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EFNS GUIDELINES

Viral meningoencephalitis: a review of diagnostic methods and guidelines for management

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Background: Viral encephalitis is a medical emergency. The prognosis depends mainly on the pathogen and host immunologic state. Correct immediate diagnosis and introduction of symptomatic and specific therapy has a dramatic influence upon survival and reduces the extent of permanent brain injury.

Methods: We searched the literature from 1966 to 2009. Recommendations were reached by consensus. Where there was lack of evidence but consensus was clear, we have stated our opinion as good practice points.

Recommendations: Diagnosis should be based on medical history and examination followed by CSF analysis for protein and glucose levels, cellular analysis, and identification of the pathogen by polymerase chain reaction amplification (recommendation level A) and serology (level B). Neuroimaging, preferably by MRI, is essential (level B). Lumbar puncture can follow neuroimaging when immediately available, but if this cannot be performed immediately, LP should be delayed only under unusual circumstances. Brain biopsy should be reserved only for unusual and diagnostically difficult cases. Patients must be hospitalized with easy access to intensive care units. Specific, evidence-based, antiviral therapy, acyclovir, is available for herpes encephalitis (level A) and may also be effective for varicella-zoster virus encephalitis. Ganciclovir and foscarnet can be given to treat cytomegalovirus encephalitis, and pleconaril for enterovirus encephalitis (IV class evidence). Corticosteroids as an adjunct treatment for acute viral encephalitis are not generally considered to be effective, and their use is controversial, but this important issue is currently being evaluated in a large clinical trial. Surgical decompression is indicated for impending uncal herniation or increased intracranial pressure refractory to medical management.

Introduction

Clinical involvement of the central nervous system (CNS) is an unusual manifestation of human viral infection. The spectrum of brain involvement and the outcome of the disease are dependent on the specific pathogen, the immunologic state of the host, and environmental factors. Although specific therapy is limited only to several viral agents, correct diagnosis and supportive and symptomatic treatment (when no specific therapy is available) are mandatory to ensure the best prognosis (for reviews see [1–7]. This document addresses the optimal clinical approach to CNS infections caused by viruses.

Classification of evidence levels used in these guidelines for therapeutic interventions and diagnostic measures was according to [8] and detailed in Tables 1a & b and 2a & b.

Methods

We searched MEDLINE (National Library of Medicine) for relevant literature from 1966 to September 2009. The search included reports of research in

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Table 1 (a) Evidence classification scheme for a therapeutic intervention, (b) Evidence classification scheme for the rating of recommendations for a therapeutic intervention

(a)
Class I: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population OR an adequately powered systematic review of prospective, randomized, controlled clinical trials with masked outcome assessment in representative populations. The following are required:
(a) Randomization concealment
(b) Primary outcome(s) is/are clearly defined
(c) Exclusion/inclusion criteria are clearly defined
(e) Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
(f) Relevant baseline characteristics are presented and substantially equivalent amongst treatment groups, or there is appropriate statistical adjustment for differences
Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e
Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment
Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.
(b)
Level A rating (established as effective, ineffective, or harmful) requires at least one convincing Class I study or at least two consistent, convincing Class II studies
Level B rating (probably effective, ineffective, or harmful) requires at least one convincing Class II study or overwhelming Class III evidence
Level C (possibly effective, ineffective, or harmful) rating requires at least two convincing Class III studies

Table 2 (a) Evidence classification scheme for a diagnostic measure, (b) Evidence classification scheme for the rating of recommendations for a diagnostic measure

(a)
Class I: A prospective study in a broad spectrum of persons with the suspected condition, using a 'gold standard' for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy
Class II: A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by 'gold standard') compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy
Class III: Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation
Class IV: Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls)
(b)
Level A rating (established as useful/predictive or not useful/predictive) requires at least one convincing Class I study or at least two consistent, convincing Class II studies
Level B rating (established as probably useful/predictive or not useful/predictive) requires at least one convincing Class II study or overwhelming Class III evidence
Level C rating (established as possibly useful/predictive or not useful/predictive) requires at least two convincing Class III studies

humans only and in English. The search terms selected were as follows: 'viral encephalitis', 'encephalitis', 'viral meningitis', 'meningoencephalitis', and 'encephalomyelitis'. We then limited the search using the terms 'diagnosis', 'MR', 'PET', 'SPECT', 'EEG', 'cerebrospinal fluid', 'pathology', 'treatment', and 'antiviral therapy'. Review articles and book chapters were also included if considered to provide comprehensive reviews of the topic. The final choice of literature and the references included are based on our judgment of their relevance to this subject. Recommendations were reached by consensus of all Task Force participants and were also based on our own awareness and clinical experience. Where there was lack of evidence but consensus was clear, we have stated our opinion as good practice points (GPP).

Definitions and scope

Encephalitis is the presence of an inflammatory process in the brain parenchyma associated with clinical evidence of brain dysfunction. It can be because of a non-infective condition such as in acute disseminated encephalomyelitis (ADEM) or because of an infective process, which is diffuse and usually viral. Herpes simplex virus type 1 (HSV-1), varicella-zoster virus (VZV), Epstein–Barr virus (EBV), mumps, measles, and enteroviruses are responsible for most cases of viral encephalitis in immunocompetent individuals [1]. However, this is also dependent on the continent and on environmental factors. Thus, West Nile virus (WNV) has become an important cause of viral encephalitis in the USA [7]. Other non-viral infective causes of

encephalitis may include such diseases as tuberculosis, rickettsial disease, and trypanosomiasis and will be discussed in the differential diagnosis section.

Encephalitis should be differentiated from encephalopathy defined as a disruption of brain function that is not because of a direct structural or inflammatory process. It is mediated via metabolic processes and can be caused by intoxications, drugs, systemic organ dysfunction (e.g. liver, pancreas), or systemic infection that spares the brain.

The structure of the nervous system dictates a degree of associated inflammatory meningeal involvement in encephalitis, and therefore symptoms that reflect meningitis are invariable concomitants of encephalitis. Moreover, in textbooks and review articles, the term 'viral meningoencephalitis' is often used to denote a viral infectious process of both the brain/spinal cord and the meninges.

Clinical manifestations and relevant environmental and personal information

The diagnosis of viral encephalitis is suspected in the context of a febrile disease accompanied by headache, altered level of consciousness and symptoms, and signs of cerebral dysfunction. These may consist of abnormalities that can be categorized into four: cognitive dysfunction (acute memory, speech and orientation disturbances, etc.), behavioral changes (disorientation, hallucinations, psychosis, personality changes, agitation), focal neurological abnormalities (such as anomia, dysphasia, hemiparesis), and seizures. After the diagnosis is suspected, the approach should consist of obtaining a meticulous history and a careful general and neurological examination.

The history

The history is mandatory in the assessment of the patient with suspected viral encephalitis. It is very important to obtain the relevant information from an accompanying person (relative, friend, etc.) if the patient is in a confused, agitated or disoriented state. The geographic location as well as the recent travel history could be of relevance in identifying possible causative pathogens that are endemic or prevalent in certain geographic regions (examples from recent outbreaks include acute respiratory syndrome, SARS, Nipah virus or avian H5N1 influenza A infections). Likewise, seasonal occurrence can be important for other pathogens such as polio and WNV. Occupation may well be important (as in a case of a forestry worker with Lyme disease). Contact with animals such as farm animals would sometimes point to the cause, as animals serve as reservoirs for certain viruses (e.g. West Nile fever during the 1999 disease outbreak in New York). A history of insect or other animal bites can be relevant for arbovirus infection as well as rabies. Past contact with an individual afflicted by an infective condition is important. The medical status of the individual is of the utmost relevance. Thus, certain viral and non-viral pathogens cause encephalitis only or much more frequently in immune-suppressed individuals.

The mode of disease course up to the appearance of the neurological signs may provide clues to the etiology. For example, enterovirus infection has a typical biphasic course. An associated abnormality outside the nervous system (bleeding tendency in hemorrhagic fever) may also point to a specific pathogen.

General examination

Viral infection of the nervous system is almost always part of a generalized systemic infectious disease. Thus, other organs may be involved prior or in association with the CNS manifestations, and evidence should be obtained either from the history or during the examination. Skin rashes are not infrequent concomitants of viral infections, parotitis may be associated with mumps, gastrointestinal signs with enteroviral disease, and upper respiratory findings may accompany influenza virus infection and HSV-1 encephalitis.

Neurological examination

The findings relate to those of meningitis and disruption of brain parenchyma function. Thus, signs of meningeal irritation and somnolence suggest meningitis, whilst behavioral, cognitive, and focal neurological signs and seizures reflect the disruption of brain function. Additional signs may include autonomic and hypothalamic disturbances, diabetes insipidus, and the syndrome of inappropriate antidiuretic hormone secretion. The symptoms and signs are not a reliable diagnostic instrument to identify the causative virus. Likewise, the evolution of the clinical signs and their severity depend on host and other factors such as immune state and age and cannot serve as guidelines to identify the pathogen. In general, the very young and the very old have the most extensive and serious signs of encephalitis.

Diagnostic investigations

General

Peripheral blood count and cellular morphology are helpful in separating viral from non-viral infections.

Lymphocytosis in the peripheral blood is common in viral encephalitis. The erythrocyte sedimentation rate (ESR) is another non-specific test that is usually within the normal range in non-disseminated viral infections, although a raised ESR might indicate the alternative possibilities of TB or malignancy [9] or that the viral infection may be widely disseminated. Other, general examinations such as chest X-ray, blood cultures, belong to the general investigation of a patient with febrile disease.

The auxiliary studies that examine viral infections of the nervous system include studies that characterize the extent and nature of CNS involvement (electroencephalography (EEG) and neuro-imaging), microbiological attempts to identify the pathogen.

EEG

Electroencephalography is generally regarded as a non-specific investigation, although it is still sometimes a useful tool in certain situations. Thus, leukoencephalitides show more diffuse slow activity in the EEG and polioencephalitides more rhythmic slow activity [10,11]. However, in practice, this hardly helps in the differential diagnosis. Likewise, the EEG findings in postinfectious encephalitides differ from infectious encephalitis only in the time schedule of the abnormalities. The main benefit of EEG is to demonstrate cerebral involvement during the early state of the disease. It is an indicator of cerebral involvement and usually shows a background abnormality prior to evidence of parenchyma involvement on neuroimaging [12]. Only in rare instances does the EEG show specific features that may give clues as to the diagnosis. Often, focal abnormalities may be observed. During the acute phase, the severity of EEG abnormalities has been shown to correlate with the prognosis [13]: fast improving EEG indicates a good prognosis and lack of improvement the opposite ([11], Class IV). The EEG abnormalities usually subside more slowly than the clinical symptoms [10].

The EEG is almost always abnormal in herpes simplex encephalitis (HSE). In addition to the background slowing, there is a temporary temporal focus showing periodic lateralized epileptiform discharges (PLEDs). It can be found during days 2–14 from the beginning of the disease [14], but is non-specific. To detect this EEG finding often requires serial recordings. In newborns, it can be faster with a frequency of 2 Hz and may be other than temporal [15].

In brain-stem encephalitis, the EEG mainly reflects the lowered consciousness and the abnormalities can be mild compared to the clinical state of the patient. In cerebellitis, the EEG is mostly normal [16].

The EEG pattern in HIV infection of the brain is very variable [10]. Likewise, the findings in ADEM are unspecific [17].

The EEG in subacute sclerosing panencephalitis (SSPE) shows a typical generalized periodic EEG pattern repeating with intervals between 4 and 15 s and synchronized with myoclonus of the patient [10].

Neuroimaging

Magnetic resonance imaging (MRI)

Magnetic resonance imaging is more sensitive and specific than Computed tomography (CT) and should be the study of choice for the evaluation of viral encephalitis. ([18–21], Class IIIC). MRI advantages include the use of non-ionizing radiation, multiplanar imaging capability, improved contrast of soft tissue, and high anatomic resolution. However, in practice, many patients who are suspected of having encephalitis often undergo CT scanning before neurological consultation.

A typical MRI protocol consists of routine T1 and T2 spin-echo sequences and a FLAIR (Fluid-attenuation inversion recovery) sequence, which is considered extremely sensitive in detecting subtle changes in the early stages of an acute condition. Gradient-echo imaging, with its superior magnetic susceptibility, is also useful in detecting small areas of hemorrhage.

Additional imaging techniques that are available and that can increase sensitivity to small yet clinically relevant lesions but are mainly used for research may include diffusion-weighted MRI that distinguishes recent from old insult; low magnetization transfer ratio that reflects myelin damage, cell destruction, or changes in water content; magnetic resonance spectroscopy that identifies and quantifies concentration of various brain metabolites; and functional MRI. CT is recommended only as a screening examination, or when MRI is unavailable ([18–20], Class IV).

Single photon emission tomography (SPECT) is more readily available than positron emission tomography (PET) and can provide information about brain chemistry, cerebral neurotransmitters, and brain function [22].

Imaging of specific disorders

HSE Computed tomography obtained early is often normal or subtly abnormal. Low attenuation, mild mass effect in temporal lobes and insula, hemorrhage and enhancement are late features. Follow-up scans 1–2 weeks after disease onset demonstrate progressively more widespread abnormalities with the involvement of contralateral temporal lobe, insula, and cingulate gyri. MRI is much more sensitive in

detecting early changes ([19,20,23], Class IIIC). Involvement of cingulate gyrus and contralateral temporal lobe is highly suggestive of herpes encephalitis. Typical early findings include gyral edema on T1WI imaging and high signal intensity in the temporal lobe or cingulate gyrus on T2WI, FLAIR, and DWI and later hemorrhage. Hypointense on T1, hyperintense on T2WI, FLAIR, high signal on DWI are additional findings [24,25]. The reinstitution of a normal spectrum over time on MRS could potentially be used as a marker of treatment efficacy [26,27].

Neonatal HSV-2 infection often causes more widespread signal abnormalities than HSV-1 encephalitis, with periventricular white matter involvement and sparing of the medial temporal and inferior frontal lobes [28].

HIV-1 Computed tomography demonstrates normal/mild atrophy with white matter hypodensity. MRI usually shows atrophy and non-specific white matter changes. MRS detects early decreases in levels of NAA and increases in choline-containing phospholipids (Cho) levels, even before abnormalities are detected by MRI and prior to clinical symptoms [29]. Neuroimaging is an important diagnostic tool for opportunistic infections. Toxoplasmosis (ring-enhancing mass(es) in basal ganglia), cryptococcosis (gelatinous 'pseudocysts'), meningoencephalitis, vasculitis, infarction, CMV encephalitis (diffuse white matter hyperintensities), ventriculitis (ependymal enhancement), progressive multifocal leukoencephalopathy (PML, white matter hyperintensities which usually do not enhance), and lymphoma (solitary or multifocal solid or ring-enhancing lesions either in deep gray and white matter or less frequent in subcortical areas) [30,31]. MRS may be able to distinguish between these different space-occupying lesions based on their chemical profiles and can serve to predict and monitor the efficacy of antiretroviral therapy [32].

VZV Central nervous system complications of VZV infection (usually because of reactivation of latent VZV in spinal and trigeminal ganglia) include myelitis, encephalitis, large- and small-vessel arteritis, ventriculitis, and meningitis [33]. Large vessel arteritis presents with ischaemic/hemorrhagic infarctions and may be revealed by MRI/MRA.

Miscellaneous In polio and Coxsackie virus infections, T2-weighted MRI may show hyperintensities in the midbrain and anterior horn of the spinal cord [34], in EBV infection in the basal ganglia and thalami [35] and in Japanese encephalitis in bilateral thalami, brainstem, and cerebellum [36]. WNV can be associated with enhancement of leptomeninges, the periventricular areas, or both, on MRI [37] as well as involvement of basal ganglia brain stem, thalamus, and cerebellum [38].

ADEM Initial CT scanning may show low density, asymmetric lesions with mild mass effect and contrast enhancement multifocal punctate or ring-enhancing lesions. However, CT is normal in 40% of cases. MRI is more sensitive and an essential diagnostic tool. T2WI and FLAIR scans present multifocal, usually bilateral, but asymmetric and large hyperintense lesions, involving peripheral white and gray matter. Lesions do not usually involve the callososeptal interface. Contrast-enhanced T1WI may show ring-enhancing lesions. Cranial nerves may enhance. DWI is variable. On MRS, NAA is transiently low and choline is normal. [19,21,39].

PML MRI is also the most sensitive imaging tool for PML [40]. T2WI initially show multiple, bilateral, non-enhancing, oval or round subcortical white matter hyperintensities in the parieto-occipital area. Confluent white matter disease with cavitary change is a late manifestation of PML. Less common imaging manifestations of PML are unilateral white matter and thalamic or basal ganglia lesions.

Rasmussen's encephalitis Rasmussen's encephalitis typically involves only one cerebral hemisphere, which becomes atrophic and so far its etiology and pathogenesis are unknown. The earliest CT and MRI abnormalities include high signal on T2WI in cortex and white matter, cortical atrophy usually of the fronto insular region, with mild or severe enlargement of the lateral ventricle and moderate atrophy of the head of the caudate nucleus. Fluorodeoxyglucose PET has been reported to present hypometabolism; Tc-99 m hexamethylpropyleneamine oxime SPECT decreased perfusion and proton MRS reduction of NAA in the affected hemisphere. However, PET and SPECT findings are non-specific. MRI may become a valuable early diagnostic tool by demonstrating focal disease progression [41,42].

Paraneoplastic limbic encephalitis In paraneoplastic limbic encephalitis MRI FLAIR and DWI depict bilateral involvement of the medial temporal lobes and multifocal involvement of the brain [43].

Virological tests in encephalitis

General

The gold standard of diagnosis in encephalitis is virus isolation in cell culture, but it has now been replaced by

the detection of specific nucleic acid from CSF or brain ([44–47], Class Ia). Intrathecal antibody production to a specific virus is similarly a strong evidence for etiology ([48,49], Class Ib). Virus detection from throat, stool, urine, or blood as well as systemic serological responses such as seroconversion or a specific IgM detection provides less strong evidence ([1,50], Class III). The CSF is a convenient specimen and is recommended for neurological viral diagnosis in general [51]. Brain biopsy is invasive and is now seldom used in routine clinical practice. However, in patients with rapidly deteriorating conditions, it has a high diagnostic yield, particularly in HIV-infected patients, but also 65% in non-HIV-infected patients, including viral encephalitis in 14% [52]. At autopsy brain specimens can be obtained for virus isolation, nucleic acid and antigen detection as well as for immunohistochemistry and *in situ* hybridization.

Viral culture

Viral cultures from CSF and brain tissue as well as from throat and stool specimens are performed in four different cell lines: African green monkey cells, Vero cells, human amniotic epithelial cells, and human embryonic skin fibroblasts. Cells are evaluated daily for cytopathic effect, and the findings are confirmed by a neutralizing or an immunofluorescence antibody test. Viral cultures from CSF are positive in young children with enteroviral meningoencephalitis but only seldom, in $< 5\%$, in other cases [53,54], (Class III).

Nucleic acid detection

For nucleic acid detection, polymerase chain reaction (PCR) technology provides the most convenient test. Assays for HSV-1, HSV-2, VZV, human herpesviruses 6 & 7, CMV, EBV, JCV of PML, Dengue virus, enteroviruses, and respiratory viruses as well as HIV can be performed from CSF samples or brain tissue. The primers are selected from a conserved region of the viral genome, and the PCR product is identified by hybridization with specific probes or by gel electrophoresis. Respiratory viruses' nucleic acid can also be detected from throat samples and enterovirus nucleic acid from stool samples. However, these cannot confirm the etiology of encephalitis. Detection of specific nucleic acid from the CSF is dependent on the timing of the CSF sample. The highest yield is obtained during the transient appearance of the virus in the CSF compartment during the first week after symptom onset, much less in the second week and only occasionally after that ([46,49], Class I). In HSE, the sensitivity is 96% and the specificity 99% when CSF is studied between 48 h and 10 days from symptoms onset [46,47]. The issue of whether or not to routinely repeat the CSF-PCR in HSE after 14 days of antiviral treatment has yet to be resolved.

Alternatively to the single PCR tests, the multiplex PCR technique is also available [55–57] as is the real time PCR [58]. The usage of microarrays that enables to look for several microbes' nucleic acid simultaneously is currently expensive, but has the potential to become a useful diagnostic technique.

Serological tests

Antibodies to HSV-1 & 2, VZV, CMV, HHV-6, HHV-7, CMV, EBV, RSV, HIV, adeno, influenza A and B, rota, coxsackie B5, non-typed entero and parainfluenza 1 viruses are measured from serum and CSF by enzyme immunoassay (EIA) tests ([1,48,59–63]; Class II). These tests are sensitive enough to detect even low amounts of CSF antibodies. Antibody levels in serum and CSF are compared at the same dilution of 1:200. If the ratio of antibody levels is ≤ 20, it indicates intrathecal antibody production provided that no other antibodies are present in the CSF, i.e. the blood–brain barrier (BBB) is not damaged [50]. The presence of several antibodies in the CSF suggests BBB breakdown, whilst the presence of specific IgM in the CSF indicates CNS disease [64]. The tests for measles, mumps, and rubella are only occasionally needed in countries with effective vaccination programs. Tests for arboviruses and zoonoses will be useful in endemic areas [50,65]. Oligoclonal bands in the CSF may usually suggest an inflammatory etiology [66].

Antigen detection

Antigens of HSV, VZV, and RSV, influenza A and B, parainfluenza 1 and 3, and adenoviruses can be studied from throat specimens with a conventional immunofluorescence (IF) test or with an EIA test and may provide a possible etiology for encephalitis. Despite promising initial results, these tests are not helpful in diagnosis using CSF samples.

In conclusion

In a patient with suspected encephalitis obtaining serum and CSF for virological tests is the core diagnostic procedure of choice. Tests should include the following: PCR test for nucleic acid detection (from CSF) and serological tests for antibodies (from CSF and serum). In undiagnosed severe cases, PCR should be repeated after 3–7 days, and serological tests repeated after 2–4 weeks to show possible seroconversion or diagnostic increase in antibody levels. In children, viral culture from throat and stool samples as well as antigen detection for herpes and respiratory viruses are recommended during the first week. Viral culture from

CSF is useful in children with suspected enteroviral or VZV disease if PCR tests are not available.

Histopathology

Encephalitis features a variety of histopathological changes in the brain, mainly depending upon the type of the infectious agent, the immunologic response by the host and the stage of the infection. The etiologic spectrum is strongly influenced by geography. Primary encephalitic processes may secondarily involve the meninges, with inflammatory infiltration resulting in usually mild CSF pleocytosis (lymphocytes with variable degree of activation, eventually plasmocytes). In encephalitis with a prominent necrotizing component, mixed CSF cellularity may also include granulocytes; this is frequently seen in HSV encephalitis and CMV (peri)ventriculitis/myeloradiculitis of HIV patients.

The histopathological basis of encephalitis is the triad of damage to the parenchyma, reactive gliosis, and inflammatory cellular infiltration [67]. This classical substrate is exemplified by (multi)nodular encephalitis, as in the majority of viral encephalitides consisting of nerve cell damage, followed by nerve cell death and neuronophagia, focal/nodular proliferation of astro- and microglia, and focal/nodular infiltration by lymphocytes, eventually macrophages. Thus, the classical encephalitic nodules are composed of the mixture of microglia, astrocytes, and lymphocytes usually around affected neuron(s) [67].

Distribution and spread of these inflammatory changes are important for etiologic considerations: four types of meningoencephalitis may be distinguished, affecting either only the meninges, the gray matter, the white matter, or both, in a focal or a diffuse manner [68]. 'Aseptic' meningitis is most commonly because of enteroviruses, HSV-2, mumps, HIV, LCM, arboviruses, measles, parainfluenza, and adenoviruses [68]. The encephalitic patterns include continuous polioencephalitis (e.g. in luetic general paresis) and patchy-nodular polioencephalitis (e.g. in poliomyelitis, rabies, acute encephalitis by flavi-, toga- and enteroviruses, HSV brainstem encephalitis), leukoencephalitis (e.g. in PML or HIV leukoencephalopathy), and panencephalitis (e.g. in bacterial septicemia with microabscesses, in Whipple's disease, SSPE, HIV encephalitis, and herpesviruses such as HSV, CMV, and VZV infection). In addition to the inflammatory quality and characteristic distribution of tissue lesions, cytological features such as inclusion bodies (intranuclear in HSV, VZV encephalitis, PML and SSPE, cytoplasmic Negri bodies in rabies) or cytomegalic cell change in CMV disease give important diagnostic clues, especially when the involved cell type is considered: every viral infection of the nervous system usually features a fingerprint signature of selective vulnerability in the nervous system [67]. However, immunosuppression and the effects of potent therapies have become notorious for being able to modify, blur or even wipe out classical features of specific viral lesions. This has become particularly striking in the recent experience with highly active antiretroviral therapy (HAART) of HIV infection: its efficiency may result in deterioration by a paradoxical activation of an inflammatory response, the immune reconstitution inflammatory syndrome (IRIS). IRIS features brain inflammation by predominantly CD8+ lymphocytes [69], including a fulminant leukoencephalitis [70] or a particularly severe and intensely inflammatory form of PML. IRIS may be responsive to steroid therapy [71].

Alternatively to direct viral damage to CNS tissue, secondary involvement by infarctions may be because of viral infection of the CNS vasculature, as seen with VZV [72] or Nipah virus [73].

The role of special techniques: Immunocytochemistry, in situ hybridization, PCR

It is in the field of infections where the techniques of immunocytochemistry (ICC), *in situ* hybridization (ISH), and PCR have a profound impact on neuropathological diagnosis. When performed appropriately with adequate controls and tissue selection, they provide an etiologic diagnosis with a high sensitivity and specificity [67,74]. Nevertheless, there are *caveats* for situations in which they may not be diagnostic:

- Production of the infectious agent may have 'burnt out' or its products may have become masked, resulting in negative ICC or ISH.
- Tissue preservation might be unsuitable for ICC or ISH, or nucleic acid amplification from paraffin embedded tissue may be blocked by yet unidentified factors.
- As PCR and ISH are very sensitive techniques, positive results may reflect presence of genomic information resulting from dormant or latent infection, and not necessarily productive and pathogenic infection.

Therefore, prerequisites for the use of ICC, ISH, or PCR for diagnosis of infections include simultaneous use of known positive and negative control tissues identically processed as the material to be examined; availability of reagents (antibodies, probes, primers) with defined specificities; adequate testing of reagents on control tissues for optimal signal to noise ratio and experience with immunocytochemical antigen retrieval techniques [67].

Viruses may exert damage to the nervous system not only by productive, but by indirect means, the best example being the immune-mediated ADEM or postinfectious/perivenous encephalitis, important for differen-

tial diagnosis from productive viral encephalomyelitis: multiple small demyelinated foci are arranged around small veins of the white matter, featuring cellular infiltration composed by lymphocytes, macrophages, and microglia [67].

Other infective causes of meningoencephalitis and differential diagnosis

The clinical distinction between viral encephalitis and non-viral infective meningoencephalitis may be difficult and is sometimes impossible. Epidemiological and demographic features, such as prevalent or emergent infections in the community, occupation, a history of travel and animal contacts may provide helpful clues. In a non-epidemic setting, the most common cause of focal encephalopathic findings is HSE; however, amongst cases with biopsy proven HSE, there were no distinguishing clinical characteristics between HSV-positive and HSV-negative patients [3].

ADEM

Acute disseminated encephalomyelitis, an autoimmune disease, with evidence of cell-mediated immunity to the myelin basic protein as its pathogenic basis [75], is characterized by monophasic focal neurological signs and a rapidly progressive course, usually with a history of febrile illness or immunization preceding the neurological syndrome by days or weeks. It may be distinguished from infective encephalitis by the younger age of the patient, prodromal history of vaccination or infection, absence of fever at the onset of symptoms and the presence of multifocal neurological signs affecting optic nerves, brain, spinal cord, and peripheral nerve roots. The disturbances of consciousness range from stupor and confusion to coma. Patients have a mild fever often with peripheral blood pleocytosis. CSF shows lymphocytic pleocytosis, with mildly raised protein and may appear similar to the CSF in viral encephalitis. The clinical course of patients with Hashimoto's encephalopathy would fit a less aggressive form of recurrent ADEM [76,77].

CNS vasculitis

Central nervous system vasculitis can be part of a systemic disease or be confined to the nervous system. Systemic symptoms, aseptic meningitis, and focal neurological deficit may occasionally simulate viral encephalitis. This is seen in both systemic vasculitis and primary CNS angiitis. In systemic vasculitis affecting the CNS, it is usually possible to make a diagnosis based on a combination of systemic and CSF serologic and immunologic tests and angiographic appearances of CNS vasculitis. In isolated angiitis, the diagnosis may be more challenging and may require brain and meningeal biopsy to secure the diagnosis.

Pseudomigraine with pleocytosis

Acute confusion, psychosis, and focal neurological deficit (hemiplegia, hemianesthesia, and aphasia) in association with migraine headache occur in familial hemiplegic migraine [78]. Sterile CSF pleocytosis has been reported in migraine patients who may present similarly [79]. It has been proposed that the pleocytosis in some of these cases is because of predisposition to viral meningitis [80]. Pseudomigraine with pleocytosis and migraine coma are more likely to represent reversible forms of ADEM [77].

Therapy

Antiviral therapy

Acyclovir is the treatment of choice for HSE (Class IA). Monophosphorylation of acyclovir is the critical step in this process and is only catalyzed by a viral thymidine kinase induced in cells selectively infected by HSV, VZV or by a phosphotransferase produced by CMV. Host enzymes subsequently phosphorylate the monophosphate to di- and triphosphate. Acyclovir triphosphate inhibits the synthesis of viral DNA by competing with 2′-deoxyguanosine triphosphate as a substrate for viral DNA polymerase. Viral DNA synthesis is arrested once acyclovir (rather than 2′-deoxyguanosine) is inserted into the replicating DNA. The incorporation of acyclovir into viral DNA is an irreversible process and it also inactivates viral DNA polymerase. Acyclovir is most effective when given early in the clinical course of HSE and reduces both mortality and morbidity [3,81,82]. The standard dose for HSE is 10 mg/kg given as an intravenous infusion over one hour three times daily (30 mg/kg/day) for 14 days. The dose for neonatal HSE is 60 mg/kg/day. The duration of treatment is 21 days for immunosuppressed patients.

Treatment with acyclovir for HSE should be commenced on clinical suspicion. Mortality rates in untreated HSE are around 70% and fewer than 3% would return to normal function. Early acyclovir therapy reduces mortality to 20–30% [81,83]. Amongst the acyclovir treated patients in the NINAID-CASG trials, 26 of the 32 (81%) treated patients survived and serious neurological disability was seen in nearly half of the survivors. Older patients with poor level of consciousness (Glasgow Coma Scale of 6 or less) had the worst

outcome. Young patients (30 years or less) with good neurological function at the time of initiating therapy did substantially better (100% survival, over 60% had little or no sequel). As more than 80% of acyclovir in circulation is excreted unchanged in urine, renal impairment can precipitate acyclovir toxicity and high dose acyclovir in overweight or obese patients may precipitate renal failure. Rarely, acyclovir can induce a toxic encephalopathy, and therefore, it is important to establish an early diagnosis of HSE to avoid diagnostic confusion.

In an immunocompetent host with acute encephalopathy and MRI, evidence of temporal or frontobasal lobe involvement supports the diagnosis of HSE and such a patient must be treated with acyclovir for a minimum of 14 days (Class IV). If acyclovir is started on admission and the MRI of brain is normal, then treatment should continue until CSF-PCR results become available and the treatment withdrawn in cases where this test is negative and an alternative diagnosis has been established. If an alternative diagnosis has not been reached and the CFS-PCR is negative for HSV, then the current consensus is to continue acyclovir therapy for at least 10 days (Class IV, [9]). There has been only a single case report of HSE with normal cerebral MRI scan, where the diagnosis of HSE was made by PCR from a CSF sample obtained on the day of admission but a repeat CSF-PCR after 8 days of acyclovir therapy was negative [84]. Recurrence of HSE has been reported weeks to 3 months later when the treatment was given for 10 days or less [85], and relapse after therapy may be as high as 5% but relapse has not been documented when higher doses were administered for 21 days [86]. Development of acyclovir resistance in HSE is a possibility following the report of acyclovir resistance in mucocutaneous herpes simplex amongst patients with AIDS and isolation of acyclovir-resistant HSV as the cause of encephalitis in organ transplant recipients and HIV patients. Foscarnet, which inhibits viral DNA polymerases by binding to the pyrophosphate binding site, is recommended in acyclovir-resistant HSE (60 mg/kg intravenously infused over 1 h every 8 h for 3 weeks). However, acyclovir-resistant HSE has not been reported in immunocompetent patients and foscarnet should be used only in patients with clinically suspected HSE who continue to deteriorate despite acyclovir therapy with a reactive CSF in whom alternative possibilities have been excluded. Foscarnet can also precipitate a dose-related, reversible renal impairment.

Acyclovir is effective against encephalitis because of VZV [81]. VZV can cause both acute and subacute encephalitis. VZV was the most common alphaherpesvirus detected in CSF samples from patients with CNS symptoms in the Western Gotaland region of Sweden [87]. Doses of acyclovir in VZV encephalitis are similar to HSE, and the treatment should be continued for 3 weeks (Class IV).

Response of CMV encephalitis to antiviral drugs (ganciclovir, foscarnet, and cidofovir) is less than satisfactory. Combination of ganciclovir (5 mg/kg intravenously twice daily) with foscarnet (60 mg/kg every 8 h or 90 mg/kg intravenously every 12 h) is advocated as induction therapy in CMV encephalitis (Class IV) followed by maintenance therapy with ganciclovir (5 mg/kg/day) or foscarnet (60–120 mg/kg/day) [88]. The recommended duration of therapy is 3 weeks for immunocompetent and 6 weeks for immunosuppressed patients (Class IV). The rationale for using combination treatment in the induction phase is that monotherapy with ganciclovir or foscarnet alone failed to improve survival.

The present treatment recommendation for HHV6 encephalitis is foscarnet (60 mg/kg every 8 h for both A and B variants). Ganciclovir (5 mg/kg every 12 h) is an alternative option only for B variant of HHV6 encephalitis [89].

There have been few successes with antiviral therapy for arboviral encephalitis. A study that evaluated high dose dexamethasone in JE found the treatment to be of no benefit [90].

Neurological complications, including encephalitis, have been widely reported in association with respiratory tract infection with seasonal influenza A or B viruses, and recently with novel influenza A (H1N1) virus. Antiviral therapy with oseltamivir (four patients) and rimantadine (three patients) were clinically effective in patients with suspected encephalitis because of H1N1 infection [91].

PML is commonly caused by JC virus and is regarded as an opportunistic infection of the CNS occurring in the setting of immunosuppression. There have been recent reports of subacutely evolving PML following treatment with rituximab, natalizumab, and efalizumab. Many antiviral drugs, including cytosine arabinoside, amantadine, ribavarin, interferon alpha, and vidarabine have been used in small case studies but none has shown a lasting impact.

No antiviral therapy is particularly effective in epizootic or enzootic viral encephalitis; however, because of the high mortality rate associated with B virus (cercopithecine herpesvirus) encephalitis in humans, it is currently proposed [3] that patients should be treated with intravenous acyclovir or ganciclovir.

Corticosteroids

Large doses of dexamethasone as an adjunct treatment for acute viral encephalitis are not considered to be

effective and their use is controversial. Probably, the best evidence for steroid therapy in this context is in VZV encephalitis. Primary VZV infection may cause severe encephalitis in immunocompetent children because of cerebral vasculitis [72,92]. Vasculitis following primary and secondary VZV infection is recognized as resulting in a chronic course in immunocompetent children and adults (granulomatous angiitis). HSE is occasionally complicated by severe, vasogenic cerebral edema where high dose steroids may have a role. Steroid pulse therapy with methylprednisolone has been observed to be beneficial in a small number of patients with acute viral encephalitis who had progressive disturbances of consciousness, an important prognostic factor for outcome [93]. The utility of adjunctive corticosteroid therapy in HSE is about to be evaluated in a multicenter, multinational, randomized, double-blind, placebo-controlled trial [94].

Based on available data, combined acyclovir/steroid treatment may be advised in immunocompetent individuals with severe VZV encephalitis and probably in other cases of acute viral encephalitis where progressive cerebral edema documented by CT/MRI complicates the course of illness in the early phase (GPP). High dose dexamethasone or pulse methylprednisolone are both suitable agents. The duration of steroid treatment should be short (between 3 and 5 days) to minimize adverse effects.

The effect of steroids on IRIS has been demonstrated in anecdotal reports [71,95] and requires confirmation in controlled trials.

Although no randomized controlled trials have been performed, treatment with high dose steroids (intravenous pulses of methylprednisolone) and/or plasma exchange is usually the recommended treatment in ADEM [76], (Class IV and GPP).

Surgical intervention

Surgical decompression for acute viral encephalitis is indicated for impending herniation or increased intracranial pressure refractory to medical management (GPP). Such intervention has been shown to improve outcome in HSE in individual cases [96].

General measures

All cases of acute encephalitis must be hospitalized. Like other critically ill patients, cases with acute viral encephalitis should have access to intensive care unit equipped with mechanical ventilators. Irrespective of the etiology, supportive therapy for acute viral encephalitis is an important cornerstone of management [2]. Seizures are controlled with intravenous anticonvulsants such as phenytoin. Careful attention must be paid to the maintenance of respiration, cardiac rhythm, fluid balance, prevention of deep vein thrombosis and aspiration pneumonia, medical management of raised intracranial pressure and secondary bacterial infections. Secondary neurological complications in the course of viral encephalitis are common and include cerebral infarction, cerebral venous thrombosis, syndrome of inappropriate ADH secretion, aspiration pneumonia, upper gastrointestinal bleeding, urinary tract infections, and disseminated intravascular coagulopathy.

Isolation of patients with community-acquired acute infective encephalitis is not required. Consideration of isolation should be given for severely immunosuppressed patients, rabies encephalitis, patients with exanthematous encephalitis, and those with a contagious viral hemorrhagic fever.

Rehabilitation

Survivors of viral encephalitis and myelitis are a heterogenous group. The nature of the infective pathogen, variability in anatomic lesions and time to treatment may all contribute to outcome. Longitudinally designed case studies, reporting cognitive and psychosocial outcome mainly following HSE were conducted prior to current era of early diagnosis and effective therapy. Whilst there are anecdotal case reports [97,98], there are too few studies on the outcome of rehabilitation following encephalitis [99] to allow any conclusions to be drawn.

Preventive measures

Currently, vaccines are available against a limited number of viruses with a potential to cause encephalitis. Universal immunization is recommended against mumps, measles, rubella, and poliovirus. European travelers to specific geographic destinations (e.g. South East Asia) should receive advice regarding vaccination against rabies and Japanese encephalitis. Preventive measures against exotic forms of emerging paramyxovirus encephalitis (Nipah and Hendra viruses) are entirely environmental (sanitation, vector control, and avoidance).

Recommendations for diagnostic tests

Viral encephalitis is still an evolving discipline in medicine. The emergence of new and re-emergence of old pathogens and the constant search for specific therapeutic measures, unavailable in most viral encephalitis cases, suggest that the following years will bring new developments in diagnosis and therapy. At present,

adherence to a strict protocol of diagnostic investigations is recommended and includes the following:

Study	Findings	Level of recommendation	Class of evidence
LP	Cells – 5–500 white blood cells, mainly lymphocytes; May be xanthochromic with red blood cells. Glucose – Normal (rarely reduced). Protein – > 50 mg/dl	A	II
Serology	CSF & Serum	B	II
PCR	Major aid in diagnosis (CSF). May be false negative in the first 2 days of disease.	A	I
EEG	Early and sensitive. Non-specific. May identify focal abnormalities	C	III
Imaging	MRI is usually more sensitive than CT, demonstrating high signal intensity lesion on T2-weighted and FLAIR images.	B	II
Viral culture	Only rarely useful		
Brain biopsy	Highly sensitive. Not used routinely.	C	III & GPP

Recommendations for therapeutic interventions

The following are the specific and symptomatic therapeutic measures available for viral encephalitis.

Interventions	Class of evidence	Level of recommendation
Acyclovir for HSE	II	A
Acyclovir for suspected viral encephalitis	IV	(-)
Acyclovir for VZV encephalitis	IV	(-)
Ganciclovir and/foscarnet for CMV encephalitis	IV	(-)
Acyclovir or ganciclovir for B virus encephalitis	IV	(-)
Pleconaril for enterovirus encephalitis	Not available	(-)
Corticosteroids for viral encephalitis	IV	
Corticosteroids for viral encephalitis	IV	
Surgical decompression	IV	

These guidelines should be regularly reviewed in light of new scientific evidence and medical experience, and updated when necessary.

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