Arch Public Health
1999, 57, 251-262

Viral infections of the central nervous system: epidemiological and clinical aspects

by

Cras P [1]

Abstract

Viral encephalitis is a rare but potentially devastating disease characterised by fever, headache, impaired consciousness and focal neurological signs. Herpes simplex 1 encephalitis (HSV-1) is the most common type of viral encephalitis in Belgium. HSV-1 encephalitis occurs with a worldwide incidence of 0.2 to 0.5/100 000 persons per year without any seasonal variation. It occurs in patients of all ages, although about one third of patients are younger than 20 and about one half are older than 50. Both sexes are affected equally. If left untreated, the disease carries a high mortality of about 70%, with many of the survivors showing serious neurological sequelae. Encephalitis caused by other herpes viridae such as varicella zoster, cytomegalovirus, Epstein-Barr virus, B virus is much less common and tends to occur in particular conditions such as immunosuppression. Arthropod born encephalitis (Togaviridae, Bunyaviridae, Reoviridae) such as Eastern and Western equine encephalitis, Japanese encephalitis, Colorado-tick fever and other forms of encephalitis almost do not occur in Western Europe. Encephalitis caused by mumps virus, rabies, human immunodeficiency virus encephalitis, slow viral infections and rabies are only mentioned here for

---

[1] University Hospital of Antwerp, Born Bunge Foundation, University of Antwerp, Edegem.

the sake of completeness. When facing a patient suffering from encephalitis, Mycoplasma pneumoniae should be considered in the differential diagnosis.

Key words

Herpes simplex encephalitis, epilepsy, acyclovir.

Introduction

Although the list of viruses that could potentially cause infections of the central nervous system (CNS) is very long, viral encephalitis is a rare neurological disease. In practice, most viral infections of the CNS are complications of systemic illnesses caused by common human pathogens.

Acute viral infections of the CNS can be divided into three major categories or localizations: viral (aseptic) meningitis, encephalitis and myelitis (1,2).

Viral meningitis is usually a self-limiting illness characterised by headache, photophobia and neck stiffness. Probably, viral meningitis is underdiagnosed and is recognised as a flu-like syndrome that is symptomatically treated and for which the patient is not hospitalised.

Encephalitis is an acute inflammatory process that affects brain tissue and is almost always accompanied by inflammation of the adjacent meninges (3). The disease is most commonly caused by viral infection. Encephalitis resulting from viral infection manifests as either acute viral encephalitis or post-infectious encephalomyelitis. Acute viral encephalitis is caused by direct viral infection of neural cells with associated perivascular inflammation and destruction of grey matter. Post-infectious encephalomyelitis follows infection with various viral or bacterial agents; the primary pathologic finding is demyelination of white matter.

In the United States, the annual incidence of encephalitis is about 1 in 200 000 children, the elderly, and immunocompromised persons are most commonly affected. Acute encephalitis is more common in the first year of life; in contrast, post-infectious encephalomyelitis is rare in infancy. According to the Centres for Disease Control and Prevention (CDC), 717 cases of primary infectious encephalitis and 143 cases of post-

infectious encephalomyelitis were reported in 1994; these numbers likely underestimate the true incidence of disease. In the USA, encephalitis was deleted from the list of nationally notifiable diseases in 1995.

The cardinal manifestations of viral encephalitis are four: fever, headache, behavioural changes with eventually alterations of mental status and focal neurological signs. Therefore, when questioning the patient and his family, due attention has to be paid to the mode of onset and time course of the disease. Any prodromal symptoms and predisposing factors such as immunosuppression should be noted. An acute encephalopathic syndrome often co-exists with meningitis and is therefore often accompanied by early mental changes and epilepsy.

By far the most common types of encephalitis and clinically the most relevant are caused by the group of herpes viruses: herpes simplex virus, varicella zoster virus, cytomegalovirus, much rarer by Epstein-Barr virus.

I will briefly review some of the more uncommon types of encephalitis and then elaborate more on the herpes viruses. Poliomyelitis is an acute generalised disease characterised by the destruction of anterior horn motor neurons, causing paralysis and muscular atrophy. It used to be the most frequent viral infection of the CNS, but since the advent of an effective vaccine, poliomyelitis has become very rare. Coxsackievirus of the B group can cause acute cerebellar ataxia and more seldom a more widespread type of encephalitis. Echo- and enteroviruses can cause a rare form of encephalitis, usually with cerebellar ataxia, in children and under some circumstances cause persistent infection resulting in a dermatomyositis-like syndrome (4). Three different types of equine encephalomyelitis have been described in the USA. The Eastern type causes more severe clinical symptoms than the Western and Venezuelan types. St Louis type encephalitis is the most common type of arthropod born encephalitis (5). California encephalitis is caused by the La Crosse virus classified among the bunyaviruses and usually results in a mild form of viral meningitis not necessarily associated with encephalitis (6). Japanese encephalitis is rare, even in Asiatic countries, is transmitted by a mosquito-born flavivirus and is said to cause a high mortality in children. Rabies is an acute viral encephalitis that is transmitted to humans through the bite of a diseased (rabid) animal, usually a dog, wolf, fox or squirrel. It has become a clinical rarity through the control rabid animals. The onset is characterised by numbness or pain in the region of the bite, accompanied by apathy or lethargy, then rapidly changing into a state of excitability and convulsions. A profuse flow of

saliva occurs and the patient refuses to accept any liquids (hydrophobia). The disease is almost always fatal. Measles virus causes a wide array of CNS involvement with encephalitis usually occurring as a post-infectious syndrome which is self-limiting. Mumps usually causes a mild meningitis or encephalomyelitis with possible peripheral involvement. Neurological complications are 3 times more frequent in boys than in girls. Deafness is the most frequent neurological complication caused by mumps virus. Influenza is very rarely a cause of viral encephalitis (7). HIV can cause a chronic encephalitis resulting in subcortical dementia. Several other diseases have been classified with viral or slow viral encephalitis, but stand apart as a special category: progressive multifocal leucoencephalopathy, subacute sclerosing panencephalitis and Creutzfeldt-Jakob disease. These diseases will not be discussed further and the reader is referred to reviews on the subject mentioned in the list of references. Acute disseminated encephalomyelitis is an auto-immune disease that is indirectly caused by a viral infection not necessarily invading the CNS.

For the purpose of conciseness, we will limit this review to encephalitis caused by herpes viridae.

Herpes simplex encephalitis

Epidemiology

Herpes simplex encephalitis may result from reactivation of latent HSV in the trigeminal ganglion or from primary infection. Two different types of herpes simplex virus exist: type 2 is responsible for neonatal herpes which is rarely complicated by encephalitis. Encephalitis in adults is mostly caused by herpes simplex virus type 1.

Humans are the sole reservoir for herpes simplex virus and exposure to the virus is so common that 95% of children are seropositive at age 15. A study of university students has shown seroconversion rates of 5-10% per year. There is no seasonal variation of the infection with symptoms that can range from mild and barely discernible to life threatening but are rarely fatal. Children that are infected at an age less than 5 will typically show oropharyngeal symptoms such as gingivostomatitis and sometimes a mononucleosis-like picture.

Herpes simplex encephalitis (HSE) occurs with an incidence of 1:250 000 to 1:500 000 per year which should result in 20-40 cases per year

in Belgium (2). In the USA herpes simplex encephalitis constitutes about 10-20% of all types of viral encephalitis, but in Belgium this ratio must be higher due to the absence of arthropod born types of encephalitis. Both sexes are affected equally and the disease occurs at all ages with one third occurring in patients under age 20 and one half in patients older than 50.

Clinical aspects

Most patients present with a focal encephalopathic process involving altered consciousness, with focal neurological signs, CSF pleocytosis (about 100/mm^3) and increased protein (mean of 100 mg%), absence of bacterial and fungal pathogens, focal encephalographic, CT or MRI changes (8). Seizures occur in only 2/3 of patients. The presence of red blood cells in the CSF is not diagnostic for HSE (table 1).

TABLE 1
Most frequent symptoms and signs

Symptom	%
Historical findings	
Alteration of consciousness	97
CSF pleocytosis	97
Fever	90
Headache\personality change\seizures	67
Vomiting	46
Hemiparesis	33
Memory loss	24
Clinical findings at presentation	
Fever	92
Personality change\dysphasia	76
Autonomic dysfunction	80
Ataxia	40
Hemiparesis	38
Seizures	38
Cranial nerve deficit	32
Visual field loss\papilledema	14

Complications of severe encephalitis include seizures, increased intracranial pressure, and respiratory decompensation. Patients should be monitored closely in facilities with appropriate resources for management of these serious adverse events. Inappropriate secretion of antidiuretic hormone is common; therefore, frequent monitoring of electrolyte concentrations is indicated.

HSV-2 encephalitis occurs primarily in neonates. Neonatal infection is acquired perinatally, and symptoms (e.g. fever, lethargy, irritability, seizures) appear within the first month of life. Neonatal HSV encephalitis is a diffuse process, and generalised encephalomalacia may result. Despite therapy with intravenous acyclovir (Zovirax), the majority of surviving infants have substantial neurological sequelae.

Diagnosis

Characteristic findings on the EEG are spike and slow wave activity and periodic lateralised epileptic discharges arising from the temporal lobe. The sensitivity of EEG amounts to about 84%, but the specificity is only 33%. Characteristic findings are periodic lateralised epileptiform discharges (PLED) that usually start out on one side and after 7-10 days become bilateral.

HSE predominantly affects the limbic system and therefore the earliest changes occur in the temporal lobe and cingulate gyri. CT scans are often normal early in the disease, while MRI can show gyral edema, hyperintense regions on T2 weighted images of the temporal lobes, with haemorrhages being a late phenomenon.

Undoubtedly the most sensitive and specific method remains the isolation of HSV from a brain biopsy. Serological exams are not clinically useful but CSF antibody exams show a four-fold rise of antibody titer after one month in 85% of patients. This lab exam is therefore only useful retrospectively. Recently, PCR has been applied for detection of herpes simplex genome in CSF (9).

Differential diagnosis

Other neurological syndromes that can cause mental changes in association with focal neurological deficits should be taken into consideration.

The differential diagnosis can be divided into treatable and non-treatable diseases such as cerebral abscess, opportunistic infectious, lupus, ALD, vascular disease, toxic encephalopathy, other viral infections, PML, subacute sclerosing panencephalitis, SSPE (table 2, table 3).

TABLE 2
Nonviral and noninfectious causes of encephalitis

Bacterial	**Protozoal**
Bartonella henselae	*Naegleria fowleri*
Bartonella quintana	*Acanthamoeba* species
Borrelia burgdorferi	*Cysticercosis*
Brucella species	*Echinococcus* species
Leptospira interrogans	*Plasmodium falciparum*
Listeria monocytogenes	*Trypanosoma* species
Mycobacterium tuberculosis	
Mycoplasma pneumoniae	**Fungal**
Rickettsia rickettsii	Blastomycosis
Treponema pallidum	Coccidioidomycosis
Brain abscess or subdural empyema	Cryptococcosis
Partially treated bacterial meningitis	Histoplasmosis
	Noninfectious
	Central nervous system haemorrhage
	Collagen vascular disease
	Exposure to certain toxins or drugs
	Inborn errors of metabolism
	Malignant disease

TABLE 3
Infectious causes of encephalitis in immunocompromised patients

Viral	**Protozoal**
Enterovirus	Amebic meningoencephalitis
Cytomegalovirus	Toxoplasmosis
Human herpesvirus 6	
Herpes simplex virus types 1 and 2	**Fungal**
JC virus	*Cryptococcus neoformans*
Measles	Coccidioidomycosis
Rubella	Blastomycosis
Varicella	Histoplasmosis
	Aspergillus species
	Candida species

Treatment

If left untreated, herpes simplex encephalitis is associated with a high mortality of about 70%.

Until a bacterial cause of CNS inflammation is excluded, parenteral antibiotics should be given. Treatment with a third-generation cephalosporin, such as cefotaxime sodium (Claforan) or ceftriaxone sodium (Rocephin), is recommended. Vancomycin (Vancocin) should be

added in geographic areas where strains of *S. pneumoniae* resistant to penicillin and cephalosporins have been reported.

The NIAID study with acyclovir showed reduction of mortality to 19% after 6 months. In this study the isolation of HSV from brain biopsy was required. Acyclovir is given 10 mg/kg every 8 hrs for 10-21 days. Relapse is possible but rare after treatment with acyclovir and other antivirals.

Prognostic factors include: age and consciousness at diagnosis with patients with a Glasgow Coma Scale (GCS) of > 10 and treatment showing the best prognosis and survival of > 90%, while GCS < 6 results in a survival of only 30%. A score of less than 6 on the Glasgow Coma Scale, age greater than 30 years, and presence of encephalitis for more than 4 days before initiation of therapy are predictive of severe sequelae or death. Most survivors of HSV encephalitis have neurological sequelae ranging from impaired new learning to severe motor and sensory deficits, aphasia, and amnestic syndrome. Encephalitis may recur despite appropriate antiviral therapy.

Varicella zoster virus

Epidemiology

Varicella zoster virus (VZV) infection is a highly contagious disease that is usually clinically expressed as chickenpox. The incidence of CNS complications with varicella is unknown but estimates vary from 0.1% to 0.75% (10). The most common complication is cerebellar ataxia with about 1:4000 cases, with acute meningo-encephalitis being very rare.

Clinical aspects

Acute meningo-encephalitis in the context of varicella is characterised by nausea, vomiting, headache, nuchal rigidity, usually moderate fever, seizures being rare. The CSF is usually normal and the EEG shows diffuse slowing.

Treatment

The disease is mostly self limiting and symptoms resolve in a few weeks, while mortality is low (0-5%).

Cytomegalovirus encephalitis

Definition

Cytomegalovirus (CMV) is an agent with high species specificity that only causes infection in humans. Infections occur in two circumstances: in newborns as cytomegalic inclusion disease and in immunocompromised patients (11). Cytomegalic inclusion disease is an infection that occurs in utero by transplacental transmission. The infection results in the appearance of large swollen cells that often contain large eosinophilic intranuclear and cytoplasmic inclusions. Intrauterine infection often results in premature birth or stillbirth. The CNS, lungs, kidneys and liver are affected. CMV infections also occur in adults, usually resulting in a mononucleosis-like syndrome and involvement of the CNS is uncommon. When encephalitis occurs, it is usually in the context of immunosuppression. Even in immunosuppressed patients, encephalitis can be subclinical and is rarely fatal.

Epidemiology

Most people are sooner or later infected by CMV and transmission has been described by many different mechanisms: sexual activity, contact with saliva, other types of close contact, blood transfusion, organ transplantation and as already mentioned transplacental infection. Viral shedding also occurs through urine and the virus has been detected in semen, breast milk and cervical secretions. Of all normal adults, 2% are shedding the virus, while this proportion is much higher in healthy gay men, where it amounts to 14%. A habitat in very crowded areas seems to contribute to the rate of infection. By the age of 1 year, 60% of infants have antibodies to CMV. About 1% of infections occur congenitally and about 10% of these newborn have neurological symptoms.

Clinical aspects

The congenital infection with neurological symptoms is a separate entity and will not further be dealt with here. In immunocompromised adults, CMV causes pneumonia, chorioretinitis, colitis, oesophagitis and gastritis. In normal adults, an encephalopathic picture may result, but in the immunocompromised patient, the clinical picture may be more severe. A problem that often arises is the distinction between the effect of HIV infection on the brain and that of CMV encephalitis.

Diagnosis

The diagnosis can be made by identification of the virus with the shell vial technique and more recently with PCR. CMV can be recovered from urine, saliva or liver biopsy specimens.

Treatment

The treatment of encephalitis consists of ganciclovir or foscarnet (12). Foscarnet (Foscavir®) is administered continuously or intermittently at 20 mg/kg initially, followed by a dose adjusted to creatinine clearance and continued for 7 days. Foscarnet causes renal insufficiency, which is related to the duration of therapy and can be prevented by adequate hydration. Convulsions can be caused either directly by foscarnet or by concomitant hypocalcemia. Local irritation at the infusion site has also been described.

Samenvatting

Virale encefalitis is een zeldzame maar potentieel vernietigende ziekte die koorts, hoofdpijn, afwisselend bewustzijn en focale neurologische aanwijzingen tot gevolg heeft. In België is herpes simplex 1 (HSV-1) de meest voorkomende vorm van virale encefalitis. Wereldwijd telt de jaarlijkse incidentie van HSV-1 encefalitis 0,2 à 0,5/100.000 personen. Hierbij kan geen onderscheid worden gemaakt tussen de verschillende seizoenen. De ziekte komt voor in alle leeftijdsgroepen, hoewel nagenoeg eenderde van de gevallen jonger is dan 20 en de helft ouder is dan 50 jaar. Het geslacht van de patiënten maakt geen verschil uit. Indien de ziekte niet wordt behandeld, veroorzaakt zij een hoge mortaliteit; de overlevenden houden er vaak ernstige neurologische letsels aan over. Encefalitis die het gevolg is van andere herpes viridae, zoals varicella zoster, cytomegalovirus, Epstein-Barr virus of B-virus, komt veel minder voor en schijnt alleen in bijzondere omstandigheden, zoals immunosuppressie, op te treden. In West-Europa komt encefalitis (Togaviridae, Bunyaviridae, Reoviridae), overgebracht door antropoden, zoals de Oosterse en Westerse paardenencefalitis, Japanse encefalitis, Coloradoteekkoorts en andere vormen van encefalitis zelden voor. Encefalitis ten gevolge van het bofvirus, rabiës, humane immunodeficiëntie virusencefalitis en langzame virale infecties worden hier alleen vermeld om volledig te zijn. Wanneer de geneesheer wordt geconfronteerd met een patiënt die lijdt aan encefalitis, zou bij de differentiaal diagnose *Mycoplasma pneumoniae* in overweging moeten worden genomen.

Sleutelwoorden

Herpes simplex encefalitis, epilepsie, acyclovir.

Résumé

L'encéphalite virale est une maladie rare mais dévastatrice. De la fièvre, des maux de tête, une conscience changeante et des symptômes neurologiques focaux font partie des symptômes. L'encéphalite due au virus herpès simplex 1 (HSV-1) est le type d'encéphalite virale le plus fréquent en Belgique. L'incidence mondiale de l'encéphalite HSV-1 varie de 1:200 000 à 1:500 000 patients par an, sans variation saisonnière. La maladie s'observe dans tous les groupes d'âge, bien qu'un tiers des cas ait moins de 20 ans et que la moitié des cas a plus de 50 ans. Il n'y a pas de différence entre les sexes. Si la maladie n'est pas traitée, elle entraîne une mortalité dans approximativement 70% des cas. Fréquemment, les survivants souffrent de graves séquelles neurologiques. L'encéphalite causée par d'autres herpès viridae comme le virus varicella zoster, le cytomégalovirus, le virus Epstein-Barr et le virus B est bien moins fréquente et a tendance à se produire dans des circonstances particulières telles que l'immuno-suppression. L'encéphalite d'origine humaine (Togaviridae, Bunyaviridae, Reoviridae) causant l'encéphalite équestre occidentale et orientale, l'encéphalite japonaise, la fièvre de la tique du Colorado et d'autres types d'encéphalite s'observent rarement en Europe occidentale. L'encéphalite causée par le virus des oreillons, la rage, l'encéphalite du virus d'immunodéficience humaine, les infections virales lentes sont seulement mentionnées de façon exhaustive. Lorsque le médecin est confronté à un patient souffrant d'une encéphalite, le pathogène *Mycoplasma pneumoniae* est à prendre en compte lors du diagnostic différentiel.

Mots-clés

Encéphalite à herpes simplex, épilepsie, acyclovir.

References

1. ROWLAND LP, Merritt's Textbook of Neurology. Eight Edition. Philadelphia: Lea and Febiger, 1989.
2. SCHELD WM, WHILEY RJ, DURACK DT. Infections of the Central Nervous System – Raven Press, New York, 1991.
3. GUTIERREZ K, PROBER C. Encephalitis. Identifying the specific cause is key to effective management. Postgrad Med 1998; 103(3): 123-5, 129-30, 140-143.
4. MUIR P, VAN LOON A. Enterovirus infections of the central nervous system. Intervirology 1997; 40(2-3): 153-166.
5. LOWRY P. Arbovirus encephalitis in the United States and Asia. J Lab Clin Med 1997; 129(4): 405-411.
6. MCJUNKIN J, KHAN R, TSAI T. California-La Crosse encephalitis. Infect Dis Clin North Am 1998; 12(1): 83-93.
7. HAYASE Y, TOBITA K. Influenza virus and neurological diseases. Psychiatry Clin Neurosci 1997; 51(4): 181-184.
8. JOHNSON M, VALYI-NAGY T. Expanding the clinicopathologic spectrum of herpes simplex encephalitis [editorial; comment]. Hum Pathol 1998; 29(3): 207-210.

9. LINDE A, KLAPPER P, MONTEYNE P et al. Specific diagnostic methods for herpesvirus infections of the central nervous system: a consensus review by the European Union Concerted Action on Virus Meningitis and Encephalitis. Clin Diagn Virol 1997; 8(2): 83-104.
10. ECHEVARRIA J, CASAS I, MARTINEZ-MARTIN P. Infections of the nervous system caused by varicella-zoster virus: a review. Intervirology 1997; 40(2-3): 72-84.
11. CINQUE P, CLEATOR G, WEBER T et al. Diagnosis and clinical management of neurological disorders caused by cytomegalovirus in AIDS patients. European Union Concerted Action on Virus Meningitis and Encephalitis. J Neurovirol 1998; 4(1): 120-132.
12. ZAKNUN D, ZANGERLE R, KAPELARI K, FISCHER H, SAILER M, MCINTOSH K. Concurrent ganciclovir and foscarnet treatment for cytomegalovirus encephalitis and retinitis in an infant with acquired immunodeficiency syndrome: case report and review. Pediatr Infect Dis J 1997; 16(8): 807-811.