ca2+, ACE Systemic lupus erythematosus and other collagen/vascular diseases Antinuclear antibodies, DNA antibodies, lupus erythematosus cells Vogt–Koyanagi–Harada syndrome Clinical syndrome Whipple’s disease Clinical features, jejunal histology ACE, angiotensin-converting enzyme; CFT, complement fixation test; CIE, countercurrent immunoelectrophoresis; CSF, cerebrospinal fluid; EIA, enzyme immunoassay; FTA-abs, fixed treponema antibody absorption test; HSV, herpes simplex virus; IFA, immunofluorescent antibody; LA, latex agglutination; PCR, polymerase chain reaction; RIA, radioimmunoassay; RMSF, Rocky Mountain spotted fever. a Aseptic meningitis: CSF pleocytosis but no bacteria stainable by Gram’s method and no growth on standard

bacterial culture media. Table 24.11.2.1 Continued

24.11.2 Viral infections 6093 for some pathogens (e.g. CMV, West Nile virus, VZV, and mumps). The viraemia associated with Japanese encephalitis is very brief and isolation of the virus from cerebrospinal fluid is difficult. Virus can occasionally be isolated from post-mortem material. Imaging of the brain and spinal cord The use of neuroimaging before a lumbar puncture (LP) has gen- erated considerable debate with some recommending cerebral imaging is performed before LP for all patients with suspected neurological infection. However, this can lead to unnecessary delays in treatment and LP, which reduces the likelihood of identifying a pathogen and potentially increasing mortality. The reason for neuroimaging is to detect cerebral herniation syn- dromes, or shift of brain compartments. If these are present and a LP is performed, there is a theoretical concern that a reduc- tion in pressure caused by the LP can precipitate a further brain shift which may lead to fatal herniation. Neuroimaging should be performed on patients who have clinical signs which may sug- gest brain shift and, if shift of brain compartments or herniation is found, LP should be delayed. Indications that brain shift might be present include focal neurological signs and reduced level of consciousness. Table 24.11.2.2 Specimens for the virological diagnosis of acute meningitis or meningoencephalomyelitis Virus Microbiological investigations CSF PCR Stool PCR Throat PCR Blood PCR Virus culture Acute serology Convalescent serology Intrathecal antibodies Avidity testing Other investigations Picornaviruses Polioviruses + + + – ++ from stool + + Other enteroviruses ++ + + + + + Parechoviruses ++ Herpesviruses Cytomegalovirus + – – – ++ Epstein–Barr + – – – + Herpes simplex type 1 ++ – – – + – – + – Herpes simplex type 2 ++ – – – + – – + – HHV-6b ++a – – – + – – – + Herpes B virus – – – ++ Herpes varicella zoster ++ – – – + Flaviviruses Japanese encephalitis virus + – – – + + ++ West Nile virus + – – – + + ++ + Tick-borne encephalitis virus –b – – +c + + + Bunyaviruses Toscana virus ++ – – – + + La Crosse – – – – – ++ ++ Other viruses Adenovirus ++ Mumps ++ + + Rabies + + ++ Nuchal skin biopsy Salivary PCR Lymphocytic choriomeningitis ++ + + HTLV-1 + ++ ++ CSF, cerebrospinal fluid; HTLV, human T-lymphotropic virus; PCR, polymerase chain reaction, TBE, tick-borne encephalitis. ++ = first line investigations; + = useful adjunctive tests; – = not useful. a quantitative PCR can be useful in differentiating active replicating infection from chromosomally integrated virus. b may be positive in the rare cases of chronically progressive TBE disease (Siberian form). c unlikely to be positive in the second phase of the biphasic infection.

section 24 Neurological disorders 6094 MRI, if available, is more sensitive that CT. As well as identifying any brain shift it is also useful for the diagnosis of the site, nature, and extent of any mass lesions, any associated oedema, sub- and epi- dural empyemas, hydrocephalus, demyelination, and other anatom- ical abnormalities (see Chapter 24.3.3). Few conditions will pathognomonic radiological appearances. Imaging will be very rarely needed in cases of straight forward viral meningitis. Herpes encephalitis may show classical temporal lobe involvement, 94% of patients have high-signal T2-hyperintense le- sions in the medial and inferior temporal regions, although this can occur in other conditions as well. MRI of the brain in West Nile en- cephalitis and other flaviviruses characteristically shows bilateral abnormalities in the basal ganglia and thalami. Leptomeningeal en- hancement is also commonly seen. Rabies encephalitis involves pre-dominantly the grey matter of the basal ganglia, thalamus, midbrain, and the pons. More discrete high-signal intensity 2- to 7-mm lesions, particularly in the subcortical and deep white matter of the cerebral hemispheres, have been associated with Nipah virus infection. Differential diagnosis Viral infections of the CNS must be distinguished from the many other conditions that produce similar

clinical features and cere- brospinal fluid abnormalities. The differential diagnoses of viral meningitis are shown in Table 24.11.2.1. Viral myelitides must be distinguished from other causes of transverse myelitis and the Brown–Séquard syndrome. These include spinal compression by tumours, abscesses, helminths or their ova, or vertebral disease. The differential diagnosis of viral myelitis includes: postinfectious and other immunopathic polyneuroradiculopathies, such as Guillain–Barré syndrome; metabolic neuropathies such as acute porphyria; paralytic rabies; neoplastic polyradiculopathies; and rarities, such as tick paralysis and herpesvirus simiae (B virus) in- fection. The lack of objective sensory loss in poliomyelitis usually distinguishes it from these other entities. The differential diagnosis of viral encephalitis includes other in- fective encephalopathies: bacterial, fungal, protozoal, and para- sitic; intracranial abscesses and neoplasms, and toxic and metabolic encephalopathies. Treatment Meningitis There is no specific antiviral treatment for almost all forms of viral meningitis. Aciclovir, which has proven anti-herpes activity, has never been trialled acutely in herpes meningitis. There is no consensus on its efficacy, resulting in a wide range of clinical practices with some who advocate no treatment and others who give up to 3 weeks of intra- venous aciclovir. A randomized trial of its pro-drug, valaciclovir (0.5 g twice daily) in recurrent HSV-2 meningitis failed to show any benefit. Encephalitis Aciclovir (10 mg per kg three times daily for 2-3 weeks) is effective in treating herpes simplex encephalitis. This subject is also discussed in Chapter 8.5.2. Therapy with aciclovir should be started imme- diately on suspicion of encephalitis. Aciclovir is also the treatment for CNS associated VZV infections (usually at 15-20 mg/kg three times daily) and the rare, but very dangerous, encephalomyelitis caused by herpesvirus simiae B. For CMV infections, ganciclovir or foscarnet should be considered. Ribavirin is effective against some RNA viruses which occasionally cause encephalitis, such as those causing Lassa fever, haemorrhagic fever with renal syndrome, Congo Crimean haemorrhagic fever and possibly Argentine haem- orrhagic fever, and Rift Valley fever. Interferons have been used by intravenous, intrathecal, or intraventricular routes in the treatment of Japanese encephalitis, rabies, VZV, and other herpesvirus encephalitides, but have not proved effective in clinical trials. Hyperimmune plasma given within 8 days of the start of symp- toms has reduced the mortality rate of Argentine haemorrhagic fever (Junin virus) from between 20% and 30% to 1% and 3%. Intravenous immunoglobulin has proved effective in the treatment of Congo Crimean haemorrhagic fever. It is also widely used in Asia for the treatment of enterovirus 71, although evidence from randomized controlled trials is lacking. It has been reported favourably in case reports or feasibility studies in many other of the encephalitides, including Japanese encephalitis and West Nile virus. Myelitis There is currently no proven treatment for enteroviral disease. In the 2014 EV68 outbreak in the United States various treatment strat- egies were employed including combinations of steroids, intravenous immunoglobulin, plasmapheresis, and an experimental drug— pocapavir. None of these seemed to give any proven benefit, although numbers were small. Although most enteroviral infections are mild, given the propensity for some serotypes to cause serious life- and limb- altering disease there is a need to develop treatments and vaccines. Supportive treatment Corticosteroids have been used in the treatment of most of the viral encephalomyelitides, both in an attempt to combat cerebral oedema (especially in herpes simplex encephalitis) and for their other anti-inflammatory effects. Convincing evidence of benefit from controlled trials is lacking, but the immunosuppressive ef- fects of corticosteroids have not led to obvious clinical deterioration. Corticosteroids (or adrenocorticotropic hormones) have also been used for postinfectious and postvaccinal encephalomyelitides, but the evidence for their efficacy is not convincing and, as they may ex- acerbate latent rabies in experimental animals, should be used only in life-threatening cases of rabies postvaccinal encephalomyelitis. Severe intracranial

hypertension should be treated with intravenous mannitol or mechanical hyperventilation. Nursing and general care are the same as for acute bacterial meningitis and tuberculous men- ingitis. Seizures should be treated but there is currently no evidence for prophylaxis, respiratory failure treated by mechanical ventila- tion, and attention given to fluid, electrolyte, and acid-base balance. Prognosis and sequelae Viral meningitis generally has an excellent prognosis, but some pa- tients with HSV-2 infection can have recurrent attacks. Additionally, there are increasing reports of neurocognitive problems following viral meningitis. Viral encephalitis and myelitis however can carry a significant mortality. Case fatality rates of some are as follows: rabies 100%;

24.11.2 Viral infections 6095 herpes simplex encephalitis (untreated) 40 to more than 75% (highest in neonates and those over 30 years old); Eastern equine en- cephalitis 50%; Japanese encephalitis 10–40%; West Nile Virus 10%, measles 10–20%; varicella 10–30%; Western equine encephalitis 8%; St Louis encephalitis 3%; California encephalitis, Venezuelan en- cephalitis, and mumps less than 1%. The mortality rate of paralytic poliomyelitis increases from 5% in young children to more than 20% in adults. Postinfectious and postvaccinal encephalomyelitides carry case fatality rates of 15–40%. Neurological sequelae are found in 5–75% of survivors of Japanese encephalitis and herpes simplex encephalitis, and are common in infants. They include intellectual impairment, loss of memory, speech abnormalities (including subtle expressive aphasias), hemi- paresis, ataxia, dystonic brainstem and cranial nerve lesions, re- current convulsions, and various behavioural and personality disturbances. Sequelae are common with postinfectious enceph- alomyelitis. Post-polio syndrome is an unusual sequel to paralytic poliomyelitis developing after an interval of many years; it is a con- dition characterized by progressive muscle weakness and wasting, attributable to depletion of anterior horn cells, which has some similarities to motor neuron disease. Prevention Prophylactic immunization against poliomyelitis and measles has virtually eradicated encephalitides caused by these viruses in many communities. Pre- and postexposure rabies immunization has also proved effective in preventing rabies encephalitis. Vaccines are also available for Japanese encephalitis, tick-borne encephalitis, mumps, and varicella. Some countries have been more successful than others in eliminating Japanese encephalitis; this is principally due to the extent of vaccine coverage for the disease. There is one live attenuated vaccine licensed for dengue virus, and a range of other vaccines are in various stages of development. Since the outbreak of West Nile infection in the United States of America, several vaccine candidates have been identified. Immune protection against infection was demonstrated in animal models and early human trials have shown good immunogenicity and toler- ability. Nipah virus vaccines are beginning to be assessed in animal models. Hyperimmune immunoglobulin has been used for passive im- munization following exposure to measles, cutaneous VZV, and rabies. Interferons have been used with some success to prevent herpesvirus infections (e.g. CMV in high-risk groups such as renal transplant recipients). However, the evidence does not yet justify their routine recommendation. Prevention of neonatal HSV-2 encephalitis can be attempted by treating any pregnant woman with signs and symptoms of genital herpes, followed by daily suppressive therapy with aciclovir. If a woman develops her first episode of genital herpes in the third tri- mester caesarean section is the recommended mode of delivery. Arthropod-borne viral encephalitides can, to some extent, be prevented by avoiding or controlling the arthropod vectors (e.g. by the use of mosquito nets, insect repellents, insecticides), by at- tempting to control the numbers of wild vertebrate reservoir species, or by immunizing domestic animals, such as horses (Eastern and Western equine encephalitides). To control rabies, the principal wild mammalian vectors can be immunized (e.g. wild foxes, racoons, and black-backed jackals have been immunized by

distributing oral vaccine in bait). Domestic dogs and cats should be immunized. To prevent the viral encephalitides transmissible from laboratory animals (e.g. lymphocytic choriomeningitis from mice and rats, herpesvirus simiae B from monkeys) their screening, quarantine, handling, and housing should be strictly controlled. Other viral infections or disorders in which viruses play a role in the pathogenesis of neurological disease Reye's syndrome Reye's syndrome is an acute encephalopathy affecting children be- tween the ages of 2 and 16 years. The exact aetiology is not under- stood but it normally follows a viral illness and there is a strong association with aspirin use. It is a diagnosis of exclusion, but is rapidly fatal in 10 to 40% of cases. The defining characteris- tics are sudden impairment of consciousness, increase in serum aminotransferase concentrations (or, if a biopsy is done, a fatty liver). Symptoms develop a few days after varicella or an upper respiratory tract or gastrointestinal illness. Clusters of cases (me- dian age 11 years) have been associated with influenza B epidemics. Since the warnings regarding the use of aspirin the incidence has markedly decreased with only a handful of cases a year in both the United Kingdom and the United States. There is no specific treatment, but mortality can be reduced by treating hypoglycaemia, cerebral oedema, respiratory failure, fluid and electrolyte disturbances, and other complications. These meas- ures are also considered in Chapter 24.11.1. Progressive multifocal leucoencephalopathy (See Chapters 8.5.19, 8.5.23, and 24.11.4.) This disease is caused by opportunistic infection by papova- viruses, most commonly JC virus and the simian virus SV40. A high proportion of normal adults have antibodies to the former and the agent appears to be ubiquitous. Progressive multifocal leucoencephalopathy occurs in patients affected by lympho- or myeloproliferative diseases, sarcoidosis, other chronic granulomatous diseases, advanced HIV, and those who are therapeutically immunosuppressed. In patients with mul- tiple sclerosis, the monoclonal antibody natiluzimab, a and other immunosuppressives, have has led to an increase in patients with progressive multifocal leucoencephalopathy. Pathology JC virus particularly invades the nuclei of the oligodendroglia leading to demyelination of the white matter. The cerebellum and brain- stem are less often involved and the spinal cord is spared. Abnormal giant forms of oligodendrocytes with eosinophilic inclusions are seen microscopically, and arrays of intranuclear virus particles can often be identified by electron microscopy. JC virus antigen can be identified by immunofluorescence or immunohistochemistry. DNA probing has revealed unintegrated virus in oligodendrocytes, astro- cytes, endothelial cells, and extraneural organs such as kidney, liver, lung, spleen, and lymph nodes.

section 24 Neurological disorders 6096 Clinical features The onset is usually with progressive signs of a focal lesion of one cerebral hemisphere, limb weakness, aphasia, or visual field defects such as homonymous hemianopia. More widespread signs gradually develop, leading to personality changes, intellectual deterioration, dysarthria or fluent aphasia, and bilateral weakness. Fits are rare. There is no systemic evidence of infection. Spontaneous temporary arrest or partial remission is common but eventual progression causes death in 6–12 months, although far more chronic cases are on record, with survival, exceptionally, to 5 years. Investigation The cerebrospinal fluid is normal apart from occasionally a mild ele- vation of protein and slight pleocytosis, and is not under increased pressure. The EEG shows a bilateral excess of slow activity. The CT scan may at first show little abnormality, but eventually large, non- enhancing, low-density lesions appear in the cerebral white matter. MRI is more sensitive. CSF can be tested by PCR for JC virus. If there is doubt the diagnosis can be confirmed by cerebral biopsy, but it is essential that white matter be included in the specimen. This may be important to distinguish lymphoma and, rarely, herpes simplex encephalitis involving white matter. Treatment In patients with progressive multifocal leucoencephalopathy asso- ciated with HIV the only treatment is to commence antiretrovirals,

although there may still be significant sequelae. In patients on im- munosuppressive treatment reduction or removal of that treatment, if possible, can also help the outcome. There remains a need to iden- tify a specific antiviral treatment for this disease. Progressive rubella panencephalitis This extremely rare disorder (see Chapter 8.5.13) may follow con- genital rubella or rubella in early childhood. It evolves insidiously some 10 years after the original illness, similar to subacute sclerosing panencephalitis due to measles virus and is characterized by pro- gressive intellectual impairment with behaviour changes, fits, ataxia, spasticity, optic atrophy, and macular degeneration. Pathological changes are those of encephalitis with perivascular infiltration. The cerebrospinal fluid may show a slight rise in white cell and protein content, elevation of γ-globulin, and of antirubella antibodies to an extent greater than the rise in the serum level, suggesting local pro- duction of antibody within the CNS. The EEG may show changes similar to those seen in subacute sclerosing panencephalitis. The mechanism responsible for the appearance of this disorder is un- known and there is no effective treatment. Vogt–Koyanagi–Harada syndrome The cause of this rare syndrome is thought to be an inflammatory autoimmune reaction to an unidentified viral infection. The disorder affects tissues having a common embryological origin, the uvea and leptomeninges and the melanoblasts, ocular pigments, and auditory labyrinth pigments originating from the neural crest. The dermato- logical features consist of patchy whitening of eyelashes, eyebrows and scalp hair, alopecia, and vitiligo. Neurological manifestations include meningoencephalitis, raised intracranial pressure, neurosensory deafness, tinnitus, nystagmus, ataxia, ocular palsies, and focal cerebral deficits. Ocular features are those of uveitis with pain and photophobia, more generalized inflammation of the eye, retinopathy, and impaired visual acuity. The condition tends to be self-limiting but may result in serious permanent ocular and neurological deficits. Steroids and immunosuppressive drugs have been used and are said to arrest the progression of at least some features of the disorder. EBV-related neurological disease EBV, as well as occasionally causing meningitis and encephal- itis, can be responsible for other neurological conditions espe- cially in immunosuppressed patients. It is an oncogenic virus and is the cause of both primary CNS lymphoma and posttransplant lymphoproliferative disorder. Again, reduction of immunosup- pression, if possible, is important in these conditions and rituximab plays an important role in the treatment. Other neurological conditions where viruses may be involved Cerebrovascular disease and herpes zoster VZV infection is well known to cause a vasculopathy and has long been associated with the development of cerebrovascular disease. A cohort study has = shown it is an independent risk factor for vas- cular disease, especially cerebrovascular disease in young adults under the age of 40. HIV also increases the risk of cerebrovascular accidents. Immune mediated encephalitis Immune mediated encephalitis is increasingly being recognized as a cause of encephalitis in both children and adults. It includes acute disseminated encephalomyelitis which is considered else- where in Chapter 24.10.2, and autoimmune encephalitis which can account for around 10% of cases of encephalitis, and is associated with a range of anti-neuronal antibodies, including those directed against N-methyl-D-aspartate (NMDA), Leucine-rich, glioma inacti- vated 1 (LGI-1) and myelin oligodendrocyte glycoprotein (MOG). Autoimmune encephalitis may sometimes follow HSV encephalitis. FURTHER READING Aurelius E, et al. (2012). Long-term valaciclovir suppressive treatment after herpes simplex virus type 2 meningitis: a double-blind, ran- domized controlled trial. Clin Infect Dis, 54, 1304–13. Baringer JR (2008). Herpes simplex infections of the nervous system. Neurol Clin, 26, 657–74, viii. Campbell GL (2011). Estimating global incidence of Japanese Ence phalitis: a systematic review. Bull World Health Organ, 89, 766–774E. Dayan GH (2012). Phase II dose ranging study of the safety and im- munogenicity of single dose West Nile vaccine in healthy adults ≥50 years of age. Vaccine, 30, 6656–64. De Jong MD, et al. (2005). Japanese encephalitis-a pathological and clinical perspective.

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