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Alan C. Jackson *Editor*

Viral Infections of the Human Nervous System

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Viral Infections of the Human Nervous System

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Foreword

As a young Army Medical Corps officer, I was assigned to work in the Department of Virus Diseases of Walter Reed Army Institute of Research during the Asian influenza epidemic of 1957. At that time, we knew nothing of the genomic structure of influenza viruses and had no idea that we were working with a recombinant of a human and a duck virus. In the spring, the influenza epidemic waned. The focus of the diagnostic laboratory was shifted to the three clinical syndromes putatively caused by viral infections of the nervous system—aseptic meningitis, encephalitis, and paralytic poliomyelitis. In those days, rabies with its long incubation period, unique clinical features, and uniformly fatal course was regarded as a strange outlier.

Amazing how the landscape has changed over the past 50 years and how two very divergent paths evolved in clinical virology. The latency and reactivation of herpesviruses, the chronic infection with measles virus in the form of subacute sclerosing panencephalitis, the prominent fetal damage caused by rubella virus, the role of viruses in demyelinating diseases (postinfectious encephalomyelitis and progressive multifocal leukoencephalopathy), and the role of infectious prions in chronic degenerative diseases led to an expanding interest in viral infections of the human nervous system.

Conversely in the middle of the twentieth century, the interest in infectious diseases faded. The discovery of antibiotics and antiviral drugs, the eradication of smallpox, and the control of measles and poliomyelitis with vaccines all led to death knells for the specialty of infectious diseases. Infectious disease services were minimized. Prominent infectious disease physicians moved into "healthcare delivery" careers; several published obituaries for the specialty. Infectious diseases were disappearing as a specialty despite the foreboding of *new* diseases such as Legionnaire's disease, a paralytic form of enterovirus 71, and the evolution of an encephalitic strain of California virus in the Midwestern USA. Then in 1981, the surprising and frightening onslaught of acquired immune deficiency disease dramatically changed all of medicine and society.

Why are we now seeing new diseases every year? Greater surveillance and reporting is one explanation, but some new diseases are caused by mutations of

familiar viruses, some result from transportation of exotic viruses to new sites, and some result from animal viruses that have been introduced into human populations. All these factors are propelled by the burgeoning global human population and its mobility and speed of global movement. Today, a new exotic virus transmitted to a human in Asia or Africa can be in your local airport or indeed at your church social within one incubation period or even a single day.

This book addresses many of the factors that have made the study of viral infections of the nervous system so compelling and raises intriguing questions that must be addressed over the next decades.

Baltimore, MD Richard T. Johnson
March 2012

Preface

Viral infections of the nervous system are a challenging group of diseases for clinicians and for researchers. The pathogenetic mechanisms involved in this group of diseases are very diverse. Although some, like enteroviral meningitis, are common. However, many are rare and have limited and unpredictable distributions, both geographically and in time (e.g., Nipah virus infection). Specialized diagnostic investigations are often necessary for definitive diagnosis, although a presumptive diagnosis should often be suspected on the basis of the clinical features. Many of these infections are serious diseases with high morbidity or mortality or with fatal outcomes (e.g., Creutzfeldt–Jakob disease and rabies). A majority of the authors are neurologists and most have either a background or a distinguished career in basic neurovirology research, which gives them unique insights in writing about these diseases. Only further research will give us a better understanding of the basic mechanisms involved in all aspects of these infections, which will, hopefully, lead to future advances in their therapy.

My interest in the field of neurovirology became solidified when 30 years ago I first read Dr. Richard T. Johnson's book entitled *Viral Infections of the Nervous System* (Raven Press, 1982). Two years later, I became a postdoctoral fellow in Dr. Johnson's research laboratory at The Johns Hopkins University in Baltimore. I hope this volume will also stimulate the interest of young people in this intriguing field. I would like to thank Dr. Beatrice Menz at Springer Basel for giving me the opportunity of putting together a volume on these infections and to all of the expert contributors for their hardwork in preparing up-to-date chapters and sharing their expertise and insights on this diverse group of diseases. They have all done a superb job.

Winnipeg, MB, Canada — Alan C. Jackson
February 2012

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Part I
Encephalitis

Measles Virus Infection and Subacute Sclerosing Panencephalitis

Banu Anlar and Kalbiye Yalaz

Abstract Measles virus can cause two acute neurological disorders: acute infectious encephalitis and postinfectious autoimmune encephalitis, each with a risk of about 1 in 1,000 measles cases. Two other rare neurological problems manifest after a latent period: subacute measles encephalitis occurring in immunocompromised individuals, and subacute sclerosing panencephalitis (SSPE) in immunocompetent hosts. SSPE develops 1–10 years after measles infection; it is usually progressive and fatal. Mental and behavioral changes, myoclonia, and ataxia are typical initial manifestations. The diagnosis is based on the demonstration of intrathecal anti-measles virus immunoglobulin G synthesis. Pathological examination of brain biopsy or autopsy material demonstrates inflammation, neuronal loss, gliosis, demyelination, and typically, inclusion bodies containing measles virus antigens or RNA. Treatment with inosiplex and interferons may induce temporary stabilization or remission in about 30–35 % of the cases. Immunization against measles virus and maintenance of immunization rates above 90 % in the population are of extreme importance for the prevention of these debilitating or fatal disorders.

Keywords Demyelinating • Immunoglobulin • Magnetic resonance imaging • Measles • Subacute sclerosing panencephalitis

Abbreviations

ADEM	Acute disseminated encephalomyelitis
CSF	Cerebrospinal fluid
EEG	Electroencephalography

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IL	Interleukin
MRI	Magnetic resonance imaging
MV	Measles virus
SSPE	Subacute sclerosing panencephalitis

1 Introduction

1.1 Measles Virus

Measles virus (MV) is a single-stranded negative-sense RNA virus in the Paramyxoviridae family. Its genome encodes eight proteins among which the haemagglutinin protein induces a strong neutralizing antibody response with life-long immunity (Moss and Griffin 2011).

MV infects humans only. Its cellular receptors are CD150 (signaling lymphocyte activation molecule, SLAM) on lymphocytes, and as shown recently, CD147 (extracellular matrix metalloproteinase inducer, EMMPRIN) on epithelial cells. CD46, a complement regulatory protein, is primarily a receptor for the vaccine virus; CD147, for wild-type MV, and CD150, for both (Naniche et al. 1993; Tatsuo et al. 2000; Watanabe et al. 2010).

1.2 Acute Measles Infection

After MV transmitted via respiratory droplets enters respiratory epithelial cells, acute infection starts in the respiratory tract, then spreads to organs including lymphoid tissue, skin, lungs, and liver. The clinical picture begins with cough, rhinitis, and conjunctivitis. Although this may appear as a common upper respiratory infection, the child with measles is sicker; the cough is more prominent with a "metallic" sound, and conjunctivitis is more remarkable. However in older children and adults the initial symptoms may be indistinguishable from common upper respiratory infections. Koplik's spots can be seen in the buccal mucosa for 24–48 h before rash erupts. After 3–4 days of prodromal period, an erythematous rash begins from the neck and face, and fever subsides. The rash proceeds caudally and fades with a brownish pink color within a week. Pediatricians currently practicing in North America may not be familiar with the clinical picture of the prodromal period. Of interest, measles can occur without rash in about 20 % of the cases and up to 60 % in subjects with preexisting low-titer antibodies (Cherian et al. 1984; Lisse et al. 1998; Prasad et al. 1995).

Widespread application of vaccination programs eliminated measles in many areas. However, epidemics have recently been observed both in developing and developed countries due to failure to maintain the 95 % immunization rate needed for eradication. Two doses of vaccine are recommended, although countries using one or two doses eliminated measles in similar periods (Sever et al. 2011). The first

dose is given between 12 and 15 months (or 9 months during epidemics) and the second, between 4 and 6 years of age in non-endemic countries (Committee on Infectious Diseases and American Academy of Pediatrics 2011). During epidemics when risk of exposure exists, the second dose can be administered from 1 month after the first dose. In addition, mass campaigns every 3–4 years are required even in vaccinated populations in order to immunize the accumulating susceptible population of children against any imported virus. It is important to note that the risk of neurological adverse effects seemingly associated with measles vaccine is approximately one per million doses while the risk of neurological complications of measles is more than two per thousand, as described below (Shu et al. 2011). Measles is a highly contagious disease and continuous surveillance is mandatory.

Neurologic complications of measles include the following clinical pictures:

1. Acute measles encephalitis during active viral infection.
2. Acute post-measles encephalomyelitis that follows the infection.
3. Subacute measles encephalitis (SME) (measles inclusion body encephalitis) encountered in immunocompromised individuals.
4. Subacute sclerosing panencephalitis (SSPE) developing after a latent period of several years.

1.3 Acute Measles Encephalitis

This is the most common acute neurological complication of measles in children: the risk of encephalitis is 22/28,000 or 0.1–0.3 % of acute measles cases, and has not changed in the last 50 years (Laboccetta and Tornay 1964; European Centre for Disease Prevention and Control ECDC 2011; Stanescu et al. 2011; Filia et al. 2011).

During acute infection MV can infect cerebral endothelial cells and invade the central nervous system (Dittmar et al. 2008). The resulting clinical picture is encephalitis or encephalomyelitis indistinguishable from other viral encephalitides except for the presence of rash. Certain cases may not show any exanthema and can be suspected only by the presence of a concurrent epidemic, or diagnosed retrospectively. Neurological symptoms appear during or, rarely, before the rash. Fever, which typically subsides after the appearance of rash in measles, recurs along with irritability, lethargy, headache, confusion, convulsions, and loss of consciousness. Neurological examination may show signs of meningeal irritation. When there is accompanying myelitis and cerebellitis, bladder or bowel dysfunction and ataxia can be observed. Interestingly, febrile seizures, i.e., seizures triggered by fever only with no clinical or laboratory evidence of encephalitis, are not common in young children with measles. Therefore, convulsions associated with measles infection should suggest encephalitis.

The cerebrospinal fluid (CSF) reveals increased opening pressure, predominantly lymphocytic pleocytosis, and an increased protein level. Electroencephalogram (EEG) may show high voltage focal or diffuse slowing that usually persists for several months. Up to 50 % of the patients with acute measles have slowing of EEG

activity without any neurological symptoms, a finding that can be considered as subclinical encephalitis (Gibbs et al. 1964). MR imaging may be normal, or show white and gray matter lesions involving the cerebral cortex or basal ganglia. Deep gray matter involvement has been suggested as a more severe variant with higher rate of complications and protracted course. Perivascular inflammation, microglial nodules, and neuronal degeneration are observed on pathological examination. MV RNA and antigens can be demonstrated in the brain tissue, as well as tumor necrosis factor-alpha mRNA (Plaza and Nuovo 2005). On the other hand, cytoplasmic and nuclear inclusion bodies and multinucleated giant cells, the typical findings of measles encephalitis, may be absent in patients with rapid, fulminant course.

As with other viruses, clinical overlap exists between acute infectious encephalitis and the postinfectious encephalitis described below. The nature and the timing of the symptoms are not always distinctive: in a series of 12 patients with encephalitis occurring 2–7 days after measles rash, four had gray matter involvement suggesting acute MV encephalitis whilst the others were more compatible with the postinfectious form (Kim et al. 2003).

Treatment is symptomatic and consists in preventing or treating hyperthermia, convulsions, secondary infections, and fluid and electrolyte disturbances. The use of corticosteroids in combination with intravenous immunoglobulin may improve the chances of recovery (Nakajima et al. 2008).

The course varies from a mild confusion recovering completely within several days to fulminant progression to coma and death within 24 h. In older literature, about 60 % of children recovered completely, 15 % died, and 25 % were left with sequelae such as mental retardation, epilepsy, behavioral problems, hearing loss, or motor deficits (Meyer and Byers 1952). Sequelae may be underestimated because certain behavioral and attention problems may go unnoticed until school age. On the other hand, a higher rate of recovery without sequelae is reported in more recent series (Kim et al. 2003).

1.4 Acute Post-measles Encephalomyelitis

This form of encephalopathy is more commonly known as acute disseminated encephalomyelitis (ADEM), and attributed to postinfectious autoimmune mechanisms. Neurological signs follow an interval of 3–10 (2–30) days after an acute viral infection. Measles was one of the frequent antecedent infections in ADEM series before the implementation of widespread immunization programs: 1/1,000 measles cases were reported to develop this clinical picture. The interval period tends to be shorter (2–4 days) in measles and other exanthematous diseases. Characteristically, the resurgence of fever in a child whose rash is fading should suggest this entity, especially if accompanied by headache and altered consciousness. Meningeal irritation, seizures, and less frequently, focal motor deficits, optic neuropathy, or myelopathy can be associated. Children <2 years old tend to have a rare but more fulminant variant: acute hemorrhagic leukoencephalitis, where morbidity and mortality are considerably higher.

The diagnosis is based on clinical signs and the history of measles, and supported by magnetic resonance imaging (MRI) showing bilateral, asymmetrical, patchy, frequently edematous white matter changes. Bilateral striatal lesions can also be observed (Lee et al. 2003). Cerebrospinal fluid may be normal or contain lymphocytes and neutrophils, or elevated protein levels. Pathologically, perivenular inflammation and myelin disruption are observed in rare cases where a brain biopsy or autopsy is performed.

As stated above, clinical features may not be distinguishable from acute encephalitis, especially in the presence of fever and the absence of a clear period of improvement after acute measles infection. The predominantly white matter involvement on MR images and the absence of significant pleocytosis may be taken as supportive of ADEM compared to infectious MV encephalitis.

1.5 Other Rare Acute Complications

Other complications of measles infection that are rarely observed or mentioned in the literature include optic neuropathy in the anterior or retrobulbar forms, manifesting as acute loss of vision during or even preceding measles (Srivastava and Nema 1963; Hirayama et al. 2010), acute transient cerebellar ataxia (Tyler 1957), isolated myelitis (Gunaratne et al. 2001), or peripheral neuropathy of the Guillain Barré type (Tomiyasu et al. 2009). Increased intracranial pressure, coma, decerebrate rigidity, herniation, and death were described in a case with no evidence of encephalitis on pathological examination, possibly due to inflammatory toxic molecules in a host with a specific, yet undefined immune deficit (Tyler 1957). On the other end of the spectrum, aseptic meningitis due to MV is a benign syndrome characterized by headache, fever, vomiting, meningeal signs, and lymphocytic pleocytosis in the CSF. The patient recovers in 1–2 weeks with supportive and symptomatic treatment (Bakir 1989; Valassina et al. 2000). Chronic infiltrative meningitis has been reported in an immunocompetent adult (Luzi et al. 1997).

1.6 Subacute Measles Encephalitis

This infection develops 1–10 months after primary measles infection in immunosuppressed hosts such as leukemia or acquired immune deficiency patients, and rarely in immunocompetent subjects. One of the largest series has recently been reported from South Africa in a group of eight HIV-positive adolescents and adults, four of whom had no history of rash (Albertyn et al. 2011).

The clinical manifestations start with myoclonia and mental changes. These symptoms resemble SSPE as described below; however, the course of SME is more rapidly progressive over weeks and months. Cognitive function declines, myoclonus, and refractory focal seizures, or, less commonly, generalized seizures are observed. Vision loss, hearing loss, and focal motor and sensory signs progress

over weeks and usually end with a fatal outcome within months. Probably, the absence of an antiviral immune response allows more rapid spread of MV in the brain compared to SSPE (see below). EEG demonstrates slowing of the background rhythm and epileptiform discharges. MRI shows multifocal areas of increased T2-signal intensity more prominently in the cortex than the white matter, unlike SSPE where white matter changes predominate. The cortical involvement explains seizures being a frequent symptom in SME.

CSF may show normal findings or mild lymphocytic pleocytosis and oligoclonal bands; however, because of the underlying immune deficiency and the intracellular location of MV, measles virus IgG is normal or mildly elevated. Although PCR studies from various samples such as urine and brain tissue may be required for definite diagnosis, these can also be negative because SME is a nonproductive MV infection. In the Albertyn et al. (2011) series, only 2/6 CSF samples had detectable MV IgG and 2/8 contained MV RNA. On brain biopsy, neuronal loss, mononuclear infiltration, glial proliferation, and more specifically, eosinophilic inclusion bodies in neuronal and glial cells were observed. These bodies consist of paramyxovirus nucleocapsids and MV antigen as detected by immunohistochemistry. Such inclusion bodies are also observed in SSPE, in which pathological findings differ from SME by more marked inflammatory infiltration and demyelination.

Recovery from SME is rare and sequelae are frequent. There is no definite treatment but ribavirin might increase the chance of survival (Mustafa et al. 1993). Among the cases reported by Albertyn et al. (2011), two survived, including one with normal mental function. Higher $CD4^+$ cell counts were a good prognostic factor. Intravenous immunoglobulin appears to be a safe and reasonable therapeutic option based on previous experience in acute measles and postinfectious encephalomyelitis. However, there are no reports of SME cases treated with intravenous immunoglobulin.

1.7 Subacute Sclerosing Panencephalitis

SSPE is among the chronic neurological disorders where the discovery of a specific etiological agent came as an exciting scientific advance in our understanding of the disease, although isolation of MV was initially unsuccessful. Filamentous particles in the brain were described (Bouteille et al. 1965), then MV was recovered from the brain and established as the cause of the disease (Adels et al. 1968; Horta-Barbosa et al. 1969). Experimental evidence of the pathogenicity of the virus was obtained by transmission of the disease with brain extracts from patients to ferrets and between ferrets (Katz et al. 1968).

1.7.1 Epidemiology

SSPE is a result of natural measles infection especially when the latter is experienced at a young age, particularly before age of 2 years. The risk of developing

SSPE varies between series, probably due to environmental factors: in USA it was calculated as 22/100,000 measles cases (Bellini et al. 2005), and is probably closer to 1/1,000 after infantile measles. However, these are statistical estimates because of under- and over-reporting of measles and the absence of serological proof in most cases. The fact is that measles vaccine coverage in over 95 % of the population stops the transmission of measles and virtually eliminates SSPE. In addition to measles occurring at a young age, rural residence, crowded households, and adverse socioeconomical conditions have been associated with SSPE.

Boys are more frequently affected with a male/female ratio of 1.5–1.8 in different series. Mortality of acute measles is slightly higher in girls, however, not to a degree to explain the sex difference in SSPE. The majority of cases have an onset between 6 and 14 years. The mean age of onset varied from a median of 13 years before 1994 to a median of 7.6 years after 1995, possibly related to age at primary measles infection (Anlar et al. 2001a, b). The youngest case reported was 5 months old, and the oldest was 49 years old.

The interval between primary measles infection and neurological symptoms of SSPE is 1–10 years; it tends to be longer in adults and shorter (e.g., several months) in young children.

1.7.2 Etiology

Molecular studies confirm that wild-type MV is responsible for producing SSPE, as all strains amplified from brain tissue indicate MV circulating at the time of primary measles infection. Mutations occurring during persistence allow the virus to bypass the host's immune system and reproduce inside the cell in a less cytopathic fashion (Reuter and Schneider-Schaulies 2010). SSPE has been observed in previously immunized children, but most of these children had natural MV infection before immunization (Miki et al. 2002). Alternatively, vaccine failure occurs with an inability to seroconvert in a minority of vaccinated individuals, especially when vaccine is given before 12 months of age.

1.7.3 Pathogenesis

The route of entry of the MV to the brain and the cellular receptor for MV are unclear. CD46 is expressed on brain endothelial cells, ependyma, choroid plexus, neurons, and oligodendrocytes; however, the wild-type MV does not use this receptor. CD150 (Piskin et al. 2007) and possibly CD147 are more likely to act as receptors in the central nervous system. Incorporation of cyclophylin-B (cellular ligand for CD147) into MV particles is a prerequisite for cellular infection in vitro (Watanabe et al. 2010).

After entry, the site of MV persistence for years is unclear: it can be the nervous or lymphoid tissues. Antigens and genome of MV have been shown in tissues of individuals with no relevant symptoms (Anlar et al. 2002a, b; Katayama et al. 1998).

In the persistent state the viral RNA is complete but membrane proteins are missing, which impedes the production of infective viral particles. On the other hand, viral antigens are expressed and induce an antibody response. MV persistence is probably facilitated by the immaturity of the immune system in infants and the transient immunosuppression caused by MV mediated by blockade of IFNa/b-induced STAT signaling. Many studies investigated host predisposition to MV persistence. However, these were patients already diagnosed with SSPE, therefore, past the persistent state, when it is impossible to distinguish changes resulting from or causing the disease. Studies at gene level included single nucleotide polymorphisms in the Toll-like receptor (TLR)-2, interleukin (IL)-2 and IL-4, MxA (a type 1 IFN-inducible protein), PD1 (co-inhibitory for T cells), and CD46 produced variable results (Pipo-Deveza et al. 2010; Torisu and Hara 2006; Yilmaz et al. 2007; Torisu et al 2004).

Whatever the factor initiating persistence is, limited expression of MV antigens on neural cells, and hypermutations in MV matrix (M) and/or fusion (F) genes allow the MV to replicate while escaping host antibodies. The mutations probably result from long persistence rather than being a primary event. The enzymes adenosine deaminase acting on RNA (ADAR1 and ADAR2) catalyzing A to I mutations are expressed in brain and can take part in these mutations (Maas et al. 2006). As a result MV spreads cell to cell without releasing infectious viral particles.

The appearance of clinical symptoms can be due to MV becoming reactivated, or the intracellular infection reaching a threshold level. Alterations in the immune or hormonal systems, minor head trauma, or infections might contribute to transition from persistent to clinically manifest state.

1.7.4 Pathology

Brain biopsy and autopsy material show infiltration of mononuclear cells into the meninges and brain tissues. $CD4^+$ and B cells tend to gather in perivascular areas and $CD8^+$ cells in parenchymatous areas. Gliosis, astrocytic proliferation, neuronal degeneration, and demyelination are observed in various degrees. Inflammatory molecules, including IFN-gamma, HLA Class II, and tumor necrosis factor (TNF)-alpha are expressed on endothelial and glial cells (Anlar et al. 2001a). MxA, the type I interferon inducible protein, is perivascularly expressed (Anlar et al. 2001b). These findings indicate chronic encephalitis, but the diagnostic finding for SSPE is the presence of inclusion bodies in the cytoplasm or nucleus of neurons and glial cells. Nuclear inclusion bodies contain viral ribonucleoproteins or protein complexes. In early stages inflammation is more prominent; in late stages, astrocytic gliosis, demyelination, necrosis, neuronophagia, neurofibrillary tangles, and apoptosis of neuronal, oligodendroglial and microglial cells are observed. MV gene expression has no direct correlation with clinical course, as patients with rapid progression may have low levels of infection (Kühne Simmonds et al. 2006).

1.7.5 Clinical Findings

The diagnosis of SSPE cases with typical presentation is straightforward, but atypical presentations are not rare (Erturk et al. 2011). Initial symptoms frequently consist of behavioral changes, forgetfulness, and decreasing school performance in the child, which are often overlooked or attributed to psychological reasons. Myoclonic–atonic episodes begin as brief head dropping, unilateral arm or facial twitching, or falling without loss of consciousness. These episodes last only a few seconds and can occur repeatedly every few hours or minutes. At this stage the neurological examination can be normal or reveal hypertonicity of one or more extremities, tremor, ataxia, and apraxia. Less frequent manifestations are seizures, encephalopathy, increased intracranial pressure, hemiparesis, hemidystonia, and vision loss. The latter may result from occipital cortical lesions, optic atrophy, or retinopathy (Yüksel et al. 2011) Symptoms worsen over weeks and months, followed by loss of speech and ambulation in most patients. The course stabilizes in certain cases with the patient remaining in a mentally impaired but ambulatory state.

Clinical staging systems have been useful, but of limited value, due to lack of standardization. Briefly, mental and behavioral changes are the symptoms of stage 1; myoclonia characterize stage 2, and loss of independent ambulation, stage 3. In the latter stage myoclonia diminish or disappear and spastic quadriparesis, autonomic disturbances, tonic spasms, and fever are observed, although the patient shows some response to environmental stimuli. After stage 3 is reached, progression into coma and death occur in a few months to few years in most (about 60 %) cases. Other cases stabilize, sometimes with regain of motor functions and even independent walking for several years. About 20 % show acute or fulminant course from the beginning, presenting with altered consciousness with progression to death within a few months. The cause of death in SSPE patients is respiratory infections or disease affecting vital functions in the brainstem.

Besides clinical staging, standardized scoring systems for neurological and intellectual deficits such as the Neurological Disability Index (NDI) and cognitive assessment scales (Dyken et al. 1982; Öktem et al. 1997) are useful for research and follow-up. The authors use a modified version of the NDI, the SSPE Scoring System (SSS), based on their observations on large numbers of patients over years (Table 1).

1.7.6 Diagnosis

Seizures or myoclonia accompanied by mental and behavioral changes in a previously normal school-age child or adolescent should raise the suspicion of SSPE. The diagnosis is supported by EEG findings and confirmed by CSF examination for measles virus IgG and measles virus-specific IgG index.

Table 1 SSPE Scoring System (SSS)

Behavioral and mental		Myoclonia (before carbamazepine)	
Irritability: absent	0	Location: no myoclonia	0
Mild hyperactivity, restlesness	1	Focal, mild	1
Moderate restlesness	2	Focal 2 body parts, moderate amplitude	2
Marked irritability or delirium, lethargy	3	More than 2 body parts	3
Stupor, coma	4	Immobility	4
Personality		**Repetition**	
Normal	0	No myoclonia	0
Mild changes (excessive talking, apathy, etc.)	1	Irregular, less than once a day	1
Oppositional behavior, aggressive	2	Irregular, less than once per hour	2
Defiant or lethargic	3	Regular, more than once per hour	3
Stupor, coma	4	Immobility	4
Introversion or autism		**Convulsions (other than myoclonia)**	
None	0	None	0
Shy or withdrawn	1	Less than once a week	1
Limited interaction, stereotypies	2	Once a month /once a week	2
Marked autistic behavior/lethargy	3	Once a week/once a day	3
Stupor, coma	4	More than once a day	4
Mental-perceptive		**Daily functions**	
Normal	0	Dresses and feeds himself/herself	0
Dull (1 year difference with peers)	1	Can feed but not dress himself/herself	1
Borderline (2–3 years difference with peers)	2	Needs help while eating	2
Marked mental deficiency or lethargy	3	Expresses hunger/thirst, cannot feed him/herself	3
Stupor, coma	4	Totally dependent	4
Speech		**Following commands**	
Normal	0	Normal	0
Mild speech disturbance (talks in sentences, mild dysarthria)	1	Mild impairment (More than 2 of 4 commands)	1
Moderate speech disturbance (single words)	2	Moderate impairment (1–2 commands)	2
Severe speech disturbance (vocalizes, incomprehensible)	3	Hears commands, does not comply	3
Stupor, coma	4	Stupor, coma	4
Motor and sensory		**Vegetative and systemic**	
Reflex-tone		Vision	
Normal	0	Normal (counts/imitates fingers from 6 m.)	0
Mild hyperreflexia or hypertonia	1	Mild impairment (counts/imitates fingers from 2 m.)	1
Mild hyperreflexia and hypertonia	2	Moderate impairment (sees moving objects)	2
Moderate hyperreflexia and hypertonia	3	Marked impairment (sees light)	3
Severe hyperreflexia and hypertonia	4	Total loss of vision	4

Strength		Hearing	
Normal	0	Normal (hears whisper 30 cm)	0
Mild weakness (4/5) or atrophy	1	Mild impairment (hears voice 30 cm)	1
Mild weakness (4/5) and atrophy	2	Moderate impairment (hears loud voice)	2
Moderate weakness (3/5) and atrophy	3	Marked impairment (reacts to loud noise)	3
Marked weakness (0–2/5) and atrophy	4	No hearing	4

Posture/movement		Sensory (touch, pressure, pain)	
Normal	0	Normal	0
Mild chorea/athetosis	1	Does not feel touch, feels pressure	1
Mild dystonia, moderate chorea/athetosis	2	Does not feel touch and pressure, feels pain	2
Moderate dystonia, choreoathetosis, mild rigidity	3	Feels only deep pain	3
Severe extrapyramidal signs	4	Does not feel deep pain	4

Coordination		Autonomic functions	
Normal	0	Normal	0
Mild impairment (can walk)	1	Mild impairment (some urine incontinence)	1
Moderate impairment (walks with assistance)	2	Moderate impairment (some urine/bowel incontinence)	2
Marked impairment (cannot walk, sits without support)	3	Marked impairment (urine/bowel incontinence or sometimes fever, sweating)	
Severe incoordination (bedridden)	4	Severe impairment (continuous incontinence and sweating episodes)	4

Upper limb movements		Nutrition	
Uses objects appropriately	0	Normal	0
Uses some objects appropriately	1	Mild impairment (occasional choking)	1
Reaches, holds, may put in mouth	2	Moderate impairment (soft food)	2
Reaches, cannot hold	3	Marked impairment (only puree)	3
Does not reach for objects	4	Severe impairment (tube feeding)	4

Total score (maximum 80)
Modified from Dyken et al. (1982) by Anlar, Altunbasak, Köse, and Yüksel

The typical EEG pattern, bilateral, high amplitude slow, or sharp-slow wave complexes, is seen particularly in stage 2. The discharges are not always synchronous with myoclonia (Fig. 1a). The background rhythm is normal in early stages and becomes slower and suppressed over months/years. Sometimes EEG abnormalities can be asymmetrical or focal (Fig. 2). The typical periodic pattern becomes accentuated after administration of 5 mg diazepam intravenously, or, when routine EEG is normal in early stages, this pattern may appear only after diazepam (Fig. 1b). This feature of SSPE contrasts with epilepsy and other degenerative disorders, in which diazepam usually has a suppressive effect on epileptiform discharges.

CSF analysis for anti-measles virus IgG titers and intrathecal synthesis (measles virus-specific IgG index) is diagnostic. CSF protein, glucose, and cell count are normal. Pressure can be elevated in up to 25 % of the cases, sometimes associated with symptoms of increased intracranial pressure (Ölmez et al. 2007). The IgG index is markedly elevated and oligoclonal bands are observed. Most of

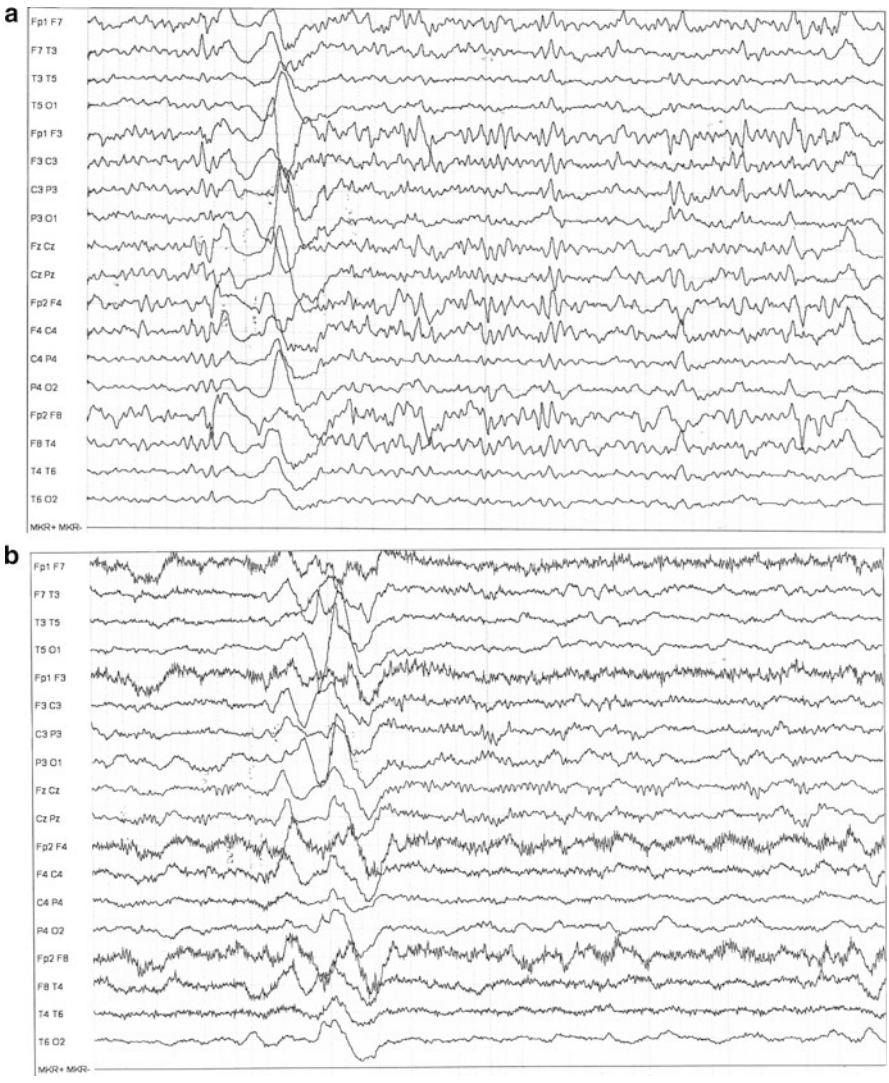

Fig. 1 (**a**) EEG in early stage: normal background rhythm and a slow-wave complex at the onset of the disease, (**b**) EEG recording of the same patient after diazepam showing slower background rhythm and persistence of paroxysmal activity

intrathecally synthesized IgG is not only against MV, but also against some other viruses at low titers (Anlar et al. 2002a, b). If the CSF protein and cells are increased or the IgG index is normal, alternative diagnoses should be considered. The presence of measles virus-specific IgM in the CSF might be associated with a more protracted clinical course (Connolly et al. 1971). The detection of MV RNA is diagnostic but may be difficult to demonstrate due to low copy numbers in the CSF (Nakayama et al. 1995).

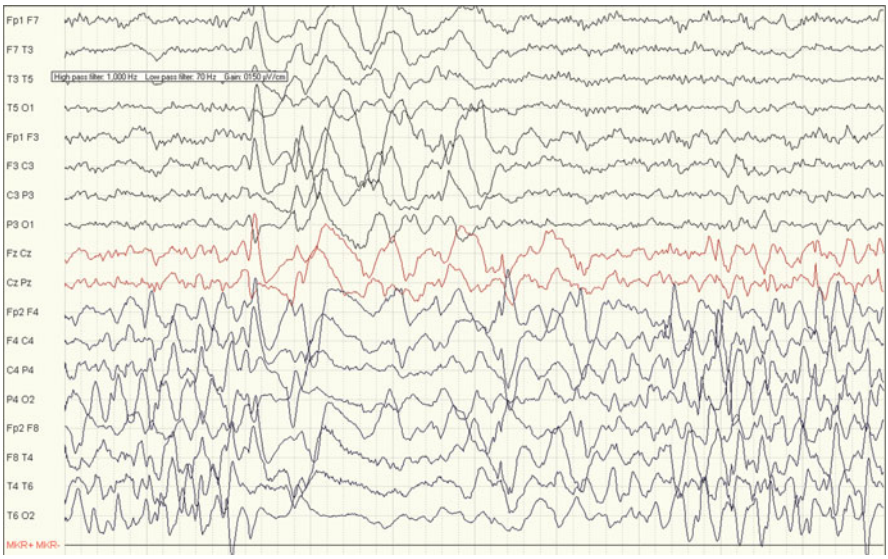

Fig. 2 Asymmetric periodic complexes in the two hemispheres

MRI is not diagnostic or even typical for SSPE, but is useful in excluding other disorders in the differential diagnosis. It can be normal in the initial stages. The most frequent finding is signal intensity changes on T2-weighted images, located in the periventricular or subcortical white matter (Fig. 3). Lesions usually progress to the midline and from the posterior to anterior regions, involving the basal ganglia and brainstem in more advanced disease. Pial or parenchymal contrast enhancement may be observed. Diffuse atrophy develops over years, more correlated with the duration of the disease rather than clinical stage (Anlar et al. 1996). The lesions have an inflammatory or demyelinating nature. Diffusion-weighted MRI may show lesions in the parenchyma appearing normal on routine MRI. MR spectroscopy may suggest neuronal loss, gliosis, demyelination, and inflammation by decreased *N*-acetylaspartate and increased choline and myo-inositol.

1.7.7 Treatment

Antiviral agents have no effect on SSPE and do not penetrate into the brain tissue when given from oral or parenteral route. Ribavirin has been administered intraventricularly to ten patients in combination with α-IFN and resulted in the reduction of MV IgG titers in the CSF (Tomoda et al. 2003). Clinically, progression slowed down in 5/10 treated patients compared to retrospective controls. However, some cases had slowed progression even before treatment was initiated.

The main drug used in the treatment of SSPE is inosine pranobex (inosiplex), a synthetic purine compound with antiviral and immunomodulatory actions. Its effect

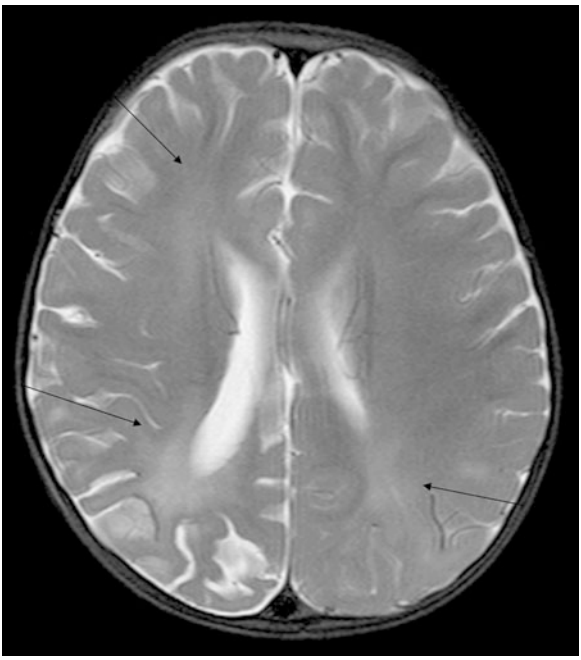

Fig. 3 Typical MRI findings on a T2-weighted image showing bilateral signal intensity changes (*arrows*) that are more prominent in the periventricular white matter surrounding the posterior horns of the lateral ventricles (forceps major)

is modest, but its safety and administration via oral route allow life-long usage. Side effects include gastric disturbance, hyperuricemia, and, rarely, renal stones. The dose is 50–100 mg/kg/day p.o. in divided doses. Inosiplex restores IFN-gamma synthesis from peripheral blood mononuclear cells in vitro and in vivo (Gadoth et al. 1989). Clinical studies comparing treated and non-treated children showed better survival, more frequent prolonged remission, and improved survival in treated patients (Jones et al. 1982, $n = 98$, Fukuyama et al. 1987, $n = 89$). On the other hand, some researchers reported no difference in outcome (Haddad and Risk 1980, $n = 18$) compared to controls ($n = 96$). Our data suggest better outcome in treated patients (Anlar and Yalaz 2011).

Interferons (IFN) have strong antiviral effects. Parenteral alpha-IFN was first given in small patient series or single cases. Intraventricular human lymphoblastoid alpha-IFN in combination with oral inosiplex resulted in improved or stable disease in about 50 % of the cases, and longer survival with slower progression compared to inosiplex alone (Yalaz et al. 1992; Anlar et al. 1997). Intrathecal application may induce meningeal inflammation, seizures, and neuropathy, and may be administered via lumbar puncture or intrathecal pump (Thurner et al. 2007). Another type of IFN, IFN beta1a might also prolong survival and delay progression when given three times per week subcutaneously with oral inosiplex (Anlar et al. 2004).

Amantadine is an antiviral medication that inhibits RNA replication. Certain series reported higher rates of remission with amantadine, a relatively safe drug given by oral route (Robertson et al. 1980).

Intravenous immunoglobulin treatment has been reported in single cases only (Gürer et al. 1996). We observe temporary improvement in some cases with acute deterioration during febrile illnesses, which is usually associated with nonspecific infections.

Corticosteroids may fasten the progression of the disease and are not indicated.

In vitro studies using small interfering RNA showed inhibition of MV replication (Otaki et al. 2007), but no in vivo studies have been published. Various natural or synthetic compounds have been studied in vitro.

Treatment approaches using antiviral and immunomodulatory agents can result in partial remission or stabilization at rates higher than expected in the natural course of SSPE. In general, patients with slow progression are more likely to benefit, perhaps because of their longer time window for drug effects. SSPE being a rare disease with a variable course among patients, and randomized controlled trials are difficult to execute. Special ethical and methodological regulations applied to rare or orphan diseases should be considered for SSPE.

The myoclonia of SSPE respond to carbamazepine, unlike other myoclonic attacks. This is a typical finding which supports the diagnosis of SSPE. Clonazepam, anti-spasticity agents, and other anticonvulsants can also be used as required. Supportive treatment is most influential on the outcome. In some cases, the persistent infection appears to stabilize and some functional repair takes place if the host is given enough time. Physical therapy, even in bedridden patients, and nutritional assistance sometimes requiring N/G tubing or gastrostomy in late stages, are important measures.

1.7.8 Prognosis

Age, sex, clinical, serological, or imaging features have not been found predictive of clinical course and outcome. To some extent, a very young age of onset appears to be associated with more rapid progression. The effects of treatment on outcome are illustrated by longer survival and higher rates of remission in treated patients. Beside clinical follow-up, EEG (and not IgG titers or imaging findings) is the best indicator of progression, stabilization, or remission. Changes in the background rhythm and the frequency of discharges correlate with, and may even precede, clinical changes.

1.7.9 Prevention

Measles vaccine prevents measles and SSPE when an immunization rate over 90 % is reached in a population. Recently the safety of the MMR vaccine has been questioned, which led to reduced immunization rates, accumulation of susceptible populations, and epidemics. Some previously immunized individuals can be susceptible due to low seroconversion or waning antibody levels in young adult age, termed as secondary vaccine failure (Paunio et al. 2000).

1.7.10 Differential Diagnosis

Patients are likely to be misdiagnosed initially, especially in populations in which SSPE is rare.

When presenting with typical symptoms and EEG findings, SSPE can be suspected and confirmed with CSF analysis. On the other hand myoclonia and mental deterioration also constitute the features of epilepsy, particularly progressive myoclonic epilepsies and mitochondrial disorders. Among neurometabolic disorders, Wilson's disease and leukodystrophies can resemble SSPE because they also present with progressive gait or movement disturbance and ataxia. Sydenham's chorea presents with irregular movements of the extremities, incoordination, and dysarthria. The absence of mental deterioration and progression are in favor of this type of chorea rather than SSPE.

Variant Creutzfeldt–Jakob disease (CJD) is a disease of young adults with myoclonus, cognitive decline, and seizures. Myoclonia in CJD are markedly related to auditory or tactile stimuli, whereas they are spontaneous in SSPE. CSF studies distinguish between the two diseases. Mass lesions and stroke are considered when SSPE starts with asymmetrical signs, and encephalitis or ADEM is considered when SSPE presents an acute fulminant course. SME's clinical features are very similar to SSPE, but the host is usually immunocompromised and CSF is negative for MV IgG. Progressive multifocal leukoencephalopathy is another slow infection of the immunocompromised host due to JC virus where cognitive and motor symptoms and white matter lesions on MRI are observed; virological studies allow differentiation. MR imaging rapidly rules out brain tumor in an SSPE patient presenting with focal signs. On the other hand, MR imaging of SSPE may be reminiscent of multiple sclerosis, especially in adult neurology clinics. However mental and behavioral symptoms are rare as initial manifestations of MS.

A recent review ($n = 307$) illustrates the wide list of differential diagnoses (Prashanth et al. 2007). In many cases, the first diagnosis was epilepsy, leukodystrophy, Schilder's disease, cerebral palsy, parkinsonism, Wilson's disease, vasculitis, spinocerebellar ataxia, motor neuron disease, nutritional amblyopia, retinitis, schizophrenia, and malingering. Clearly, a high index of suspicion is needed in order to prevent diagnostic delays and avoid unnecessary diagnostic and therapeutic interventions.

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