

Chapter 2

Myxoviruses

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Paramyxoviruses

The *Paramyxoviridae* are enveloped, nonsegmented, negative-sense RNA viruses. The family is divided into two subfamilies, the *Paramyxovirinae* and *Pneumovirinae*. Of the five genera that comprise the *Paramyxovirinae*, three are known to cause disease in humans: *Respirovirus*, *Rubulavirus*, and *Morbillivirus*. The *Pneumovirinae*, in turn, consist of two genera pathogenic for humans, *Pneumovirus*, and the recently identified *Metapneumovirus* [1].

Parainfluenza

Epidemiology

The parainfluenza viruses (PIV) are members of the *Respirovirus* genus. Although four serotypes of PIV have been identified, PIV4 is infrequently isolated from clinical samples. Transmission of PIV occurs through large droplets that inoculate the eyes and nose via respiratory aerosols or autoinoculation [2]. By 2 years of age, more than 90% of children have been infected with PIV3. PIV1 and PIV2 infection is normally not encountered until after 2 years of age. PIV4 is also found in this age group, with more than 50% of children younger than 5 years of age possessing antibodies to PIV4 [3].

PIV are ubiquitous worldwide. They cause disease throughout the year, but peak activity is observed during the spring and fall months.

Clinical Manifestations

PIV can cause both upper and lower respiratory tract disease, with the former predominating. Up to 50% of PIV-related upper respiratory tract infections are complicated by otitis media. PIV, in particular PIV1, typically cause croup that may

be severe enough to warrant treatment with corticosteroids and hospitalization. PIV3 infection can cause pneumonia and bronchiolitis, predominantly in infants younger than 1 year of age. PIV can also cause laryngitis, tracheitis, and a nonfocal febrile illness [3].

Neurological Manifestations

PIV have been causally linked to multiple neurological syndromes, including meningitis, meningoencephalitis, Guillain-Barré, Reye, and demyelinating syndromes. The reported ages of patients have ranged from newborn to elderly adults. However, more than half of the reported patients have been younger than 2 years of age. Reported underlying conditions or concurrent illnesses have included severe combined immunodeficiency, *Haemophilus influenzae b* meningitis, human immunodeficiency virus infection, and malignancy [4–16].

The principle neurological diagnosis among patients with PIV central nervous system (CNS) infections has been aseptic meningitis. The most common reported clinical presentation consisted of fever, rhinorrhea, and emesis. Other symptoms observed include headache, lethargy, irritability, and vertigo [4,10–13]. Nuchal rigidity has been infrequently reported [11,13]. PIV have also been linked to febrile seizures. In one study, 11% of patients with febrile seizure were associated with PIV infection. Most patients seem to recover without neurological sequelae. However, in patients in whom profound underlying immunodeficiency exists, death may occur [5].

Neuropathology

Because of the generally favorable outcome of neurological illnesses resulting from PIV infection, little is known regarding the pathophysiology and neuropathology of PIV-associated neurological syndromes. Even in a patient who died of disseminated PIV3, autopsy revealed no abnormalities within the brain despite isolation of the virus from the cerebrospinal fluid (CSF) [5].

Diagnosis

Cytochemical analysis of the CSF reveals a predominantly mononuclear pleocytosis that ranges from 10 to 913 cells/mm³. In almost all cases, the CSF protein and glucose levels are normal [4,6,7,9,11–13]. In all cases of neurological disease reported, PIV was isolated from the CSF using cell culture. Although all PIV serotypes, with the exception of PIV1, have been isolated from the CSF, PIV3 has been the overwhelmingly dominant serotype identified.

All four types of PIV were isolated from children with PIV-associated febrile seizures in one study, but none were from the CSF [17]. In a separate report, two patients with simple febrile seizures yielded PIV3 and PIV2 from the CSF [18].

Treatment

Neurological disease, similar to respiratory disease that results from PIV, is self-limiting. As such, only supportive care is required as treatment.

Mumps

Introduction

The earliest descriptions of mumps dates to Hippocrates in the fifth century BC. Hamilton et al. published the initial report of CNS involvement with mumps in 1790, describing mumps-associated neurological findings in a patient who succumbed to the disease. In the early 19th century, Hintz observed an association between epidemic parotitis and deafness [19,20].

Epidemiology

Mumps is a member of the genus *Rubulavirus* within the subfamily *Paramyxovirinae*. Before the introduction of an effective mumps vaccine in 1967, cases were seen annually, with epidemics approximately every 3 to 4 years in the United States. In epidemic years, the rate of infection reached as high as 250 cases per 100,000 population [19,20]. In temperate climates, mumps infections are observed during the winter and spring months. This seasonality does not hold true for the tropical regions. Currently, because of widespread use of mumps vaccine, no seasonality is observed among mumps cases in the United States. Other countries around the world that have implemented vaccination programs have observed a reduction in mumps cases exceeding 85% [21].

In 2003, the total number of mumps cases in the United States was only 270, the lowest number ever reported [22,23]. Although significant strides have been made in reducing the annual number of mumps cases, outbreaks continue to occur [24,25]. Two large outbreaks of mumps in Great Britain (2004–2005) and the United States (2005–2006) attest to the latter.

In Great Britain, the outbreak was attributed to decreased immunization rates secondary to vaccine shortages in combination with the lack of use of a booster dose of mumps vaccine. The outbreak in the United States was thought to be the result of multiple factors that included a large susceptible population because of lack of 100% effectiveness of the two-dose measles, mumps, rubella (MMR) vaccine regimen, delayed diagnosis by physicians, and close living quarters (i.e., college dormitories) among the people most affected [24,25].

Mumps is considered one of the classic diseases of childhood. Typically, children between the ages of 5 and 9 years were most commonly affected, with children younger than the age of 5 years comprising the next largest group. However, since institution of mumps vaccination, many more cases now occur in individuals older than the age of 10 years.

Clinical Manifestations

Mumps is a highly contagious disease that is transmitted via respiratory droplets. Infectivity rates approach 60 to 100% among susceptible individuals. An important source of virus spread is persons experiencing asymptomatic infections. The incubation period for mumps is 16 to 18 days, but ranges from 14 to 24 days. Individuals experiencing mumps are infectious 3 days before and 4 days after parotid enlargement. Shedding of virus in the urine may occur for 10 to 14 days after the onset of parotid enlargement [26].

The classic patient with mumps presents with a prodrome consisting of headache, anorexia, vomiting, malaise, and fever 1 to 2 days before the onset of parotitis, the hallmark of the disease. The fever can be as high as 103°F but, in some cases, is low grade or completely absent. After the prodrome, swelling of the parotid gland(s) begins. In 70 to 80% of cases, the parotid enlargement is bilateral. The parotid swelling reaches its maximum on the third day and persists for 2 days before receding.

Up to 30% of infections are asymptomatic or so mild as to go unrecognized. Other associated clinical manifestations of mumps are diverse. Up to 38% of post-pubertal males develop epididymo-orchitis. In postpubertal females, oophoritis occurs in 7%. Other reported manifestations include pancreatitis, myocarditis, nephritis, arthropathy, and rash [20].

Neurological Manifestations

Mumps virus should be recognized as an important etiologic agent of neurological disease. CNS involvement in mumps infection has been reported to occur in 0.5 to 10% of all mumps infections. The reported rates of meningitis and encephalitis per mumps case are 1 and 2.6 per 1000, respectively. During epidemics, as many as 30% of mumps-infected patients experience neurological illnesses [21,26–28].

During the pre-vaccine era, mumps was the leading cause of both meningitis and encephalitis. Meyers et al. reported that mumps was the second most common cause of aseptic meningitis as well as the most common cause of encephalitis between 1953 and 1958 [29]. Mumps virus was responsible for up to 25% of known causes of viral meningitis [28,30]. Among reportable cases of encephalitis to the Centers for Disease Control and Prevention (CDC) in 1967, mumps was the most common etiology, comprising approximately 36% of the cases. Nine years after the inception of the mumps vaccine, only 3.5% of encephalitis cases reported to the CDC were caused by mumps virus, a testament to the effectiveness of the vaccine [28]. Although clinical data regarding the 2006 mumps outbreak in the United States remains incomplete, at least 21 of the 3860 cases had reported neurological complications. These included meningitis in 10, encephalitis in 5 and deafness in 6 patients.

CNS involvement during mumps infection occurs most commonly in children. Children younger than 10 years of age account for more than 70% of the cases [31–33]. Interestingly, CNS involvement occurs three times more often in male than in female patients.

Mumps meningitis and/or encephalitis may occur with or without associated parotitis. Approximately 50% of patients do not have parotitis. Typically, in patients with parotitis, the meningitis presents during the first week after its onset. However, the onset of the meningitis may occur as late as 3 weeks after parotitis or may even precede it [32–34]. In contrast, mumps-associated encephalitis typically appears weeks later.

Although it is common to describe the CNS involvement in mumps as either meningitis or encephalitis, many patients have combinations of both, or rather, meningoencephalitis. In patients with mumps aseptic meningitis alone, the commonly reported signs and symptoms include fever, headache, vomiting, and neck stiffness. Azimi et al. observed the fever to last, on average, 3.1 days, but could persist for as long as 7 days. Other associated signs and symptoms may include abdominal pain, diarrhea, and sore throat [31].

In their report, Koskiniemi et al. described patients with mumps-associated encephalitis alone. These patients were primarily boys (4:1) and had a mean age of 7.3 years (range 1.2–13.7 yr). As with meningitis, patients presented with fever and commonly had parotitis before the onset of encephalitis. Neurological signs and symptoms consisted of impaired locomotion and balance (36%), seizures (24%), psychic disorder (22%), and sensory disturbance (12%). Progression to coma was reported in 7%. The average length of hospitalization was 10.9 days (3–41 d) [35].

Mumps-associated deafness has been estimated to occur in 0.5 to 5 per 100,000 cases of mumps. It is typically unilateral and results in permanent hearing loss [20,36]. The presence of meningitis or encephalitis is not a prerequisite for its development and it has been reported to occur even in patients with asymptomatic mumps infection. Other neurological diseases attributed to mumps infection include Guillain-Barré syndrome, transverse myelitis, cerebellitis, facial palsy, and an illness similar to subacute sclerosing panencephalitis (SSPE) [20,37–39].

Neurological sequelae after mumps meningitis are rare. Azimi et al. [31] and Johnstone et al. [40] reviewed the outcomes of 181 patients with mumps meningitis

and found that all recovered without sequelae. Additionally, among patients followed for up to 40 months after recovery from their illness, none developed deafness.

In contrast, the outcome is less favorable in patients with encephalitis, in whom sequelae are observed in 25%. These sequelae include behavioral disturbances, impaired ability to concentrate, ataxia, and dysarthria. Overall, mortality is rare and has been associated with infections in immunocompromised hosts or individuals with severe underlying conditions [35,41].

Hydrocephalus has been reported in 16 cases after mumps meningitis and/or encephalitis. This complication has been diagnosed from 1 day to 19 years after the initial mumps infection [42].

Neuropathology

Because death from mumps-associated CNS disease is rare, limited reports exist that discuss its pathology. A serofibrinous leptomeningitis with hyperemia and edema primarily localized at the base of the brain has been described. Donohue et al. found pathology similar to that of CNS-associated measles infection, consisting of perivascular edema and inflammation. Areas of demyelination have been identified in the cerebrum, cerebellum, basal ganglia, thalamus, midbrain, pons, and medulla [43,44].

In 1968, Johnson and colleagues provided a potential explanation for the development of hydrocephalus by demonstrating that suckling mice developed aqueductal stenosis after intracerebral injection of mumps virus. Additionally, nucleocapsids of the mumps virions have been visualized within ependymal cells of the CNS in both animal models and patients with mumps meningitis and/or encephalitis [45–48].

Diagnosis

Cytochemical analysis of the CSF in mumps meningitis reveals a predominant lymphocytic pleocytosis. The CSF leukocyte count is commonly less than 500 cells/mm³ but has been reported to be as high as 5000 cells/mm³ [31,34]. In some, a polymorphonuclear majority may be observed [40]. Pleocytosis has also been reported in patients with clinically apparent mumps infection in the absence of neurological signs or symptoms [43]. Abnormalities in the CSF protein concentration are reported in up to one third of cases and can be as high as 200 mg/dl [31,34]. In the majority of patients, the CSF glucose concentration is normal. However, hypoglycorrhachia has been reported to occur in 6 to 28% of cases [31,34,40]. In one report, persistent hypoglycorrhachia was observed for as long as 4 days [32].

In patients with encephalitis, CSF pleocytosis of less than 500 cells/mm³ (range 0–1853 cells/mm³) in association with a normal protein concentration and a slightly depressed glucose concentration is generally seen [35].

Electroencephalograms (EEGs) are abnormal in patients with mumps-associated encephalitis. Koskiniemi et al. noted that EEG abnormalities were present in all patients evaluated during the first week of illness [35]. The characteristic EEG findings in the majority of cases have been classified as moderate to severe slowing. However, lateralization and even focal temporal lobe slow wave changes have been reported. An abnormal EEG persisted for as long as 2 weeks in almost one third of the cases [35,49].

Magnetic resonance imaging (MRI) scanning has greater sensitivity than computed tomographic (CT) scanning in identifying brain abnormalities in patients with mumps-associated CNS disease. Findings on neuroimaging of patients with mumps meningitis and/or encephalitis are varied and include cerebral edema, transverse myelitis, and demyelinated areas, including the thalamus, caudate, and cerebellum [50]. Hydrocephalus has been identified in association with aqueductal stenosis.

The diagnosis of mumps occurs through isolation of the virus by cell culture, amplification of its genome by polymerase chain reaction (PCR), or evidence of a fourfold rise in serologic titers. Mumps is easily cultured from CSF, saliva, or throat swabs [20]. Recent data have shown that PCR is an effective and more rapid diagnostic methodology. Poggio and colleagues demonstrated that reverse transcriptase (RT)-PCR was equivalent to culture in detecting mumps from the CSF [51]. In situations in which cell culture or PCR are unsuccessful in establishing the diagnosis, a fourfold rise in serologic titers using either hemagglutination, complement fixation, or enzyme-linked immunosorbent assay (ELISA) assays can be used. Caution must be taken in interpreting these results because antibodies to mumps may cross-react with those to PIV [52].

Treatment and Prevention

No specific therapy is available for the treatment of mumps infection. Immunoglobulin has been shown to be beneficial in the prevention of orchitis, but a similar effect has not been observed for other mumps-related complications [53,54]. The lack of an effective treatment for mumps and its complications emphasizes the importance of the mumps vaccine in preventing this illness. Mumps vaccine is a live attenuated virus that is commonly administered concomitantly with measles and rubella virus vaccines (i.e., MMR vaccine). In controlled studies, the efficacy of mumps vaccine after a single dose approached 95%. In the United States, administration of the vaccine occurs in children after their first birthday and again between 4 and 6 years of age.

A recognized complication of the use of mumps vaccine is the development of aseptic meningitis. In the United States, where the Jeryl Lynn strain of mumps virus is used, the reported rate of aseptic meningitis is 1 in 800,000 doses. In contrast, the Urabe strain used in Japan has reported rates of aseptic meningitis as high as 1 in 2000 doses. The onset of mumps vaccine strain-associated meningitis occurs 2 to 3

weeks after immunization and seems to be clinically similar to that observed with natural infection [19,55,56]. Wakefield et al. have also suggested that the MMR vaccine is associated with the subsequent onset of autism. Numerous published studies have refuted this hypothesis [57,58].

Measles

Introduction

Measles, a disease caused by a paramyxovirus in the genus *Morbillivirus*, was first described in the 7th century [59]. Cell culture isolation of measles virus, however, was not possible until 1954. Shortly thereafter, the measles virus was adapted to grow in chick embryo tissue culture, paving the way for vaccine development [60,61].

Epidemiology

Before the licensure of inactivated measles vaccine in 1963, measles was a common illness in the United States, resulting in up to 500,000 cases and 500 deaths a year [62,63]. Epidemics occurred every 2 to 5 years during the winter–spring months, and were more frequent in urban populations. Children were most commonly affected, with more than 50% of the measles cases reported occurring in those 5 to 9 years of age [64,65].

Pneumonia caused up to 60% of deaths, whereas encephalitis contributed another 20%. Children younger than 5 years of age and adults older than 20 years had the greatest risk of mortality [63].

After introduction of the live attenuated measles vaccine in United States in 1965, a dramatic decrease in the incidence of measles was observed. Most significantly, since 1992, only one measles-associated death has been reported in the United States [66]. Measles, however, remains a frequent cause of illness and death in developing countries. More than 30 million people worldwide are infected with measles virus every year, resulting in more than 700,000 deaths. Measles is the fifth leading cause of death among children younger than 5 years of age and the leading cause of death caused by a vaccine-preventable disease.

Clinical Disease

Measles has an incubation period of 8 to 12 days. Two to 4 days before the onset of rash, a prodrome consisting of fever, cough, coryza, conjunctivitis, and generalized malaise begins. During the prodromal period, a pathognomonic enanthem, Koplik spots, appears in the oropharynx. These blue and/or white papules on an erythematous

base are initially located on the buccal mucosa opposite the first lower molar. They generally spread to involve most of the buccal and labial mucosa [64,67].

The classic exanthem of measles becomes apparent approximately 14 days after exposure. The rash initially erupts on the ears and forehead as erythematous macules and papules that spread in a centrifugal pattern to cover the face, neck, trunk, upper extremities, buttocks, and lower extremities sequentially. Three to 4 days after the onset of the rash, the rash begins to fade in the same progression as it appeared, such that by day 6 or 7 it has completely resolved. In some cases, the rash may be present for up to 10 days [67,68]. As the rash resolves, a fine desquamation may be noted. During the evolution of the rash, the fever reaches its peak by the second or third day and normally resolves, as does the conjunctivitis and rhinorrhea, 24 hours thereafter. The cough may persist for as long as 10 days.

Atypical measles was observed in individuals immunized with the killed measles vaccine and subsequently infected with natural measles. Use of the killed vaccine was abandoned in 1968 in the United States. Atypical measles is characterized by the lack of a typical prodrome and by an erythematous, maculopapular rash, which begins on the wrists and ankles and progresses cephalad. Prominent symptoms in atypical measles are headache, abdominal pain, and myalgias. Almost all cases have pulmonary involvement. The illness typically lasts 1 to 2 weeks [69,70].

Modified measles occurs in patients who are partially immunized. Clinically it is a milder form of classic measles. The incubation period is similar to that of classic measles. However, the prodromal period is of shorter duration and milder. Koplik spots are rarely present [69]. The exanthem is similar to typical measles in distribution and progression; however, it does not coalesce.

Complications associated with measles involve numerous organ systems. Otitis media is the most frequent complication and occurs in up to 15% of cases. Pulmonary involvement has been observed in more than 50% of children with measles [68,71]. Myocarditis and pericarditis have also been reported [69]. Measles infects the intestines in most patients and has been associated with diarrhea. In developing nations, malnourished children with measles frequently die because of persistent diarrhea [68].

Neurological Manifestations

Neurological complications are a common and potentially fatal consequence of measles infection. Acute postinfectious encephalitis (APE) occurs in 0.5 to 1 of every 1000 cases of measles. Although previously it was thought that the incidence of SSPE was 1 in 100,000 natural infections [72–74], a more recent report, based on data from the 1989 to 1999 measles resurgence in the United States, indicates that the true incidence is approximately 7 to 11 cases per 100,000 case of measles [75]. In a review of measles deaths from 1964 to 1971, a neurological cause was found in 21% of cases [63]. Of the 165 measles deaths reported in the United States from 1987 to 1992, 11% were attributed to APE [66]. Measles inclusion body

encephalitis (MIBE) is an even rarer complication that has been described almost exclusively in immunosuppressed individuals [76].

Acute Postinfectious Encephalitis

APE occurs most often in children younger than 10 years of age, with a majority of cases occurring in children between 2 and 8 years of age. Male and female patients are equally affected [72,77,78].

In the majority of cases, the onset of APE occurs after the fourth day of the exanthem and generally no later than the eighth day. Less commonly, APE has been observed as early as the prodromal phase or as late as after the resolution of the rash [72,79]. In immunosuppressed patients, the presentation may be delayed to as long as 6 months after the acute illness [80]. The pathophysiology of APE is unknown, although it is hypothesized to be an immune-mediated complication.

The clinical presentation of APE is variable. Typically, a child with a resolving rash and normal temperature will have recrudescence of high fever and onset of drowsiness and listlessness. Frequently, patients recover and never require hospital admission [78,81]. However, some may develop sudden onset of seizures and rapidly progress to coma. The most common symptoms are convulsions, lethargy, coma, and irritability (Table 2.1). Convulsions have been noted in approximately 50% of patients with APE. Progression to coma occurs in up to 30% of patients. Additional signs and symptoms include cranial nerve defects, abnormal reflexes, and paralysis [72,77,79]. The outcome of APE is generally poor. Mortality has been reported to range from 10 to 38% [66,77–79,81,82]. In immunocompromised children, APE almost universally results in death. As many as 69% of children may experience neurological sequelae after APE [77,82]. These have included a decrease in cognitive function, recurrent seizures, paresis, choreoathetoid movements, and behavioral disorders [77,82].

Table 2.1 Signs and symptoms associated with acute postinfectious encephalitis secondary to measles [72,77,79]

Symptoms	Percent
Convulsions	43%
Lethargy/drowsiness	35%
Coma	30%
Irritability	21%
Stupor	20%
Headache	10%
Delirium	8%
Nuchal rigidity	35%
Babinski sign	24%
Nystagmus	9%
Clonus	7%
Ataxia	6%

Neuropathology

Attempts to isolate measles virus or detect its genome or viral proteins from the brain tissue of patients with APE have been unsuccessful. Additionally, no intrathecal production of measles virus specific antibodies has been documented. This has led to the speculation that APE may be an immune-mediated complication of measles [83–85]. The finding of antibodies to myelin basic protein in the CSF of these patients supports this hypothesis [85]. Potential mechanisms for the induction of autoimmunity include altered presentation of myelin antigens, molecular mimicry by measles viral proteins with those of myelin antigens, and dysregulation of host immune responses to measles virus [83]. Histologic examination of the brains of cases of APE reveals perivascular lymphocytic infiltration and perivenular demyelination [84,85].

Subacute Sclerosing Panencephalitis

In the early 1930s, Dawson noted viral-like inclusion bodies in the neurons of two patients who died of an insidious neurodegenerative disease. To differentiate this from epidemic encephalitis, it was named “inclusion encephalitis [86].” In 1945, van Bogaert described a similar entity as “subacute sclerosing leukencephalitis” (SSPE) [87]. In 1950, the name subacute sclerosing panencephalitis was suggested [88]. A tentative link between SSPE and measles was made when Bouteille et al. noted viral structures in the brains of patients with SSPE similar to measles virus on electron microscopy (EM) [87]. A definitive link between measles and SSPE was established in 1967 when Connelly and colleagues reported the presence of measles antigens in brain specimens of patients with SSPE [89]. Cocultivation techniques eventually led to the recovery of the measles virus from the brains of patients with SSPE [90]. PCR techniques and in situ RNA hybridization have further substantiated the role of measles virus in SSPE [65].

SSPE primarily affects children and adolescents. The average age at onset is 9 years, and boys are more frequently affected than girls, in a ratio of 2–4:1 [74,91,92]. Children who acquire natural measles infection at an early age are at increased risk of developing SSPE. Those who develop measles at younger than 1 year of age have, in fact, a 16 times greater risk of suffering from SSPE than those who acquire measles at 5 years of age or older [87].

The mean interval to onset of SSPE after measles infection is 7 years. However, onset may occur as soon as 2 years or as late as 10 years after infection. Although the initial reports describe SSPE as a disease that occurs in three stages [93,94], clear demarcation of each stage is not possible. Initial subtle personality changes and progressive intellectual decline are followed by motor involvement. Myoclonic jerks are initially observed in the head and subsequently involve the trunk, arms, and legs. Generalized tonic-clonic and partial seizures may develop.

Ocular involvement has been observed in 10 to 50% of the cases. Ophthalmologic findings may include papilledema, papillitis, optic atrophy, chorioretinitis, or cortical blindness [87,95].

As the disease inexorably progresses, the patient becomes increasingly stuporous and eventually enters into a comatose state. Motor involvement progresses to quadriplegia, spasticity, and myoclonus may disappear. Decerebrate and decorticate posturing may be observed. Autonomic dysregulation occurs at the advanced stages of SSPE, and death often is a result of hyperpyrexia, cardiovascular collapse, or hypothalamic dysfunction. On average, the length of time from onset of symptoms to death is 1 to 3 years [87,96]. A spontaneous remission rate has been documented in up to 10% of the cases and can occur at any stage of the disease. Factors that favor remission are age at onset younger than 12 years, disappearance of periodic complexes and normalization of background on EEG, and an increase in measles titers in the CSF [97].

Neuropathology

As stated previously, defective measles virus can only be recovered, and with great difficulty, from the brain tissue of patients with SSPE [83,90]. Brain tissue from these patients has been found to contain interfering particles, which may play a role in viral persistence. Moreover, mutations in specific viral genes result in mutant viruses that are unable to replicate and bud from the cell membrane [98]. Multiple abnormalities in the M protein of measles virus are considered to be a hallmark of the disease. However, abnormalities of the fusion (F), or hemagglutinin (H), proteins have also been associated with persistent viral infection.

Both the grey and white matter are involved in the disease. During the early phases of SSPE, there is mild inflammation of the meninges and parenchyma of the brain. Neuronal degeneration, perivascular cuffing, infiltration by plasma cells and lymphocytes, astrocyte proliferation, gliosis, and demyelination can be seen. Intranuclear and intracytoplasmic inclusion bodies, which are composed of measles virus nucleocapsids, may be observed within neurons and glial cells [87].

As the disease progresses, there is evidence of atrophy of the cerebral cortex. Widespread neuronal degeneration is evident. The meninges and parenchyma have focal or diffuse perivascular infiltrates composed of lymphocytes, plasma cells, and phagocytes [87].

Measles Inclusion Body Encephalitis

MIBE, first described in the 1970s, occurs almost exclusively in immunosuppressed individuals [76]. MIBE has been associated with wild-type measles virus as well as vaccine strains of measles virus [99].

The overwhelming majority of cases have occurred in children and adolescents. The onset of MIBE occurs within 1 year (typically, 1 to 7 mo) after acute measles infection or immunization with live, attenuated measles vaccine [76]. It may also occur after a clinically inapparent measles infection. In one review, nearly 20% of cases had no exposure to individuals with measles or history of clinical measles [76].

An altered level of consciousness is seen in all cases. Fever is typically absent. Difficult to control seizures are an almost universal finding. Seizures may be focal, or may take the form of *epilepsia partialis continua* in up to one third of the cases. Death occurs in approximately 85% of individuals with MIBE within 1 year of diagnosis. The majority of survivors are left with significant neurological sequelae [76].

Neuropathology

The pathogenesis of MIBE is unknown, but suspected to be similar to that of SSPE. On light microscopy, lymphocytic perivascular infiltration, neuronal loss, and astrocyte and microglial proliferation are seen in the presence of minimal inflammation. Glial cells and neurons are found to contain eosinophilic intranuclear and intracytoplasmic inclusions. EM reveals paramyxovirus nucleocapsids [76].

Diagnosis

Acute Postinfectious Encephalitis

In patients with APE, cytochemical analysis of the CSF demonstrates a mild mononuclear cell pleocytosis. In the majority of cases, the CSF white blood cell count is between 10 and 99 cells/mm³, but can be as high as 700 cells/mm³ [72,77]. The CSF protein concentration may also be elevated, whereas the glucose level is typically normal [72]. Measles virus or its genome has been isolated from the CSF and brain by cell culture and PCR techniques in patients with APE [100–102].

All patients with APE have abnormal EEG findings. Even in patients without overt clinical evidence of encephalitis, abnormal EEGs were observed in 51% of cases [103]. EEG findings include diffuse slowing with asynchronous bursts of delta waves, and diffuse, irregular slow waves and spikes. Repeat EEGs years after APE may continue to show abnormalities [72,104].

MRI scan findings have consisted of high signal intensity lesions throughout the brain on T2-weighted imaging. Cortical lesions have been observed in all regions of the cerebral cortex. Multiple lesions may be seen in the basal ganglia and thalami. Additional areas involved have included the deep white matter, corpus callosum, external capsule, striata, and centrum semiovale [105,106]. Using single-photon emission computed tomography, Kim et. al. demonstrated that patients with measles encephalitis have multiple areas of hypoperfusion, even in the face of a normal MRI scan result [106].

Subacute Sclerosing Panencephalitis

The diagnosis of SSPE can be established based on clinical history, serologic testing, molecular diagnostics, and EEG. Hemagglutination inhibition or complement

fixation assays document extremely elevated ($>1:1280$) antibody titers [107]. Measles antibody can also be detected in the CSF. Cytochemical analysis of the CSF is normal in most cases. However, on closer analysis of the CSF protein, an increase in gammaglobulin may be observed. This may be evaluated by the presence of an oligoclonal band in the CSF [87,108]. With the advent of molecular techniques, RT-PCR has recently been used to identify measles virus in brain tissue of patients in whom the diagnosis of SSPE is suspected.

EEG is an important diagnostic modality in SSPE. During the early stages of the disease, the EEG results may be normal. However, in the presence of myoclonus, the EEG finding of periodic complexes is diagnostic. Three types of periodic complexes have been observed. Type 1 complexes consist of high voltage (200–500 mV) discharges of polyphasic, stereotyped delta waves with or without background suppression. The interval between complexes is 4 to 10 seconds and as the disease progresses the interval shortens. Type 2 has similar delta waves as type 1, but is intermixed with rapid spikes. Type 3 complexes are characterized by prolonged spike waves that are interrupted by giant delta waves [87,109].

The role of neuroimaging in diagnosis is not clearly defined. Several studies have shown no clinical correlation between disease severity and MRI and CT scan abnormalities [110–112]. Findings present on MRI scans in patients with SSPE have consisted of periventricular white matter lesions, cortical gray matter changes, cerebral atrophy, and basal ganglia involvement.

Inclusion Body Encephalitis [76]

In MIBE, the CSF analysis generally fails to reveal any abnormalities. If abnormal, the CSF changes are generally limited to mild pleocytosis and increased CSF protein concentration. Unlike SSPE, high measles antibody titers in the CSF are unusual. Findings on EEG examination consist of diffuse slowing and spike wave activity. At the time of presentation, results of neuroimaging studies are generally normal. Subsequent neuroimaging abnormalities have included cerebral edema, atrophy, and ventricular dilation.

Similar to SSPE, measles viruses associated with MIBE are replication-deficient variants. As would be expected, their detection by cell culture would be the exception rather than the rule. The definitive diagnosis of MIBE requires brain biopsy to search for the presence of measles virus particles, antigens, or nucleic acid in tissue. Measles genome has been detected in the brain tissue of MIBE patients using RT-PCR.

Treatment

Acute Postinfectious Encephalitis

Supportive care is the cornerstone of therapy for APE. Anticonvulsants for seizures, intravenous fluids for management of electrolytes, and antipyretic medications and cooling techniques for fever are important in the care of these patients. Additionally,

patients with increased intracranial pressure should be monitored closely. The use of mannitol may be indicated in the setting of cerebral edema [69,113].

Subacute Sclerosing Panencephalitis

Attempts to treat SSPE have relied on the use of antivirals or immunomodulating agents. Amantadine was one of the first antiviral agents to show a beneficial effect in preventing the progression of disease. Inosiplex has provided the greatest benefit in terms of long-term survival and remission [114–116]. Inosiplex acts by inhibiting viral replication and augmenting the immune response of host cells [96]. Gascon et al. have demonstrated that inosiplex alone was as effective as the combination of inosiplex and intrathecal interferon- α in improving outcome or stabilizing neurological status of patients with SSPE. Additionally, it was demonstrated that both treatments led to improvement or stabilization of neurological symptoms in approximately 30% of patients, a substantial improvement over a spontaneous remission rate of 5 to 10% [117].

Inclusion Body Encephalitis

Therapy is supportive and focused on controlling the associated seizures. If the patient is receiving immunosuppressive therapy, an attempt to withhold immunomodulating medications should be made. Ribavirin has been used in the therapy of MIBE with very limited success [76,118].

Prevention

The greatest impact on APE and SSPE has been the prevention of measles infection. Measles vaccine should be administered to children older than 1 year of age. Although there may be a risk of SSPE after vaccination, it is extraordinarily rare, occurring in 1 per 1 million vaccines versus 7 to 11 per 100,000 unvaccinated children [75]. Use of measles vaccine should be avoided in severely immunosuppressed children.

Nipah and Hendra Viruses

Introduction

Nipah and Hendra viruses are closely related viruses in a newly created genus *Henipavirus* within the *Paramyxoviridae* family. Unlike other paramyxoviruses, these are zoonotic viruses that have been recently identified as a cause of severe and often times fatal disease in humans [119].

Epidemiology

The natural reservoirs of Nipah and Hendra viruses are the fruit bats of the pteropid bat species, commonly referred to as “flying-foxes.” Animals infected by these viruses include dogs, cats, horses, and pigs.

Outbreaks of Hendra virus have occurred among horses in Australia. The equine disease is characterized by a severe respiratory disease in association with ataxia that is often fatal [119]. Disease in humans caused by Hendra virus has only been observed in persons who have handled or worked closely with infected animals. No human-to-human transmission has been documented [119]. To date, only three human cases have been reported, and all have been in workers closely involved in the care of horses with Hendra virus infections. Two fatalities have been reported, one as a result of severe respiratory disease and the other from encephalitis [120,121].

In contrast, Nipah virus has been associated with a larger number of cases of human disease. Similar to Hendra virus, almost all cases have occurred in persons working with infected animals. The first reported human outbreak of Nipah virus occurred among pig farmers in Malaysia. Disease occurred predominantly in male patients who had an average age of 37 years (range 13–68 yr). A striking feature of this disease was its severity; it had a mortality rate of 32% [122].

Clinical Disease

The clinical manifestations of Hendra virus infection are not well characterized because of the paucity of cases that have been reported. Two patients suffered fever, myalgias, and lethargy 1 week after contact with the infected horses. One patient was ill for 6 weeks but had a complete recovery. The other suffered severe respiratory disease and died 6 days after the onset of illness [120,123].

In Nipah virus infection, clinical disease is apparent within 2 weeks of the initial contact with the infected animal, but may occur as late as 2 months after exposure. The initial presenting signs and symptoms consist of fever, headache, dizziness, and emesis. In individuals with severe disease, signs of multisystem organ failure are present [122].

Neurological Manifestations

Neurological involvement in human Hendra virus infection has been reported in only one case. This patient initially suffered from fever, headache, sore throat, and neck stiffness and was diagnosed with aseptic meningitis. Although full recovery was achieved, 13 months later he developed fever, recurrent seizures, coma, respiratory failure, and, ultimately, death [121].

Unlike Hendra virus infections, cases of Nipah virus infection are commonly associated with neurological complications. A decreased level of consciousness and brainstem dysfunction have been observed in up to 55% of patients. Seizures, primarily general-

ized, were present in 23% of cases. Clinical signs of cerebellar dysfunction are common [122]. Other reported neurological signs and symptoms include areflexia, segmental myoclonus, hypertension, hypotension, tachycardia, dysarthria, and dysphagia [122].

Patients who survive Nipah virus encephalitis may develop a repeat episode of encephalitis as long as 1 year after the initial infection. The clinical presentation in these patients is one of acute onset characterized by fever, headache, seizures, dizziness, focal neurological signs, myoclonus, and an altered level of consciousness. Fatalities have been reported in 18% of these patients [124,125]. Lastly, some individuals who initially had asymptomatic or nonencephalitic Nipah virus infection may develop encephalitis up to 1 year after their initial infection.

Neuropathology

Little data exist on the pathogenesis and pathology of Hendra and Nipah virus infections because of their recent identification as human pathogens. In the sole patient with Hendra virus encephalitis, autopsy of the brain revealed a leptomeningitis characterized by lymphocytic and plasma cell infiltrates. Additionally, foci of necrosis were noted in the neocortex, basal ganglia, brainstem, and cerebellum. Nucleocapsids of the Hendra virions were observed in cell remnants by EM, and immunohistochemical staining of brain tissue detected the presence of Hendra virus [121].

Autopsies of patients with Nipah virus encephalitis reveal a diffuse vasculitis with the most severely affected organ being the brain. The vascular endothelium has evidence of vessel-wall necrosis, thrombosis, as well as neutrophil and mononuclear cell infiltration. Syncytial giant cell formation is also observed in affected vessels. Viral and eosinophilic cytoplasmic inclusions can be observed in neurons by EM and light microscopy, respectively. Additionally, immunohistochemical staining can identify Nipah viral antigens within infected endothelial and brain cells [126].

Diagnosis

In Hendra virus encephalitis, initial CSF cytochemical analysis may reveal a polymorphonuclear pleocytosis with an elevated protein concentration [121]. Subsequent CSF analyses demonstrate a lymphocytic predominant pleocytosis with elevated protein concentration. In cell culture, Hendra virus produces syncytial formation when grown in Vero cells. The Hendra virus genome may be detected from clinical specimens using PCR. Viral inclusions are identified using EM within infected tissue. ELISAs are available to detect the presence of IgG and IgM antibodies against Hendra virus [119,120].

In Nipah virus encephalitis, CSF cytochemical analysis reveals a predominantly lymphocytic pleocytosis (0–842 cells/mm³). Nipah virus-specific antibodies may be found in the CSF in one third of patients. The virus can be isolated from the CSF, but typically only in the most severe cases. Additionally, virus has been cultured from respiratory secretions and urinary specimens of acutely infected patients [122,125,127].

In the Hendra virus-infected individual, MRI scan findings consisted of increased signal within the grey matter that progressed to be more diffuse and pronounced within 1 week of onset of illness [121].

MRI scan findings can be suggestive of Nipah virus infection. Typically, findings consist of multiple, small (2–7 mm) lesions throughout the subcortical and deep white matter of the cerebral hemispheres on T2-weighted images. Additional areas where lesions may be located include the cortex, brainstem, thalamus, and corpus callosum [122]. In patients with relapsed encephalitis, MRI scan findings demonstrated patchy confluent cortical gray matter lesions [124].

EEGs in patients with Nipah virus infection are often abnormal. Goh et al. reported that the most common finding was diffuse slow wave activity with focal sharp waves. Focal abnormalities are primarily located in the temporal region. In comatose patients, EEG demonstrated bilateral temporal periodic complexes consisting of sharp and slow waves every 1 to 2 seconds [122].

Treatment

Supportive care is the principle treatment for both Hendra and Nipah virus infections. Close monitoring of the neurological status as well as the potential for respiratory failure is imperative. Additionally, cardiovascular support may be indicated in the most severe cases.

No antiviral agent has been approved for use in the treatment of Hendra or Nipah virus infections. Chong et al. administered ribavirin in an open label study of patients with acute Nipah virus encephalitis. They observed a 36% reduction in mortality among treated patients. However, because of the small number of cases in this series, it is still not clear whether this treatment should be routinely used [128].

Orthomyxovirus

Introduction

Influenza A and B viruses are common respiratory pathogens associated with significant morbidity and mortality. Although their target organ is the respiratory tract, involvement of the CNS is known to occur. As in the case of respiratory disease, neurological complications may result in death or permanent neurological sequelae.

Epidemiology

Influenza viruses are single-stranded RNA viruses in the *Orthomyxoviridae* family. They are divided into three distinct antigenic types: A, B, and C. Influenza A and

B are the major human pathogens. In the United States, annual winter epidemics occur that last approximately 6 weeks. Children have the highest attack rates and transmit the disease to adults, resulting in a secondary peak of disease. Children under the age of 2 years and the elderly are at greatest risk for severe influenza disease. Additionally, individuals with preexisting medical conditions (e.g., asthma, heart disease, and diabetes) are at increased risk for fatality as a result of influenza infection [129,130].

Transmission of influenza virus occurs through respiratory droplets. Sneezing and coughing are the most common mechanisms of viral spread. Transmission may also occur through direct and indirect contact with respiratory secretions. The incubation period is 2 to 3 days but can be as long as 7 days. The peak of viral shedding occurs simultaneously with the most severe symptoms. Viral shedding persists for 1 week in influenza A and up to 2 weeks in influenza B infections [130].

Clinical Manifestations

Constitutional and respiratory signs and symptoms comprise the most common clinical manifestations of influenza disease. Typically, children present with acute onset of fever, headache, cough, and rhinorrhea. In comparison with adults, children are more likely to experience anorexia, abdominal pain, vomiting, and nausea. Influenza B virus-associated illness presents similarly, except that adults typically have a milder respiratory disease than children. Complications associated with influenza infection include laryngotracheobronchitis (croup), myositis, secondary bacterial infections, and myocarditis [129,130].

Neurological Manifestations

Neurological complications have been observed after both influenza A and B infections. The most commonly reported neurological complication is febrile seizures. [131]. Additionally, influenza virus infections have been associated with encephalopathy/encephalitis. Because of the uncertain pathogenesis of this entity, the remainder of this section will use the term encephalopathy. Other less commonly associated neurological diseases include the Guillain-Barré syndrome and transverse myelitis, both of which have been observed after influenza immunization [132–134]. From the mid-1960s to mid-1980s, encephalopathy was primarily reported in patients with Reye syndrome. Today this syndrome is rarely observed [135].

Febrile seizures have been observed in 19.5% of hospitalized patients with influenza A infection, with equal prevalence in male and female patients. In comparison with adenovirus or PIV, patients hospitalized with influenza A seem to be both at greater risk for febrile seizures (odds ratio [OR] 1.97), as well as for recurrent seizures during the same admission (OR 4.3) [131].

Encephalopathy is a rare complication of both influenza A and B virus infection. Initial reports of influenza A encephalopathy appeared in the 19th century [136]. However, it was not until the H2N2 influenza A pandemic of 1958 that cell culture and serologic confirmation of influenza A virus-associated encephalopathy was reported [137]. Nearly 10 years later, a link between influenza B virus and encephalopathy was established [138]. Recently, avian influenza virus (influenza A H5N1) was shown to cause a fatal encephalopathy in two children [139]. The pathogenesis remains unknown. Children, especially those 5 years of age or younger, seem to be at greatest risk for influenza-associated encephalopathy [140–142].

Influenza-associated encephalopathy may occur from within the first days to weeks after the onset of respiratory symptoms. Reports from Japan indicate that the onset of the encephalopathy is commonly very early, typically occurring within 1 week of the onset of respiratory disease. Morishima and colleagues observed that in approximately 80% of patients, CNS disease developed within 1 day of the onset of influenza symptoms [143]. A report from the United States indicates that approximately 60% of patients with influenza A virus-associated encephalopathy developed neurological symptoms within 4 days of the onset of respiratory symptoms [144]. However, neurological symptoms may present as late as 3 weeks after the onset of illness [144,145]. Similar to influenza A virus, almost all patients with influenza B virus-associated encephalopathy present during the first week after the onset of their illness [142,146].

Individuals with influenza-associated encephalopathy initially present with the signs and symptoms of typical influenza: fever, headache, cough, and vomiting. The onset of neurological disease is heralded by altered mental status and/or seizures. During the 1998 to 1999 influenza season in Japan, 100% of patients with encephalopathy had altered level of consciousness, and 80% experienced seizures [143]. In contrast, among eight children with influenza A-associated encephalopathy during the 2003–2004 season in the United States, one half presented with seizures and one quarter presented with altered mental status [144]. Interestingly, 27% of patients with influenza B virus-associated encephalitis had speech abnormalities [142]. Other reported neurological signs and symptoms include abnormal deep tendon reflexes, meningismus, abnormal movements, facial nerve palsy, and paresthesias [142–145].

The hospital course of patients with influenza virus-associated encephalitis also seems to be very variable. In Japan, many patients rapidly deteriorate to a state of coma that may be associated with multisystem organ failure. Fatality rates in that country have been reported to be as high as 25 to 37%. Influenza A virus-associated encephalopathy accounts for a majority of the fatal cases [141,143,147]. Although severe disease with onset of coma and multisystem organ failure has been observed in other parts of the world, its incidence and mortality rate have been dissimilar. In a report from Austria, a 10% mortality was associated with influenza A virus-associated encephalopathy [145]. In the largest case series of patients with influenza A-associated encephalopathy from the United States, no deaths occurred and only one patient had neurological sequelae, consisting of severe static encephalopathy [144].

The risk of fatality seems to be significantly less in patients with influenza B virus-associated encephalopathy. To date, only two deaths have been reported. One death was in a patient with concomitant respiratory syncytial virus infection and a second patient died of acute necrotizing encephalopathy [138,146]. Significant

neurological sequelae, including cognitive difficulty and speech delay, have been reported in survivors of influenza B virus-associated encephalitis [142].

Neuropathology

The neuropathology of influenza-associated encephalopathy is variable. Autopsy findings in acute necrotizing encephalopathy demonstrates petechial hemorrhages and congestion of thalamic vessels surrounded by tissue necrosis [148]. In a case of influenza A-associated encephalopathy, influenza virus was detected within brain tissue by both RT-PCR and immunohistochemistry. In this case, although edema was noted, no inflammatory cells were present in the involved areas [149]. In contrast, other investigators have been unable to detect the influenza genome in the brain tissue of cases despite the presence of massive cerebral edema [143]. Because of the lack of fatalities in cases of influenza B virus, little is known regarding its neuropathology.

Diagnosis

Evaluation of the CSF may reveal a mild lymphocytic pleocytosis, but as many as 90% of cases have normal CSF cell counts [143]. However, in one report, CSF pleocytosis was observed in 67% of patients [145]. The mean white blood cell count was 268 cells/mm³. Abnormal CSF glucose and protein concentrations are rare.

Although an infrequent finding, the influenza genome has been amplified from the CSF using RT-PCR in patients with influenza A- and B-associated encephalopathy [143,145,150–152]. In Japan, hyperammonemia and hypoglycemia have been observed in 11% and 4% of patients, respectively. Additionally, increased liver transaminases, elevated lactate dehydrogenase levels, and thrombocytopenia have been associated with a poor prognosis [143].

EEG examination commonly demonstrates diffuse slowing. Focal slowing, periodic lateralized epileptiform discharges, and generalized and focal spikes have also been reported [144,145,153].

Abnormalities in neuroimaging are frequently observed in patients with influenza A virus-associated encephalopathy. The most notable findings on CT or MRI scan are edema, hemorrhage, and symmetric lesions. Although the latter are commonly seen in the thalamus, they may also occur in the cerebral white matter, cerebellum, and brainstem [154]. Morishima and colleagues observed findings of acute necrotizing encephalopathy in approximately 10% of cases they studied [143]. Additional findings observed in cases of influenza A virus-associated encephalopathy include cerebral edema in association with low-density cerebral lesions, single or multifocal cerebral lesions, and reversible splenium lesions in the corpus callosum [145,155]. Influenza B virus-associated encephalopathy seems to have fewer abnormalities present on MRI or CT scan. In addition to acute necrotizing encephalopathy, the only additional abnormality reported has been cerebral edema [142,146].

Treatment

Supportive care is the primary treatment for influenza-associated encephalopathy. Amantadine may be used in cases of influenza A virus-associated encephalopathy, although no studies have evaluated its effectiveness, and resistance has been increasingly noted. Oseltamivir, a neuraminidase inhibitor, active against both influenza A and B viruses, has also been used. However, unlike amantadine, drug could not be detected in the CSF after oral administration in one reported case [156].

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