

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

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Viral encephalitis is a medical emergency. The spectrum of brain involvement and the prognosis are dependent mainly on the specific pathogen and the immunological state of the host. Although specific therapy is limited to only several viral agents, correct immediate diagnosis and introduction of symptomatic and specific therapy has a dramatic influence upon survival and reduces the extent of permanent brain injury in survivors. We searched MEDLINE (National Library of Medicine) for relevant literature from 1966 to May 2004. Review articles and book chapters were also included. Recommendations are based on this literature based on our judgment of the relevance of the references to the subject. Recommendations were reached by consensus. Where there was lack of evidence but consensus was clear we have stated our opinion as good practice points. Diagnosis should be based on medical history, examination followed by analysis of cerebrospinal fluid for protein and glucose contents, cellular analysis and identification of the pathogen by polymerase chain reaction (PCR) amplification (recommendation level A) and serology (recommendation level B). Neuroimaging, preferably by magnetic resonance imaging, is an essential aspect of evaluation (recommendation level B). Lumbar puncture can follow neuroimaging when immediately available, but if this cannot be obtained at the shortest span of time it should be delayed only in the presence of strict contraindications. Brain biopsy should be reserved only for unusual and diagnostically difficult cases. All encephalitis cases must be hospitalized with an access to intensive care units. Supportive therapy is an important basis of management. Specific, evidence-based, anti-viral therapy, acyclovir, is available for herpes encephalitis (recommendation level A). Acyclovir might also be effective for varicella-zoster virus encephalitis, gancyclovir and foscarnet for cytomegalovirus encephalitis and pleconaril for enterovirus encephalitis (IV class of evidence). Corticosteroids as an adjunct treatment for acute viral encephalitis are not generally considered to be effective and their use is controversial. 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 immunological state of the host and a range of environmental factors. Although specific therapy is limited to only 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 Koskiniemi *et al.*, 2001; Chaudhuri and Kennedy, 2002; Redington and Tyler, 2002; Whitley and Gnann, 2002). 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 Brainin *et al.* (2004) and detailed in Tables 1–4.

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Table 1 Evidence classification scheme for a therapeutic intervention

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.
- d. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias.
- e. Relevant baseline characteristics are presented and substantially equivalent among 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.

Table 2 Evidence classification scheme for the rating of recommendations for a therapeutic intervention

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 3 Evidence classification scheme for a diagnostic measure

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 with 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)

Table 4 Evidence classification scheme for the rating of recommendations for a diagnostic measure

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

Methods

We searched MEDLINE (National Library of Medicine) for relevant literature from 1966 to May 2004. The search included reports of research in human beings only and in English. The search terms selected were: 'viral encephalitis', 'encephalitis', 'meningoencephalitis' and 'encephalopathy'. We then limited the search using the terms 'diagnosis', 'MR', 'positron emission tomography' (PET), 'single photon emission tomography' (SPECT), 'electroencephalography' (EEG), 'cerebrospinal fluid', 'pathology', 'treatment' and 'antiviral therapy'. Review articles and book chapters were also included if they were considered to provide comprehensive reviews of the topic. The final choice of literature and the references included was based on our judgment of their relevance to this subject. Recommendations were reached by consensus of all Task Force participants (Tables 1–4) 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 due to a non-infective condition such as in acute disseminated encephalomyelitis (ADEM) or to 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 immuno-competent individuals (Koskiniemi *et al.*, 2001). 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 which is 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 determines 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 meningo-encephalitis 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 disturbances), behavioural changes (disorientation, hallucinations, psychosis, personality changes, agitation), focal neurological abnormalities (such as anomia, dysphasia, hemiparesis, hemianopia etc.) 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 might be important to obtain the relevant information from an accompanying person (relative, friend, etc.) if the patient is in a confused, agitated and disoriented state. The geographical location as well as the recent travel history could be of relevance to identify causative pathogens that are endemic or prevalent in certain geographical regions (the recent example being severe acute respiratory syndrome). Likewise, seasonal occurrence can be important for other pathogens such as polio virus. 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 and the 1999 outbreak of the disease 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 immunosuppressed individuals such as patients with AIDS or those who receive medications that affect the immune system (e.g. cancer and organ transplant patients).

The mode of disease course up to the appearance of the neurological signs may provide clues to the aetiology. For example, enterovirus infection has a typical biphasic course. An associated abnormality outside the nervous system (bleeding tendency in haemorrhagic fever, the hydrophobia in rabies patients) 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. Evidence for such an involvement 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 reflect meningitis, while behavioural, 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. Erythrocyte sedimentation rate is another non-specific test that is usually within normal

range in viral infections. Other, general examinations such as chest X-ray, blood cultures, belong to the general work-up of febrile disease.

The auxiliary studies that examine viral infections of the nervous system include studies that characterize the extent and nature of CNS involvement (EEG and neuroimaging), microbiological attempts to identify the pathogen and histopathology will be discussed here.

EEG is generally regarded as a non-specific investigation, although it is still sometimes a useful tool in certain situations. Thus, leucoencephalitis shows more diffuse slow activity in the EEG and polioencephalitis shows more rhythmic slow activity (Vas and Cracco, 1990; Westmoreland, 1999). However, in practice this hardly helps in the differential diagnosis. Likewise, the EEG findings in post-infectious encephalitis 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. Only in rare instances does the EEG show specific features that may give clues to the diagnosis.

Acute viral encephalitis

The EEG is an early and sensitive indicator of cerebral involvement and usually shows a background abnormality prior to the initial evidence of parenchyma involvement on neuroimaging. This may in some instances be helpful in the differential diagnosis of aseptic meningitis. Often, focal abnormalities may be observed. During the acute phase, the severity of EEG abnormalities do not usually correlate with the extent of the disease. However, a fast improving EEG indicates a good prognosis, while lack of improvement of the EEG recording carries a non-favorable prognosis (Vas and Cracco, 1990, class IV). Although there may be seizures in the acute phase, interictal epileptiform EEG activity is a rarity. The EEG abnormalities usually subside more slowly than the clinical symptoms (Westmoreland, 1999).

Herpes simplex encephalitis

In 80% of the patients there is a typical finding in the EEG. In addition to the background slowing there is a temporal focus showing periodic lateralized epileptiform discharges. This finding is temporary; it can be found during days 2–14 from the beginning of the disease, most often during days 5–10 (Lai and Gragas, 1988). Detection of this EEG finding often requires serial recordings. The repetition interval of these pseudo-periodic complexes is from 1 to 4 s; in newborns it can be faster with a frequency of 2 Hz. Also the localization in newborns may be other than temporal (Sainio *et al.*, 1983).

Brain-stem encephalitis

In brain-stem encephalitis the EEG mainly reflects the lowered consciousness and the abnormalities can be mild compared with the clinical state of the patient. Intermittent rhythmic delta activity (IRDA) has also been described in these patients.

Cerebellitis

In cerebellitis the EEG is mostly normal (Schmahmann and Sherman, 1998).

HIV

The EEG pattern in human immunodeficiency virus (HIV) infection of the brain is very variable, with background, paroxysmal and focal abnormalities (Westmoreland, 1999). Likewise the findings in ADEM are unspecific encephalitic abnormalities (Tenenbaum *et al.*, 2002).

Subacute sclerosing panencephalitis

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 (Westmoreland, 1999)

Neuroimaging of encephalitis

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is more sensitive and specific than CT for the evaluation of viral encephalitis (Dun *et al.*, 1986; Schroth *et al.*, 1987; Dale *et al.*, 2000; Marchbank *et al.*, 2000, class IIIC). The advantages of MRI include the use of non-ionizing radiation, multiplanar imaging capability, improved contrast of soft tissue, and high anatomical resolution. On the basis of previous data it should be the imaging technique of choice in determination of encephalitis. It allows earlier detection and treatment of inflammatory processes. MRI also provides valuable information for patient follow-up. However, in practical terms many patients with suspicion of encephalitis often undergo CT scanning before neurological consultation.

A typical MRI protocol consists of routine T1 and T2 spin-echo sequences and a fluid-attenuation inversion recovery (FLAIR) 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 haemorrhage.

New MR imaging techniques are being applied to the study of various brain diseases. These technologies

include procedures that can increase sensitivity to small, yet clinically relevant lesions, these techniques may be useful for imaging protocols of patients with suspicion of encephalitis:

(i) Diffusion-weighted MRI (DWI) enables separation of cytotoxic from vasogenic oedema and distinguishes recent from old insult, which can often be difficult on routine T2 and FLAIR imaging.

(ii) Low magnetization transfer ratio (MTR) reflects myelin damage, cell destruction or changes in water content.

(iii) Magnetic resonance spectroscopy (MRS) identifies and quantifies concentration of various brain metabolites. Spectroscopy is capable of differentiating normal from pathological brain and provides tissue specificity greater than that of imaging instances.

(iv) Functional MRI (fMRI) uses very rapid scanning techniques that in theory can demonstrate alterations in blood oxygenation.

CT

CT is recommended only as a screening examination with subtle clinical suspicion of encephalitis or when MRI is unavailable (Dun *et al.*, 1986; Schroth *et al.*, 1987; Marchbank *et al.*, 2000, class IV).

SPECT

SPECT is more readily available than PET and has been utilized in the study and diagnosis of encephalitis (Launes *et al.*, 1988). It can provide information about brain chemistry, cerebral neurotransmitters and brain function. It can also demonstrate hypoperfused tissue that seems normal on structural imaging.

PET

Although the gold standard in acquiring functional imaging data, remains a complex, costly and not readily available technique.

In summary, structural information is provided by CT scan and MRI while functional and metabolic data are provided by MRS, fMRI, SPECT and PET.

Imaging of specific disorders

Herpes simplex encephalitis. CT obtained early is often normal or subtly abnormal. Low attenuation, mild mass effect in temporal lobes and insula, haemorrhage and enhancement are late features. Follow-up scans 1–2 weeks after disease onset demonstrate progressively more widespread abnormalities with the involvement of contra lateral temporal lobe, insula and cingulate gyri. Contrast enhancement and changes of subacute haemorrhage may become readily apparent. MRI is much more sensitive in detecting early changes (Schroth *et al.*, 1987; Marchbank *et al.*, 2000; Chaudhuri and Kennedy,

2002, class IIIC). Involvement of cingulate gyrus and contra lateral temporal lobe is highly suggestive of herpes encephalitis. Typical early findings include gyral oedema on T1-weighted (T1WI) imaging and high signal intensity in the temporal lobe or cingulate gyrus on T2WI, FLAIR and DWI and later haemorrhage. Hypointense on T1, hyperintense on T2WI, FLAIR, high signal on DWI are additional findings (Ito *et al.*, 1999; Tsuchiya *et al.*, 1999). In acute lesions, MRS reveals metabolic changes in relation to neuronal death such as a decrease of N-acetyl aspartate (NAA) signal. Resultant gliosis is reflected as an increase in inositol and creatine resonances. The reinstatement of a normal spectrum over time could then potentially be used as a marker of treatment efficacy (Menon *et al.*, 1990; Salvan *et al.*, 1999).

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 (Hinson and Tyor, 2001).

HIV-1. CT 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. Later, with cognitive dysfunction, further reductions in NAA and increases in Cho levels may be seen (Rudkin and Arnold, 1999). In the later stages of AIDS, the most common diseases affecting the brain parenchyma are secondary to opportunistic infection or malignancy and are predominantly focal. Neuroimaging is an important diagnostic tool for opportunistic infections. Toxoplasmosis (ring enhancing mass(es) in basal ganglia), cryptococcosis (gelatinous 'pseudocysts'), meningoenophalitis, vasculitis, infarction, cytomegalovirus (CMV)-encephalitis (diffuse white matter hyperintensities), ventriculitis (ependymal enhancement), progressive multifocal leucoencephalopathy (PML, white matter hyperintensities which usually do not enhance), lymphoma (solitary or multifocal solid or ring-enhancing lesions either in deep grey and white matter or less frequent in subcortical areas) (Thurnher *et al.*, 2001; Yin *et al.*, 2001). MRS may be able to distinguish between these different space-occupying lesions based on their chemical profiles. 1H-magnetic resonance spectroscopy can serve to monitor the efficacy of antiretroviral therapy and may even be used to predict the responsiveness to drug therapy (Wilkinson *et al.*, 1997).

VZV. CNS complications of VZV infection (usually caused by reactivation) include myelitis, encephalitis, large- and small-vessel arteritis, ventriculitis, and

meningitis (Gilden *et al.*, 2000). Large vessel arteritis presents with ischemic/haemorrhagic infarctions and MRI supported by angiography usually reveals these complications (Gilden *et al.*, 2000; Redington and Tyler, 2002).

Miscellaneous viral infections. In *polio* and *coxsackie* virus infections, T2-weighted MRI may show hyperintensities in the midbrain and anterior horn of spinal cord (Shen *et al.*, 2000). In *EBV* infection hyperintensities in the basal ganglia and thalami may be observed on T2-weighted MRI (Shian and Chi, 1996). *West Nile virus* (WNV) can be associated with enhancement of leptomeninges, the periventricular areas, or both, on MRI (Sejvar *et al.*, 2003). T2-weighted MRI of *Japanese encephalitis* can show hyperintensities in bilateral thalami, brainstem and cerebellum.

ADEM. Initial CT may show low density, flocculent, 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 grey matter. They do not usually involve the callosal interface. Contrast-enhanced T1-weighted images may show ring-enhancing lesions. Cranial nerves may enhance. DWI is variable. On MRS, NAA is transiently low and choline is normal (Schroth *et al.*, 1987; Dale *et al.*, 2000; Bizzi *et al.*, 2001).

PML. MRI is also the most sensitive imaging tool for *PML* (Berger and Major, 1999). T2-weighted sequences initially show multiple, bilateral, non-enhancing, oval or round subcortical white matter hyperintensities in the parietooccipital area. Confluent white matter disease with cavitory 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 (RE) typically involves only one cerebral hemisphere, which becomes atrophic. The earliest CT and MRI abnormalities include high signal on T2-weighted MR images in cortex and white matter, cortical atrophy that usually involves 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-99m hexamethylpropylamine 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 (Chiapparini *et al.*, 2003).

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. T2-weighted turbo spin-echo images fail to show changes (Thuerl *et al.*, 2003).

Virological tests in encephalitis

General

The gold standard of diagnosis in encephalitis is virus isolation in cell culture, now to be replaced by the detection of specific nucleic acid from CSF or brain (Rowley *et al.*, 1990; Echevarria *et al.*, 1994; Lakeman and Whitley, 1995; Tebas *et al.*, 1998, class Ia). Intrathecal antibody production to a specific virus is similarly a strong evidence for aetiology (Levine *et al.*, 1978; Koskiniemi *et al.*, 2002, class Ib). Virus detection from throat, stool, urine or blood as well as systemic serological responses like seroconversion or a specific IgM provides less strong evidence (Burke *et al.*, 1985; Koskiniemi *et al.*, 2001, class III). The CSF is a convenient specimen and is recommended for neurological viral diagnosis in general (Cinque and Linde, 2003). Brain biopsy is invasive and not used in routine clinical practice. At autopsy brain material will 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 infection but only seldom, in < 5%, in other cases (Muir and van Loon, 1997; Storch, 2000, class III). As brain biopsy is reserved only for unusual and diagnostically difficult cases, viral cultures are only rarely available from brain tissues

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 herpesvirus 6 and 7, CMV, EBV, enteroviruses and respiratory viruses as well as for 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 as well as *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* can also be detected from throat samples and enterovirus nucleic acid from stool samples. However, these cannot confirm the aetiology of encephalitis. PCR for *C. pneumoniae* can also be performed from a CSF sample. Detection of specific nucleic acid from the CSF depends on the timing of 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 (Lakeman and Whitley, 1995; Koskiniemi *et al.*, 2002, class I). In herpes simplex encephalitis (HSE) the sensitivity is 96% and the specificity 99% when CSF is studied between 48 h and 10 days from the onset of symptoms (Lakeman and Whitley, 1995; Tebas *et al.*, 1998).

Instead of the single PCR tests, the multiplex PCR are gaining ground in diagnostics (Tenorio *et al.*, 1993; Pozo and Tenorio, 1999). The sensitivity has been improved and it approaches that of the single PCR and the specificities are equal. Real-time PCR makes it possible to get the result in a shorter time while observing the yield cycle by cycle (Kessler *et al.*, 2000). The usage of microarrays for detection of viral nucleic acid is still expensive, but has the potential to become a regular diagnostic technique. Several microbes can be studied at the same time and identification of the genotype will be easier than using the current conventional methods.

Serological tests

Antibodies to HSV-1, HSV-2, VZV, CMV, HHV-6, HHV-7, CMV, EBV, respiratory syncytial virus (RSV), HIV, adeno, influenza A and B, rota, coxsackie B5, non-typed entero and parainfluenza 1 viruses as well as *Mycoplasma pneumoniae* are measured from serum and CSF by using enzyme immunoassay (EIA) tests and antibodies for *Chlamydia pneumoniae* by microimmunofluorescence test (MIF) (MacCallum *et al.*, 1974; Levine *et al.*, 1978; Julkunen *et al.*, 1984; Socan *et al.*, 1994; Koskiniemi *et al.*, 1996; Gildea *et al.*, 1998; Koskiniemi *et al.*, 2001, class II). These tests are sensitive enough to detect even low amounts of antibodies from the CSF. The antibody levels in serum and CSF are compared with each other in the same dilution of 1:200. If the ratio of antibody levels is ≤ 20 , it indicates intrathecal antibody production within the brain provided that no other antibodies are present in the CSF, i.e. the blood-brain barrier (BBB) is not damaged. The presence of several antibodies in the CSF suggests BBB breakdown, while the presence of specific IgM in the CSF indicates CNS disease (Burke *et al.*, 1985). The

tests for measles, mumps and rubella are only occasionally needed in countries with effective vaccination programmes. Tests for arboviruses and zoonoses will be useful in endemic areas (Burke *et al.*, 1985; Wahlberg *et al.*, 1989).

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 aetiology for encephalitis. In spite of 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 of diagnostic procedure. Tests should include: PCR (single, multiplex or microarray) test for nucleic acid detection (from CSF) and serological tests for antibodies (from CSF and serum samples). 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 immunological response by the host, and the stage of the infection. The aetiological spectrum is strongly influenced by geography. It should also be noted that primary encephalitic processes may secondarily involve the meninges as well, 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/myelorradiculitis of HIV patients.

The histopathological basis of encephalitis is the triad of damage to the parenchyma (usually nerve cell damage or loss, eventually demyelination), reactive gliosis and inflammatory cellular infiltration (by haematogenous elements in the immunocompetent host) (Budka, 1997).

This classical substrate is exemplified by (multi)nodular encephalitis, as in the majority of viral encephalitis 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) (Budka, 1997).

Distribution and spread of these inflammatory changes are important for aetiological considerations: six types of encephalitis may be distinguished, either focal or diffuse affecting either the grey matter, the white matter, or both (Love and Wiley, 2002). 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), leucoencephalitis (e.g. in PML or HIV leucoencephalopathy), and panencephalitis (e.g. in bacterial septicaemia with micro-abscesses, in Whipple's disease, SSPE, HIV encephalitis, and herpesviruses such as HSV, CMV and VZV infection). Abscesses and granulomas may be randomly distributed in the brain. 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 (Budka, 1997). However, immunosuppression and the effects of potent therapies have become notorious for being able to modify, blur or even wipe out the classical features of specific viral lesions.

The role of special techniques: immunocytochemistry, *in situ* hybridization, PCR

Arguably, it is in the field of infections where the techniques of immunocytochemistry (ICC), *in situ* hybridization (ISH) and PCR have the most profound impact on neuropathological diagnosis. When performed appropriately with adequate controls and adequate tissue selection, they provide an aetiological diagnosis with high sensitivity and specificity (Budka, 1997; Johnson, 1998). Nevertheless, there are *caveats* for situations in which they may not be diagnostic:

(i) Production of the infectious agent may have burnt out, or its products may have become masked, resulting in negative ICC or ISH.

(ii) Tissue preservation might be unsuitable for these techniques, e.g. ICC or ISH may be falsely negative on overfixed tissue, or nucleic acid amplification from

paraffin-embedded tissue by PCR may be blocked by yet unidentified factors.

(iii) As PCR and ISH are very sensitive techniques, positive results may just reflect the presence of genomic information resulting from dormant or latent, and not necessarily productive and pathogenic infection.

Therefore, prerequisites for the use of ICC, ISH or PCR for neuropathological diagnosis of infections include simultaneous use of known positive and negative control tissues which were 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 highest sensitivity and sensitivity (optimal signal to noise ratio) in the respective laboratory and experience with immunocytochemical antigen retrieval techniques such as enzyme digestion, microwave treatment or autoclaving (Budka, 1997).

Viruses may exert damage to the nervous system not only by productive virus infection of the nervous system, but by indirect means as well. The best example is the immune-mediated *ADEM* or *post-infectious/perivenous encephalitis* as a sequel of exanthematous viral disease of childhood (e.g. measles, varicella, rubella, mumps, influenza). This is very important for differential 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 (Budka, 1997).

Other infective causes of meningoencephalitis and differential diagnosis

Clinical distinction between viral encephalitis and non-viral infective meningoencephalitis is difficult, often 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 acute bacterial meningitis, meningeal symptoms of intense headache, photophobia and vomiting appear early and are usually more severe than the encephalopathic features. Presence of multiple cranial neuropathies is also suggestive of a primary meningeal process. History of continued fever and a subacute onset of symptoms with progressive obtundation and/or features of raised intracranial pressure are more typical of suppurative intracranial infections such as brain abscess. Tuberculous meningitis (TBM) also presents similarly, and in children, symptoms of TBM are often subacute in onset. In a non-epidemic setting, the most common cause of focal encephalopathic findings is HSE; however, among cases

with biopsy-proven herpes encephalitis, there were no distinguishing clinical characteristics between patients positive for HSV and those who were negative (Whitley and Gnann, 2002).

ADEM

ADEM, an autoimmune disease, with evidence of cell-mediated immunity to the myelin basic protein as its pathogenic basis (Behan *et al.*, 1968), is characterized by focal neurological signs and a rapidly progressive course in a usually afebrile patient, usually with a history of febrile illness or immunization preceding the neurological syndrome by days or weeks (post-infectious or post-vaccinal encephalomyelitis). 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. ADEM classically presents as a monophasic illness developing after certain viral infections or immunizations (post-infective and post-vaccinal ADEM). In the prodromal phase, patients experience migrainous-type headache with meningism. The disturbances of consciousness range from stupor and confusion to coma. There is usually preservation of the abdominal reflexes and 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 (Chaudhuri and Behan, 2003).

CNS vasculitis

CNS 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 serological and immunological tests and angiographic appearances of CNS vasculitis. In isolated angiitis diagnosis may be more challenging and even require brain and meningeal biopsy to secure the diagnosis where diagnostic uncertainties persist.

Pseudomigraine with pleocytosis

Acute confusion, psychosis and focal neurological deficit (hemiplegia, hemianaesthesia and aphasia) in

association with migraine headache occur in familial hemiplegic migraine (Feely *et al.*, 1982). Sterile CSF pleocytosis (pseudomigraine) has been reported in migraine patients who may present similarly (Schraeder and Burns, 1980). It has been proposed that the CSF pleocytosis in some of these cases is due to recurrent predisposition to viral meningitis (Casteels-van Daele *et al.*, 1981). Pseudomigraine with pleocytosis and migraine coma are likely to represent reversible forms of ADEM (Chaudhuri and Behan, 2003).

Therapy

Anti-viral therapy

In two randomized controlled trials, acyclovir (10 mg/kg every 8 h given intravenously for 10 days) was found to be more effective than vidarabine (15 mg/kg/day) in improving survival rates of adult patients with biopsy-proven HSE (Skoldenberg *et al.*, 1984; Whitley *et al.*, 1986). Acyclovir is a safe treatment and given the higher risk associated with diagnostic brain biopsy, it has become an established practice that treatment for viral encephalitis is commenced on suspicion before a specific aetiological diagnosis is possible (Chaudhuri and Kennedy, 2002). When given early in the clinical course of HSE before the patient becomes comatose, acyclovir reduces both mortality and morbidity in treated patients. Acyclovir is also the treatment of choice for neonatal HSE; however, there is no definitive evidence from trials that it is more effective than vidarabine. Acyclovir has a relatively short half-life in plasma and is usually given intravenously 10 mg/kg every 8 h in adults (total daily dose 30 mg/kg). The daily dose of acyclovir for neonatal HSE is 60 mg/kg (double the adult dose). As more than 80% of acyclovir in circulation is excreted unchanged in urine, renal impairment can rapidly precipitate acyclovir toxicity and therapeutic doses should be adjusted according to the renal clearance. Rare relapses of HSE have been reported after weeks to 3 months later when the duration of acyclovir treatment was 10 days or less (Davis, 2000). With conventional therapy, relapses of HSE may be higher than expected (5%) but do not occur if higher doses were administered for 21 days (Ito *et al.*, 2000). Although there have been no randomized trials, an accepted policy in clinical practice is to give acyclovir treatment for CSF PCR-positive HSE for 14 days in immunocompetent adult patients and 21 days for immunosuppressed patients. Use of vidarabine for HSE is limited to the unlikely and rare patients who cannot receive acyclovir because of side-effects.

Besides HSV, acyclovir is also effective against VZV and the doses and duration of therapy for VZV

encephalitis are similar to HSE (GPP). In CMV encephalitis, combination therapy with ganciclovir (5 mg/kg intravenously twice daily) with foscarnet (60 mg/kg every 8 h or 90 mg/kg every 12 h) is currently advised (GPP). Acyclovir is ineffective in CMV encephalitis. Antiretroviral therapy must be added or continued in HIV infected patients (Portegies *et al.*, 2004).

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 (Whitley and Gnann, 2002) that patients should be treated with intravenous acyclovir or ganciclovir.

Newer antivirals like valciclovir appear promising in HSV and VZV encephalitis but remain to be evaluated by formal trials (Biran and Steiner, 2002). Pleconaril is a new 'broad spectrum' antiviral with potential for use in enteroviral encephalitis and is undergoing clinical evaluation (Pevear *et al.*, 1999).

Corticosteroids

Large doses of corticosteroids (dexamethasone) as an adjunct treatment for acute viral encephalitis are not generally considered to be effective and their use is controversial. Probably the best evidence for steroid therapy is in VZV encephalitis. Primary VZV infection may cause severe encephalitis in immunocompetent children due to cerebral vasculitis (Hausler *et al.*, 2002). Vasculitis following primary and secondary VZV infection is recognized to lead to a chronic course in immunocompetent children and adults (granulomatous angiitis). HSE is occasionally complicated by severe, vasogenic cerebral oedema with CT or MRI evidence of midline shift 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 (Nakano *et al.*, 2003).

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 oedema 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) in order to minimize adverse effects (e.g. gastrointestinal haemorrhage, secondary fever and infections).

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 (Cohen *et al.*, 2001, class IV and GPP).

Surgical intervention

Surgical decompression for acute viral encephalitis is indicated for impending uncal herniation or increased intracranial pressure refractory to medical management (steroids and mannitol, GPP). Such intervention has been shown to improve outcome in HSE in individual cases (Yan, 2002).

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 aetiology, supportive therapy for acute viral encephalitis is an important cornerstone of management (Chaudhuri and Kennedy, 2002). Seizures are controlled with intravenous phenytoin. Careful attention must be paid to the maintenance of respiration, cardiac rhythm, fluid balance, prevention of deep vein thrombosis, 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 for patients with community acquired acute infective encephalitis is not required. Consideration of isolation should be given for severely immunosuppressed patients, rabies encephalitis, patients with an exanthematous encephalitis and those with a contagious viral haemorrhagic fever.

Rehabilitation

Survivors of viral encephalitis and myelitis are a heterogeneous group. Nature of the infective pathogen, variability in anatomic lesions and time to treatment contribute to outcome. Longitudinally designed case studies, reporting cognitive and psychosocial outcome following mainly herpes simplex virus encephalitis were conducted prior to current era of early diagnosis and effective therapy. While there are anecdotal case reports (Wilson *et al.*, 2001; Miotto, 2002, and others) there are too few studies on the outcome of rehabilitation following encephalitis (Moorthi *et al.*, 1999) to enable to draw any conclusions.

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 travellers to specific geographical destinations (e.g. Southeast 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, suggests 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:

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 and 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 and 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	
Surgical decompression	IV	

These guidelines will be updated when necessary and in any case in not more than 3 years.

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