CLINICAL PICTURE

A 40 years old female patient presented clinically with fever, grand male fits, disturbed level of consciousness and meningeal irritation signs.

RADIOLOGICAL FINDINGS

Figure 1. Herpes simplex encephalitis. Precontrast MRI T1 (A,B) and postcontrast MRI T1 (C). Notice the cortical (gray matter) hypointensity involving the temporal lobes bilaterally, more on the right side (A,B). The signal changes are almost exclusively cortical involving the medial (amygdala, hippocampus) and the lateral temporal cortical area and extending posteriorly over the lateral surface of the right temporal lobes. The T1 hypointensity can be seen extending to the subcortical white matter area in the right temporal lobe (B). There is also a central hypointense zone involving the midbrain. In the postcontrast image (C) cortical enhancement is seen over the medial surface of the temporal lobes, more over the left side.
Figure 2. Herpes simplex encephalitis. Postcontrast MRI T1 images. Notice the cortical (gray matter) hypointensity involving the temporal lobes bilaterally, more on the right side (A,B). The signal changes are almost exclusively cortical involving the medial (amygdala, hippocampus) and the lateral temporal cortical area, bilaterally more on the right side. Notice the insular hypointensity on the left side (A).

Figure 3. Herpes simplex encephalitis. MRI T2 images showing involvement of the temporal lobes bilaterally, more on the right side. Both the medial and the lateral surfaces are involved on the right side, while on the left side only the medial surface is involved. The signal changes extend to the subcortical white matter on the right side. The MRI signal changes most probably represent edema.
Figure 4. MRI FLAIR images (A,B) and precontrast MRI T1 image (C). The temporal lobes abnormalities are better visualized on FLAIR images (A). Notice the insular involvement seen as a hyperintense band on The FLAIR image (B) and as a hypointense band on the precontrast T1 image. (C)

Figure 5. Herpes simplex encephalitis. Postcontrast MRI T1 images. Notice the cortical (gray matter) hypointensity involving the temporal lobes bilaterally, more on the right side (A,B). The signal changes are almost exclusively cortical involving the medial (amygdala, hippocampus) and the lateral temporal cortical area, bilaterally more on the right side. Notice the insular hypointensity on the left side (B)
Figure 6. MRI study in a patient suffering from herpes encephalitis, A,B,C MRI T1 precontrast, D,E MRI T2, F,G,H,I are FLAIR MRI images. Notice the T1 hypointensity predominantly involving the bitemporal cortex more on the right side, the insular, the occipital orbital frontal (F) and the cingulate cortex, again more on the right side. The T1 involved zones are hyperintense on the T2 and FLAIR studies. Notice that the encephalitic process is predominately cortical (A,B,C). Temporal lobes involvement is more medially than laterally. The MRI signal changes are predominantly due to vasogenic edema, the signal intensity of edema is different from the CSF in flair studies.
The advent of effective antiviral therapy has focused new attention on the prompt and specific diagnosis of viral infections of the CNS. In general, most acute viral infections are benign and short-lived, and clinically significant CNS disease is an uncommon complication of systemic viral infection. Four distinctive categories of viral encephalitis are recognized: acute viral encephalitis, postinfectious encephalomyelitis, slow virus infections, and chronic degenerative diseases of the CNS of presumed viral origin. Hematogenous spread appears to represent the most common portal of entry. Transient viremia then leads to seeding of distant sites, often including the CNS. Alternatively, viruses can gain entry into the CNS by peripheral, retrograde intraneuronal route, as exemplified by the herpes simplex virus. The major causes of nonepidemic, sporadic acute viral encephalitis in the United States are herpes simplex virus type 1 (HSV-1) in adults and herpes simplex virus type 2 (HSV-2) in neonates. Another example of intraneuronal translation of virus, which is only mentioned to in this article, is rabies, which spreads centripetally from the initial inoculation site and ultimately involves the limbic system, spinal cord, and cerebellum.
Arthropodborne viruses, including St. Louis encephalitis (SLE), western equine encephalitis (WEE), eastern equine encephalitis (EEE), and Venezuelan equine encephalitis (VEE), are common causes of sporadic and epidemic acute encephalitis in the United States. These agents are transmitted by mosquitoes and ticks and show considerable geographic and seasonal variability.

**HERPES ENCEPHALITIS: INTRODUCTION, PATHOLOGY**

Herpes simplex virus infections, ranging from cold sores to severe genital lesions, affect more than 40 million people in the United States. Both the initial episode and recurrent disease can cause devastating problems. However, appropriate treatment can decrease medical and psychosocial consequences in many patients. This article explains the characteristics of herpes simplex infections and outlines treatment options that hold promise for a greatly improved quality of life for many patients.

Herpes simplex virus is a microbe that has afflicted human beings for thousands of years. Descriptions of the condition it causes date back to the time of Hippocrates. Currently, about 600,000 new cases of herpes simplex infection are diagnosed in the United States annually (1). The total number of people affected in this country alone is in excess of 40 million.1,2

Herpes simplex actually belongs to a family of eight related viruses, including herpes simplex virus types 1 (HSV-1) and 2 (HSV-2), varicella-zoster virus, Epstein-Barr virus, and cytomegalovirus. All of these organisms are double-stranded DNA viruses, which permanently infect their target cells.

- **Characteristics of herpes simplex**

A unique aspect of the herpes-virus is its ability to travel up local nerve endings to the dorsal root ganglia, where it remains latent until some factor triggers reactivation. The Greek translation of the word "herpes" aptly describes this tendency of the virus "to creep".3

The latency of the herpesvirus increases its potential for transmission. The ease of its transmissibility is a serious concern, given the significant risk and morbidity of herpes infection. Psychosocial distress, increased risk of HIV infection, and perinatal transmission are all factors that can complicate this painful disease. Appropriate treatment becomes critical to decreasing morbidity.

HSV affects the skin, mucous membranes and, less frequently, the esophagus and brain. Skin infections are usually located in the orolabial, genital, or anorectal areas. Of the two serotypes, HSV-1 infection is primarily oropharyngeal and HSV-2 infection is primarily genital. However, HSV-1 has been found in genital lesions, and HSV-2 has been found in oral lesions. Orofacial herpes affects the trigeminal ganglion, whereas genital herpes involves the sacral ganglion.

Herpes simplex infection generally occurs in two phases: the initial, primary infection, followed by secondary, recurrent disease at the same site. In the first phase, the virus spreads by close person-to-person contact with lesions or mucosal secretions (eg, saliva, cervical discharge) as well as by respiratory droplets. Contrary to previous belief, the virus can be transmitted during asymptomatic periods, although the risk of transmission is higher during symptomatic reactivation.

Once the virus is transmitted, incubation takes from 2 to 10 days. The virus then spreads to regional lymph nodes, causing tender lymphadenopathy. Pain and tenderness, paresthesias, and burning at the inoculation site may follow, accompanied by malaise, fever, and headache. Grouped vesicles appear on an erythematous base and then umbilicate, erode, and form a crust. At this point, the lesions are numerous and more scattered than in recurrent disease.4,5

Recurrent herpes, in contrast, is milder and of shorter duration than the primary infection. A variety of triggers (eg, sunlight, fever, menstruation, stress, local skin trauma) can reactivate the virus. Systemic symptoms and lymphadenopathy are rare. The frequency of recurrence depends not only on the anatomic site but also on the virus type. Genital herpes recurs more often than labial herpes, and HSV-2 infection is more likely to recur than HSV-1.

- **Diagnosis**
Most cases of herpes simplex infection are recognized by the morphologic characteristics of the disease (small, grouped vesicles on erythematous bases, which then become pustules, umbilicate, and later crust). Diagnostic tests are used when vesicles appear in unusual sites and configurations. The Tzanck test is the most commonly used diagnostic tool for detecting a herpes infection. When viewed under the microscope, infected epithelial cells collected from herpetic vesicles demonstrate typical characteristics. Nuclear changes include centrally located eosinophilic masses surrounded by a clear halo (Cowdry type A bodies), and the cells have a perinuclear ground-glass appearance. Infected cells also fuse to become multinucleated giant cells, which are characteristic of herpes infection.

These changes, however, are not unique to herpes simplex. Therefore, the Tzanck test cannot be used to differentiate HSV from varicella-zoster virus. Direct immunofluorescence studies of biopsy specimens from skin, liver, or brain allow more specific detection of the virus. With indirect immunofluorescence, a fourfold rise in IgG titer in paired serum samples is needed to establish a diagnosis of primary herpes. Culture is the most definitive method for detecting herpes infection.

- **HSV-1 infections**

HSV-1 infection is generally referred to as "fever blisters" or "cold sores." About 75% of HSV-1 lesions occur above the waistline. Between 40% and 50% of the US population is infected with HSV-1, and most infections are spread during the initial, subclinical phase.

Recurrent herpes labialis is a common problem, affecting 20% of the adult population in the United States. In HSV-1 recurrence, the prodromal symptoms may last from 2 to 24 hours, and new lesions appear over 1 to 2 days. The vesicles rapidly become pustules, which usually become crusty within 48 hours. Viral shedding occurs over 3 to 5 days. The lesions last 2 to 10 days and heal without scarring.

Neonatal infection may be acquired from the mother's vaginal secretions during the birth process. Transfer can also occur during handling of the infant by family members or other people infected with the virus. Interestingly, the prevalence of the disease in children ranges from 10% to 100% in various populations, and it is seldom observed in babies less than 1 year of age.

Among the many clinical expressions of HSV-1, the easiest to recognize is the typical cold sore or fever blister. However, more serious manifestations may occur, including acute gingivostomatitis, an infection of the mouth and pharynx, usually affecting children between the ages of 1 and 5; an upper respiratory syndrome; eczema herpeticum, also known as Kaposi's varicelliform eruption; keratoconjunctivitis; acute herpetic meningoencephalitis; inoculation herpes; and erythema multiforme.

Eczema herpeticum is seen in patients with preexisting skin disorders, such as atopic dermatitis and Darier's disease. It has also occurred with such diseases as pemphigus, Wiskott-Aldrich syndrome, and chronic dermatitis. The disease develops into widespread cutaneous infection with HSV and resembles impetigo. Onset of symptoms (e.g., fever, chills, malaise) is abrupt, and clusters of umbilicated vesicles appear in areas of abnormal skin. New lesions form over 7 to 10 days and spread widely, coalescing into larger erosions. They may become secondarily infected with staphylococcal or streptococcal organisms. Crusts last 1 to 2 weeks, and lesions heal in 2 to 6 weeks.

Keratoconjunctivitis caused by herpesvirus is the leading cause of infectious blindness in the United States. It initially presents with superficial corneal ulcers, which can be seen on slit-lamp examination. The disease may cause recurrent erosion of the conjunctiva and cornea that progresses to blindness.

Inoculation herpes is an occupational hazard for physicians, dentists, and nurses. One form is herpetic whitlow, or cutaneous herpes simplex of the finger, which is most commonly seen in healthcare professionals, children with gingivostomatitis, and women with genital herpes. Another form is herpetic gladiatorium, or wrestler's herpes, which is a cutaneous or ocular HSV-1 infection transmitted through direct skin-to-skin contact. Erythema, painful vesicles, and erosion are all symptoms in such herpes infections.

One of the major consequences of HSV-1 infection is an allergic response called erythema multiforme. Viral antigens have been detected in lesions that occur with this response. A symmetric rash develops in these patients,
who may be of any age. The rash is most common on the extremities and may recur with each episode. About 15% of the patients have a history of recurrent herpes. Lesions may be macular, papular, or urticarial but are mostly targetoid. The disease generally lasts 2 to 3 weeks, and treatment is usually limited to symptomatic relief with histamine or steroid regimens.

Encephalitis is one of the most life-threatening complications of HSV infection. Without therapy, the mortality rate exceeds 70% and only about 9% of surviving patients return to normal health. The virus is recovered from the cerebrospinal fluid in 25% to 40% of patients, and polymerase chain reaction (PCR) studies are used to diagnose disease in culture-negative patients. The PCR technique is highly accurate, with a sensitivity of 95% and specificity of 94%. A full 98% of patients with herpes encephalitis have positive results on PCR testing within 3 to 18 days after the onset of neurologic symptoms. Herpes simplex encephalitis occurs in immunocompetent patients, but the risk of disseminated disease tends to be increased in immunocompromised patients.

Reactivation of the latent ganglionic infection, which may occur spontaneously or be precipitated by various factors (e.g., local trauma, immunosuppression, hormonal fluctuations, emotional stress) may lead to a hemorrhagic, necrotizing infection of both the gray and white matter (panencephalitis) in the temporal lobe cortex. In the case of herpetic encephalitis, after the initial infection, which usually occurs in the oropharynx through contact with infected secretions, HSV-1, a large double-stranded DNA virus is transported by retrograde transneuronal spread of virus along a division of the trigeminal nerve, where the virus remains indefinitely dormant in the trigeminal ganglion. Reactivation of the latent ganglionic infection, which may occur spontaneously or be precipitated by various factors (e.g., local trauma, immunosuppression, hormonal fluctuations, emotional stress) may lead to a hemorrhagic, necrotizing infection of both the gray and white matter (panencephalitis) in the temporal lobe cortex. The diagnosis of HSV-1 encephalitis is established by neuroimaging studies, preferably MR imaging and examination of the CSF. The characteristic abnormality on MR scan is high signal intensity on T2-weighted images in the medial and inferior temporal lobe. Examination of the CSF reveals a lymphocytic pleocytosis and elevated protein concentration. A 100% PCR positivity has been reported in the detection of HSV DNA in the CSF. The classic constellation of pathologic features of HSV infection consists of intense perivascular and interstitial lymphocytic inflammation resulting in hemorrhagic necrosis in the most severely involved regions and later, in the course of the disease, by microglial nodules in brain parenchyma. Typical eosinophilic Cowdry A inclusions are identified in nuclei of infected cells, including neurons, glia, and endothelial cells. Viral antigens also are demonstrable by immunohistochemistry in infected tissue, and viral DNA can be detected by in situ hybridization or PCR techniques.

Figure 9. Right, Coronal section showing mesial temporal lobe, insular necrosis in a case of herpes simplex virus (HSV) encephalitis. Left, Typical homogenous, eosinophilic Cowdry A inclusion in HSV encephalitis.

- Radiological pathology of herpes simplex encephalitis

Encephalitis refers to a generalized and diffuse infection of the brain. Encephalitis is most often the result of viral infection. With improvement in the prevention and treatment of bacterial diseases along with an increase in immunosuppressed patients, as seen in acquired immunodeficiency syndrome (AIDS) and in the course of treatment of transplant patients and cancer patients, central nervous system (CNS) infection resulting from viruses has become more widespread. Viruses can affect the CNS in many different ways and can be grouped according to the site of infection and tempo of disease process. Viruses may lead to the development of meningitis, acute
infective encephalitis, acute disseminated encephalomyelitis, subacute or chronic encephalitis, or encephalopathy, or encephalopathy of undetermined cause. Viruses known to involve the CNS are summarized in Table 1. Infection of the CNS by a virus begins with the local growth of virus in nonneural tissue. Spread of virus to the CNS primarily occurs by the hematogenous or neural route. Most viruses, however, gain access through the bloodstream. After establishment and growth at the entry site, the enteroviruses, measles, mumps, adenoviruses, cytomegaloviruses and the arboviruses all result in a viremia.

**TABLE 1. TYPES OF VIRUSES**

<table>
<thead>
<tr>
<th>RNA CONTAINING VIRUSES</th>
<th>REPRESENTATIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PICORNA VIRUSES (ENTEROVIRUSES)</td>
<td>POLIOVIRUSES, COXSACKIE VIRUSES</td>
</tr>
<tr>
<td></td>
<td>ECHOVIRUSES, ENTROVIRUSES</td>
</tr>
<tr>
<td>TAGOVIRUSES (ARBOVIRUSES)</td>
<td>RUBELLA</td>
</tr>
<tr>
<td>ORTHOMYXOVIRUSES</td>
<td>MEASLES, MUMPS, INFLUENZA</td>
</tr>
<tr>
<td>Rhabdovirus</td>
<td>RABIES</td>
</tr>
<tr>
<td>Retrovirus</td>
<td>HIV VIRUS</td>
</tr>
<tr>
<td>DNA CONTAINING VIRUSES</td>
<td>REPRESENTATIVE</td>
</tr>
<tr>
<td>HERPES VIRUSES</td>
<td>HERPES SIMPLEX; VARICELLA - ZOSTER;</td>
</tr>
<tr>
<td></td>
<td>CYTOMEGALOVIRUSES; EPSTEIN-BARR VIRUSES</td>
</tr>
</tbody>
</table>

The virus must be protected from the host's immune system as viruses in the bloodstream are cleared by the reticuloendothelial system. Measles virus and probably mumps virus achieve this protection by entering and growing in lymphocytes. Human immunodeficiency virus enters mononuclear cells that carry the CD4 antigen that, in part, acts as a virus receptor. Poliovirus infects and grows in the lymphoid tissue of the gut. Many arboviruses grow in the spleen or lymph nodes, with some growing in the endothelium of small vessels. Maintenance of viremia, however, does not explain how the blood-borne viruses gain access to a seemingly impenetrable blood-brain barrier. Once the virus is within the lymphocyte, blood-borne access to the CNS has been shown to occur through perivascular spaces; some viruses infect glial cells adjacent to undamaged small vessels by traversing the endothelium by pinocytosis, and some viruses grow in and through endothelial cells. Entrance of virus into the cerebrospinal fluid can occur by growth in the epithelial cells of the choroid plexus with subsequent seeding.

- Most viruses, however, gain access through the bloodstream. The virus must be protected from the host's immune system as viruses in the bloodstream are cleared by the reticuloendothelial system. The virus probably achieves this protection by entering and growing in lymphocytes. Once the virus is within the lymphocyte, blood-borne access to the CNS has been shown to occur through perivascular spaces; some viruses infect glial cells adjacent to undamaged small vessels by traversing the endothelium by pinocytosis, and some viruses grow in and through endothelial cells. Entrance of virus into the cerebrospinal fluid can occur by growth in the epithelial cells of the choroid plexus with subsequent seeding.

- Viruses can gain entry into the CNS by peripheral, retrograde intraneuronal route, as exemplified by the herpes simplex virus.

Once the virus has made its way into the CNS, two major factors affect the general pathologic features: First is the cell type infected, and second is the host's immune response. The various cell populations within the CNS vary in the susceptibility to different viruses. The degree or lack of an immune response also plays a key role in the type and degree of brain damage. The tempo of the entire process is also a variable that leads to the varied appearance of CNS viral infections.

Different cell populations in the CNS are susceptible to different groups of viruses, as has been shown experimentally in animals and less well in humans. Coxsackievirus, echovirus, and mumps virus rarely infect neurons but frequently infect the meninges. Most frequently, polioviruses infect neurons, particularly motor neurons, leaving sensory pathways untouched. Rabies infects chiefly neurons and to a much lesser extent
Oligodendrocytes. The herpesvirus infects neuron and glial cells with a predilection for these cell populations in the limbic system. The JC virus attacks only oligodendrocytes, resulting in demyelination. Specific viral receptors on host target cells may explain the cells' susceptibility to a particular virus.

Herpes simplex virus-1 may invade the brain of immunologically competent adults representing a primary infection, a reinfection, or an activation of latent infection. The virus presumably enters the CNS by primary spread along sensory nerve pathways, gaining access to sensory neurons and then to the brain.

The remarkable localization of herpes simplex encephalitis to the subfrontal and medial temporal lobes of the brain might be explained by entry of the virus via the olfactory mucosa and by its spread along the olfactory bulb and nerve. Or by reactivation of the endogenous virus harbored within the trigeminal ganglia, the site of latency for herpes simplex virus-1 in patients with recurrent oral and ocular infections. HSV-1 latently infects the trigeminal ganglia of humans and retrograde spread of reactivated virus to the CNS probably occurs. However, HSV-1 encephalitis may complicate either primary or recurrent infection, and patients with recurrent oral herpes infections can develop herpes encephalitis with a different strain of HSV-1. In children and adults, HSV-1 exhibits tropism for the frontotemporal regions of the brain.

Figure 10. Section at the level of the anterior commissure showing softening and disruption of the right lateral temporal lobe with some hemorrhage in a case of herpes encephalitis

Host immune responses influence the acquisition of infection, severity of disease, resistance to development, and maintenance of latency, and frequency of re-activation. In general viral replication time in the CNS is 18 hours, which is very rapid, and this might explain the very rapid dissemination of the disease in the brain once herpes encephalitis is left untreated for a few days. The role that host immunity plays is, as yet, undefined.
The host immune response can generally be divided into two categories: a humoral response against the virus and a cell-mediated response directed against the infected cell. Acquired antibody after previous infections or vaccination is the main defense against reinfection. Local infectivity is quelled by IgA antibody in the respiratory tract, tears, saliva, or gut. Circulatory IgA or IgM restricts blood-borne dissemination. Antibody in tissue spaces prevents spread of infection between cells, but this defense can be evaded by viruses that can fuse cell membranes, such as herpesvirus and measles. The host-infected cell may become antigenic if portions of the viral proteins are exposed on the cell surface. Viral antigens expressed on the cell's surface may then lead to cell death.

**Host immune response**

1. Acquired antibody after previous infections or vaccination is the main defense against reinfection.
2. The host-infected cell may become antigenic if portions of the viral proteins are exposed on the cell surface.
3. A third type of immune response that results in neurologic damage does not require the presence of virus in the CNS. Immune complexes produce the neurologic damage when they are deposited on small blood vessels within the CNS and peripheral nervous system, leading to inflammatory changes.

The herpesvirus infects neuron and glial cells with a predilection for these cell populations in the limbic system. In children and adults, HSV-I exhibits tropism for the frontotemporal regions of the brain.

**Figure 11.** Coronal section showing softening and hemorrhage in the cingulate gyri as well as hemorrhagic discoloration in the right inferior frontal and insular cortices in a case of herpes encephalitis.

**Figure 12.** Schematic of the typical areas of involvement by herpes simplex virus. Note the propensity of involvement in the medial temporal lobes, in the insular cortex and the cingulate cortex.
death by a number of different immune pathways. A third type of immune response that results in neurologic damage does not require the presence of virus in the CNS. Immune complexes produce the neurologic damage when they are deposited on small blood vessels within the CNS and peripheral nervous system, leading to inflammatory changes.

The pathologic features in all forms of viral encephalitis tend to be similar with a few exceptions. The brain often appears normal macroscopically, particularly early on in the disease process. Meningeal opacity, vascular congestion, and generalized or localized brain swelling are common macroscopic findings.

Microscopically the changes are those of acute necrotizing meningoencephalitis with variable degrees of reactive changes, such as lymphophagocytic reactions and capillary proliferation. Intranuclear inclusions can be found but not necessarily easily, especially adjacent to areas showing extensive rarefaction and necrosis. In patients who survive for weeks or months, the brain shows cortical atrophy or postnecrotic porencephalic cyst formation in the same distribution, but intranuclear viral inclusions and HSV antigens are not likely to be demonstrated.
Nuclei of infected neurons and astrocytes often contain eosinophilic Cowdry type A inclusion bodies, and when studied by EM, contain herpesvirus particles. Perivascular cuffing and glial nodules are additional common features. In infants, necrosis tends to be more widespread and may progress to extensive cystic encephalomalacia.

Microscopically, infiltration of the brain by inflammatory cells is almost always present. Cellular infiltration is usually present diffusely throughout the brain even in types of viral disease that may affect some parts of the brain more severely. Early on, the cellular infiltrate usually consists largely of polymorphonuclear cells. Later on, the exudate changes and is composed of lymphocytes, plasma cells, and large mononuclear cells. Perivascular cuffing as the result of a single layer of mononuclear cells in the Virchow-Robin spaces of small venules and thicker cuffs of lymphocytes around larger vessels are characteristic. If tissue necrosis is lacking, the inflammatory cells remain confined to the perivascular spaces, but in the presence of necrosis, there is migration of leukocytes into the necrotic brain tissue.

Figure 16. Viral encephalitis. At this power note the perivascular cuffing and the cellularity of the adjacent brain parenchyma. B, The perivascular cells can be recognized as mononuclear inflammatory cells.

Microscopic response of host cells includes hypertrophy and proliferation of microglial cells, astrocytosis, neuronal changes, and the presence of inclusion bodies. Hypertrophy and proliferation of the microglial cells particularly involves the cortex and deep gray matter. This is not a specific response. Reactive astrocytes are commonly present where tissue necrosis has occurred. This response also is not specific for encephalitis. Fibrous gliosis may accompany chronic disease. Neuronal changes are also nonspecific and are usually the result of terminal hypoxia or brain swelling. These nonspecific neuronal changes include loss of Nissl substance, swelling of the perikaryon, or shrinkage of the cytoplasm. Cytoplasmic vacuolation is a feature of the spongiform encephalopathies. Inclusion bodies may be present in many different cells of the CNS and within the nucleus. Inclusion bodies are a specific indication that the brain has suffered a viral insult.

The brain damage caused by acute infective encephalitis is the result of viral intracellular growth and the host's inflammatory reaction. The most common viral groups to cause acute infective encephalitis are the herpesviruses, rabies, arthropod-borne viruses, and enteroviruses (polio). Brain necrosis is an important pathologic feature of acute infective encephalitis. The necrosis may range from selective neuronal necrosis to complete brain infarction.
The pathology of HSE is quite characteristic and almost diagnosable from the macroscopic examination of the brain: swelling due to massive edema, necrosis, and petechial hemorrhages, occasionally large hemorrhages, involving the limbic lobe bilaterally or unilaterally. The anterior medial temporal lobe is most severely involved bilaterally though not necessarily symmetrically, and the insular cortex, orbital cortex, and cingulate gyri may also be involved. Most of these pathological changes are due to the host immune response rather than the offending pathogen.
Localization of the disease to the frontotemporal region is an important feature that distinguishes HSV encephalitis from many other CNS infections. Other forms of viral encephalitis is usually more diffuse and is never localized to the frontotemporal region.

Figure 19. A, A case of herpes encephalitis with gross haemorrhagic necrosis of the temporal lobe. B, This is a gross photograph of a section of brain showing hemorrhagic and necrotic lesions throughout the brain parenchyma, especially the insula, medial frontal and medial temporal cortex, corpus callosum, and medial occipital regions in a case of herpes encephalitis.

Encephalitis is an inflammatory disease of the brain and may be caused by bacteria, fungi, protozoans or viruses. The majority of diffuse infections of the CNS are viral in origin. The infection of the brain typically occurs during the initial exposure; however, some viruses like the herpes virus can cause disease many years after the primary exposure. Virulent organisms are able to bypass the body's defense mechanism and produce general inflammation. The brain responds to these virulent organisms with an infiltrate of inflammatory cells along a perivascular distribution. Neuronal destruction results in cytotoxic and vasogenic oedema with the subsequent formation of glial nodules.

Figure 20. A, This is a gross photograph of a section of brain showing multiple small, punctate hemorrhages throughout the brain parenchyma (arrows). B, This is a closer view of the previous section of brain showing multiple small, punctate hemorrhages throughout the brain parenchyma (arrows).

It is well known that herpes simplex virus has a peculiar tendency to invade cerebral arterioles. The resulting arteritis leads to segmental narrowing, thrombosis, and beading along proximal branches of the anterior and middle cerebral artery on angiography. Pathologic studies in fatal cases show necrotizing granulomatous arteritis and occasional viral particles and antigens in the media of affected blood vessels. Neuroimaging studies reveal infarction in the ipsilateral internal carotid artery territory.
In herpetic vasculopathy, (either caused by immune complexes damage when they are deposited on small blood vessels, or by direct invasion by the herpes virus) the damaged blood vessels are leaky with increase in permeability of the blood-brain barrier to macromolecules, such as the plasma proteins and various other molecules, whose entry is limited by the capillary endothelial cells (blood brain barrier). The major physiologic consequence of this altered vascular permeability is vasogenic edema. The observed brain edema may also have a cytotoxic component emanating from hypoxia caused by complete occlusion of the affected blood vessels. Increased intracranial pressure resulting from cerebral edema produce vomiting and obtundation. In extreme instances, cerebral edema may produce transtentorial herniation with brain stem compression and eventual respiratory arrest and death. Edema is usually very sever in herpes encephalitis. Vasculopathy with leaking blood vessels is responsible for the contrast enhancement frequently observed in herpes encephalitis. Vasculopathy occasionally result in brain infarction due to inflammatory vaso-occlusive changes. The involvement of the blood vessels may be destructive, producing multiple small, punctate hemorrhages throughout the brain parenchyma which is very frequently seen in pathological specimen (though infrequently seen radiologically) of herpes encephalitis.

There is also a small vessel vasculopathy that is characterized by endothelial swelling and minimal inflammation that leads to deep white matter ischemic and demyelinative lesions. The diagnosis of HSV vasculitis is suggested by the temporal relationship to the herpes simplex encephalitis and the results of appropriate laboratory studies.  

**Nonspecific changes**

- Early on, the cellular infiltrate usually consists largely of polymorphonuclear cells.
- Later on, the exudate changes and is composed of lymphocytes, plasma cells, and large mononuclear cells. Perivascular cuffing as the result of a single layer of mononuclear cells in the Virchow-Robin spaces of small venules and thicker cuffs of lymphocytes around larger vessels are characteristic.
- Hypertrophy and proliferation of the microglial cells particularly involves the cortex and deep gray matter with the formation of glial nodules.
- These nonspecific neuronal changes include loss of Nissl substance, swelling of the perikaryon, or shrinkage of the cytoplasm.
- Vasculopathy, (either caused by immune complexes damage when they are deposited on small blood vessels, or by direct invasion by the herpes virus) are quite common in herpes encephalitis.
- In patients who survive for weeks or months, the brain shows cortical atrophy or postnecrotic cyst formation (cystic encephalomalacia) in the same distribution, but intranuclear viral inclusions and HSV antigens are not likely to be demonstrated.  

**Specific changes (indication that the brain has suffered a viral insult)**

- Inclusion bodies may be present in many different cells of the CNS and within the nucleus.
- Typical eosinophilic Cowdry A inclusions are identified in nuclei of infected cells, including neurons, glia, and endothelial cells. Viral antigens also are demonstrable by immunohistochemistry in infected tissue, and viral DNA can be detected by in situ hybridization or PCR techniques.
Figure 21. A, This is a low-power photomicrograph showing a section of brain with numerous perivascular hemorrhages (arrows) and some areas that appear hypercellular. B, This is a medium-power photomicrograph showing a blood vessel with perivascular hemorrhage (1), areas with loss of brain parenchyma, and edema (2). Even at this power, it can be seen that many of the cells are shrunken and dark red, suggesting that they are necrotic.

Figure 22. A, This is a high-power photomicrograph of the previous section. At this power it is easier to see the blood vessel with the perivascular hemorrhage and mild perivascular lymphocytic cuffing (1). In addition, the areas of edema and loss of neurophil (2) can be better appreciated. Red shrunken neurons and glia with pyknotic nuclei (3) are also evident at this power. B, This is another high-power photomicrograph showing a blood vessel with perivascular hemorrhage and mild perivascular lymphocytic cuffing (arrow). In addition, there are numerous red shrunken neurons and glia with pyknotic nuclei throughout this section.

Figure 23. A, This is a high-power photomicrograph demonstrating clear areas, which indicate edema, and numerous shrunken red necrotic cells (1). At this power, it can be seen that eosinophilic intranuclear inclusion bodies have displaced chromatin to the periphery of the nucleus in some cells (2). B, This is a high-power photomicrograph showing several necrotic cells (arrows).

Figure 24. A, This is a high-power photomicrograph demonstrating cells containing intranuclear inclusion bodies (arrows). B, This is another high-power photomicrograph of a cell containing an intranuclear inclusion body (arrow). Note that the nuclear chromatin has been pushed to the outer edges of the nucleus.
Herpesviruses represent a large group of viruses, including herpes simplex virus type 1 (HSV-1), HSV-2, cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, B virus, herpesvirus 6, and herpesvirus 7. CNS infection is the result of heterogeneous spread or neuronal transmission. Perivascular cuffing and inflammatory infiltrates are key features of herpes infection. Hemorrhage and necrosis are more commonly seen with the more aggressive HSV-1, HSV-2, and B virus infections.

HSV-1 commonly results in necrosis of the temporal lobes. HSV-1 is the cause of 95% of all herpetic encephalitis and the most common cause of sporadic encephalitis.
HSV-1 commonly results in necrosis of the temporal lobes and occipital frontal gyri with less frequent involvement of the insular cortex, cerebral convexity occipital cortex, and cingulate gyrus. Involvement is usually bilateral and may be symmetric. The putamen is frequently spared. In adults, it is likely that HSV-1 encephalitis is the result of reactivation of latent infection with transmission of virus along axon cylinders. The trigeminal ganglion is likely the most common site of viral reactivation with spread along branches of cranial nerve V.

Brain biopsy is not needed to diagnose herpes encephalitis because imaging can effectively assist in the differential diagnosis and because there is a relatively nontoxic treatment for HSV encephalitis in the form of acyclovir. Imaging is a critical tool in the workup of these patients. Familiarity with the imaging appearance of HSV-1 encephalitis may help to suggest a specific diagnosis.
Figure 29. (A,B,C) A case of herpes encephalitis, precontrast CT scan. Notice the bitemporal, hypodensity, more in the left side. Also notice insular, and cingulate, and posterior orbital frontal hypodensity, more on the left side. A haemorrhagic component is noticed at the left temporal lobe. The CT hypodensity represent vasogenic edema secondary to the associated vasculopathy. (D,E,F) A precontrast CT scan showing a case of herpes encephalitis, notice the left medial temporal hemorrhagic zone surrounded by edema.

Imaging has come a long way since Balfour et al, 9 in 1967 published one of the first reports of herpes simplex encephalitis. Since that report, many articles have been published showing uptake of technetium pertechnetate in various regions of the brain but most commonly in the temporal lobes in patients with herpes encephalitis. Go et el, 20 studied 12 patients with herpes encephalitis and reported a sensitivity of 83% for radionuclide scintigraphy. In their group of patients, the earliest radionuclide scintigraphy was positive at 2 days after symptom onset. In two cases studied with Tc-99m-hexamethyl-propyleneamine oxime (HMPAO) single-photon emission computed tomography (SPECT), there was increased activity within the temporal lobe early on in the disease process with decreased activity seen in the chronic stage. 37

The most important pathological process that influences neuroimaging studies in herpes encephalitis is vasculopathy with the resultant of brain edema, hemorrhage, infarction and contrast enhancement. Most of the changes seen in MRI and CT scan are due to edema. With resolution of brain edema following successful treatment, both MRI and CT scan studies revert back to normal. In some cases with extensive tissue necrosis, or when the condition is complicated by brain infarction, some residual CT scan or MRI pathological changes (mostly reflecting astrogliosis and encephalomalacia) might persist.

Figure 30. CT scan showing a case of resolved herpes encephalitis, notice the frontal infarction

CT scan may demonstrate hypodense temporal lobe lesions with or without involvement of the frontal lobes. 23 This hypodensity may be difficult to detect early on in the disease process. In one series of 12 patients, the sensitivity of CT scanning was 75% in patients with herpes encephalitis, with the earliest imaging findings at 3 days after symptom onset. 20 Although hemorrhagic temporal lobe lesions in the appropriate clinical setting are highly suggestive of HSV-1 encephalitis, hemorrhage is infrequently seen by CT scan, although present pathologically. 23 Parenchymal enhancement as seen by contrast-enhanced CT scan is infrequent. 23

MR imaging is the initial study of choice because MR imaging can demonstrate the early edematous changes of herpes encephalitis on T2-weighted images with characteristic involvement of the temporal lobes and inferior frontal lobes. 8,9,30 Although the infection classically spares the basal ganglia, basal ganglia involvement may be present. Fluid attenuated inversion-recovery (FLAIR) imaging is even more sensitive than T2-weighted images in the depiction of gray matter and white matter changes. This hyperintense T2 signal abnormality can be seen 48 hours after the onset of signs and symptoms. 32
Figure 31. A,B MRI precontrast MRI T1; C,D,E,F,G MRI T2 images; H,I MRI proton density images. Notice involvement of the cingulate/limbic area, basal frontal area, paraventricular area, basal ganglionic areas, bilateral anterior frontal areas, and brain stem/para4th ventricular areas. The involved areas are hypointense on the T1 images and hyperintense on the T2 and proton density images. The encephalitic patches are numerous and involving the medulla, the pons and the midbrain. This patient survived when treated by acyclovir, and except for a small frontopolar infarction, the follow up MRI study revealed normal findings, indicating that all the demonstrated abnormalities are due to reversible brain edema.

The lesions demonstrated by MRI or CT scan (hyperintense on the T2 weighted images, hypointense on the T1 weighted images and hypodense on CT scan) represent brain edema in the acute stage. The MRI signal changes start first in the cerebral cortex and then spread to the subcortical white matter and rapidly disseminate within the brain. Later (in the chronic stage) the MRI signal changes result from with astrogliosis, encephalomalacia or residual infarction.
MR imaging often reveals bilateral temporal lobe involvement. \(^{18,33}\) Early on in the disease process, contrast enhancement is absent, but gyriform enhancement occurs with disease progression. The detection of meningeal and parenchymal enhancement in patients with herpes encephalitis can be improved with the use of magnetization transfer saturation imaging. \(^{13}\)

Disease starting or spreading to the brain stem and cerebellum was reported before. \(^{46}\) It is always associated with, as yet undefined, impairment of the host immunity. According to Hamilton et al \(^{47}\), extensive demyelination characterizes herpetic lesions in the brain stem and cerebellum because of oligodendroglial cell tropism.

Although a frequent microscopic feature, focal hemorrhage is not commonly encountered radiologically. Except for hyperacute hemorrhage, all forms of parenchymal hemorrhage are more readily detected with MR imaging when compared with CT scan. When hemorrhage is present, the hemorrhagic type of herpes simplex encephalitis appears as irregular areas of increased density (interspersed in low-density areas) assuming a punctate pattern on CT scan and as high signal intensity foci visualized on noncontrast TI-weighted images. MR imaging is also well suited to monitor treatment response. \(^{29}\) As with other chronic processes in the brain, a late sequela of infection is atrophy.

Magnetic resonance imaging is able to detect subtle changes in brain water due to oedema, which aids in earlier diagnosis and shows the extent of the disease more fully. Findings on MR imaging of abnormal signal in the temporal lobes and variable extension into the frontal lobes with sparing of the basal ganglia are highly characteristic of HSV infections. Also, MR imaging is better able to monitor the resolution of the disease as a result of early treatment. Brain infarctions might be demonstrated in some cases of herpes encephalitis.

Table 2. Radiological abnormalities in herpes encephalitis
Acyclovir, an acyclic analogue of guanosine, is the antiviral drug of choice for treatment of neurologic disease associated with herpes simplex virus-1 or herpes simplex virus-2 infection. Its mechanism of action depends on a virus-specified thymidine kinase that phosphorylates acyclovir to its monophosphate derivative. Acyclovir monophosphate is phosphorylated further by cellular kinases to acyclovir triphosphate, which binds to virus-induced DNA polymerase, acting as a DNA chain terminator. Because acyclovir is taken up selectively by virus-infected cells, the concentration of acyclovir triphosphate is 40 to 100 times higher in infected cells than in uninfected cells. In addition, virus-induced DNA polymerase exhibits a 10- to 30-fold greater affinity for acyclovir triphosphate than do cellular polymerases. For these reasons, the drug exhibits low toxicity for uninfected cells and is therefore well tolerated clinically. Acyclovir is highly specific for the herpes virus and a clinical response to acyclovir has also a diagnostic implications as its action depends on a virus-specified thymidine kinase. No clinical response will occur if the offending organism is other than the herpes virus.

The relative safety of acyclovir has led to the common practice of presumptive treatment of patients who exhibit typical clinical signs and symptoms of the disease with typical radiological findings. The outcome of acyclovir therapy depends on the age of the patient and level of consciousness when treatment is initiated.

Massive brain edema is observed in most of patients. Corticosteroids are probably not useful in the treatment of edema associated with HSE. Data from animal studies have shown even potentiation of disease. Brain edema in all patients responded dramatically, even when massive, to acyclovir. It seems quite logic that treatment of the cause of brain edema is the best treatment of brain edema.

**Drug Category: Antivirals** - The goals of using antivirals are to shorten the clinical course, prevent complications, prevent development of latency and subsequent recurrences, decrease transmission, and eliminate established
**Drug Name**: Acyclovir (Zovirax) - Has demonstrated inhibitory activity against both HSV-1 and HSV-2 and is taken up selectively by infected cells; rate of mortality from HSE before use of acyclovir was 60-70%—since acyclovir, it is approximately 30%.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Adult Dose</th>
<th>Pediatric Dose</th>
<th>Contraindications</th>
<th>Interactions</th>
<th>Pregnancy</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>10 mg/kg/dose IV or 500 mg/m²/dose IV q8h</td>
<td>Administer as in adults</td>
<td>Documented hypersensitivity</td>
<td>Half-life prolonged and toxicity increased by concomitant probenecid or zidovudine</td>
<td>B</td>
<td>Use caution in patients with renal failure or receiving other nephrotoxic drugs concurrently</td>
</tr>
</tbody>
</table>

**Drug Category: Anticonvulsants** - These agents are used to terminate clinical and electrical seizure activity as rapidly as possible and prevent seizure recurrence.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Adult Dose</th>
<th>Pediatric Dose</th>
<th>Contraindications</th>
<th>Interactions</th>
<th>Pregnancy</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine (Tegretol) - Effective in treatment of complex partial seizures; appears to act by reducing polysynaptic responses and blocking posttetanic potentiation. Once a response is attained, attempt to reduce dose to minimum effective level or to discontinue drug at least once q3mo.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>200 mg PO bid or 100 mg suspension PO qid; increase at weekly intervals by no more than 200 mg/d tid/qid (bid with extended release) until best response obtained; not to exceed 1600 mg/d</td>
<td>Administer as in adults</td>
<td>Documented hypersensitivity, history of bone marrow depression, concomitant MAOIs, concomitant danazol</td>
<td>May decrease primidone and phenobarbital levels; serum concentrations may be increased by concurrent primidone or phenobarbital; plasma levels and toxicity may increase with concurrent cimetidine—interaction of greatest clinical importance when cimetidine added to carbamazepine during first 4 wk of therapy; levels increase 38-123% within 30 d of danazol administration</td>
<td>D</td>
<td>Do not use concomitantly with MAOIs; discontinue MAOIs for &gt;14 d before carbamazepine administration This drug is not a simple analgesic; do not use for relief of minor aches or pains; use caution in patients with increased intraocular pressure Obtain complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, as baseline;</td>
</tr>
</tbody>
</table>
monthly CBC, differential, platelets during the first 2 mo and thereafter yearly or every other year
May produce drowsiness, dizziness, or blurred vision; patients should observe caution while driving or performing other tasks requiring alertness, coordination, or physical dexterity

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Phenytoin (Dilantin)- A hydantoin, its primary site of action appears to be motor cortex, where it may inhibit spread of seizure activity; may reduce maximal activity of brain stem centers responsible for tonic phase of grand mal seizures. Dose should be individualized; if daily dosage cannot be divided equally, larger dose should be given before bedtime. Phosphorylated formulation, fosphenytoin, available for parenteral use (IV/IM).</th>
</tr>
</thead>
</table>
| Adult Dose | Initial: 100 mg PO/IV tid or 125 mg suspension PO tid
Maintenance: 300-400 mg/d PO/IV divided tid (qd/bid if extended release); increase to 600 mg/d (625 mg/d suspension) prn; not to exceed 1500 mg/d |
| Pediatric Dose | Initial: 5 mg/kg/d PO/IV divided bid/tid
Maintenance: 4-8 mg/kg PO/IV divided bid/tid; not to exceed 300 mg/d
>6 years: May require minimum adult dose (300 mg/d); not to exceed this dose |
| Contraindications | Documented hypersensitivity; SA block, sinus bradycardia, second- and third-degree AV block, Adams-Stokes syndrome (because of effects on ventricular automaticity) |
| Interactions | Toxicity may be increased by amiodarone, benzodiazepines, chloramphenicol, cimetidine, disulfiram, ethanol (acute ingestion), fluconazole, isoniazid, metronidazole, miconazole, omeprazole, phenacemide, phenylbutazone, succinimides, sulfonamides, trimethoprim, and valproic acid; effects may be decreased by barbiturates, carbamazepine, diazoxide, ethanol (chronic ingestion), rifampin, theophylline, antacids, charcoal, and sucralfate; may decrease effects of acetaminophen, amiodarone, carbamazepine, cardiac glycosides, corticosteroids, dicumarol, disopyramide, doxycycline, estrogens, haloperidol, methadone, meyrapone, mexiletine, oral contraceptives, quinidine, theophylline, and valproic acid |
| Pregnancy | D - Unsafe in pregnancy |
| Precautions | Death from cardiac arrest has occurred after too-rapid IV administration, sometimes preceded by marked QRS widening; discontinue if hepatic dysfunction occurs; discontinue if skin rash appears—do not resume if rash is exfoliative, bullous, or purpuric; use caution in patients with diabetes (may raise blood glucose) or acute intermittent porphyria
May cause blood dyscrasias; obtain baseline CBC and urinalysis, repeat monthly for several months thereafter |
Figure 34. A case of herpes encephalitis treated with acyclovir, notice the massive brain oedema before treatment (A), also notice the gradual reduction of brain oedema in (B) and complete resolution of brain oedema in (C) following treatment with acyclovir, this was coupled with dramatic clinical improvement. Notice the residual frontal infarction that became apparent after resolution of the encephalitic process.

CHRONIC ACTIVE ENCEPHALITIS

<table>
<thead>
<tr>
<th>Types of chronic active encephalitis</th>
<th>Histopathological findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subacute sclerosing panencephalitis (SSPE)</td>
<td>- NEURONAL CELL BODIES ARE INVOLVED TO A VARIABLE DEGREE RESULTING IN DESTRUCTION OF THE CELL BODIES</td>
</tr>
<tr>
<td></td>
<td>- PERIVASCULAR LYMPHOCYTIC AND PLASMA CELL INFILTRATIONS</td>
</tr>
<tr>
<td></td>
<td>- MICROGLIAL CELL PROLIFERATION WITH ROD CELL FORMATION</td>
</tr>
<tr>
<td></td>
<td>- EXTENSIVE DEMYELINATION AND MARKED ASTROCYTIC PROLIFERATION</td>
</tr>
<tr>
<td>Progressive rubella encephalitis</td>
<td></td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalitis</td>
<td></td>
</tr>
</tbody>
</table>

- **SSPE**

Subacute sclerosing panencephalitis is a slowly progressive and fatal encephalitis. The disease usually occurs 3-10 years following a measles infection and is believed to be caused by this virus. Pathologically both gray and white matter are involved. In the gray matter, gliosis and perivascular infiltration by lymphocytes are found. Demyelination of variable degrees and gliosis are usually seen in the white matter. Eosinophilic inclusion bodies are often found in oligodendrocytes and neural cells in the cortex. These changes are also found in the caudate nucleus, putamen, globus pallidus, pons and thalamus.
Rubella panencephalitis

Figure 35. A case of SSPE, notice white matter lesions, A, perivascular cuffing, B, and intranuclear inclusions bodies C,D

Magnetic resonance imaging of subacute sclerosing panencephalitis shows lesions in the white matter of decreased intensity on the T1- and increased intensity on the T2-weighted images. Lesions of increased signal are seen in the white matter on the T2-weighted images that are not seen on CT.

Figure 36. MRI of a case of SSPE showing extensive white matter hyperintensity
Rubella virus, like measles virus, has been recognized to cause a slowly progressive panencephalitis. Most causes have occurred in patients with congenital rubella syndrome. The disease is characterized by inflammation with perivascular round cell infiltrations associated with extensive demyelination and reactive gliosis. Pathological changes are most marked in the cerebellum. Intracellular inclusion bodies and virus particles have been recognized. Immune-mediated vasculitic damage have been recognized and is thought to represent the primary pathogenic mechanism.

- **Immune Deficiency Related viral encephalitic diseases**

  The frequency of neurologic symptoms from infections has become more evident with the current increase in immunosuppression due to organ transplantation, aggressive cancer chemotherapy and AIDS. Approximately one-third of AIDS patients have neurologic signs and symptoms during the course of the illness and 10-20% have neurologic complaints prior to the manifestation of AIDS. Neurologic involvement is even higher in autopsy cases where 73-80% have histologic evidence of severe disease. Neurologic involvement may be related to the direct effects of the human immunodeficiency virus (HIV), or secondary to infections or neoplasms. It is often difficult to ascribe a particular problem to a specific agent because multiple pathogens may be present. Both systemic and CNS infections contracted by AIDS patients are usually not bacterial in origin, but caused by opportunistic organisms.

  The most common CNS infection in AIDS is caused by the neurotropic HIV virus. This virus causes both a subacute encephalitis (producing a progressive dementing encephalopathy) and a chronic meningitis. The centrum semiovale is the most common site of involvement, but all white matter tracks may be affected. Clinically, the subacute encephalitis progresses to a subcortical dementia known as AIDS dementia complex (ADC) which occurs in more than one-half of the patients with AIDS.

  Magnetic resonance imaging in early HIV encephalitis shows bilateral areas of increased signal intensity in the deep white matter on the T2-weighted images. Late findings included atrophy and areas of diffuse increased signal intensity in the periventricular region, centrum semiovale and frontal lobes. No mass effect or enhancement with gadolinium is seen. Early CT findings may be normal. Late findings include atrophy and diffuse decreased attenuation of the deep white matter, which does not enhance. For detecting these abnormalities, MR imaging is significantly more sensitive than CT. A diffuse periventricular white matter pattern on MR imaging in patients with AIDS strongly suggests AIDS and further evaluation is usually not indicated.

  Progressive multifocal encephalopathy (PML) is a viral infection affecting 2-7% of all AIDS patients. The disease is caused by a papovirus and results in demyelination with necrosis of the white matter. Electron microscopy shows the oligodendrocyte nuclei to be filled with viral particles. These oligodendrocytes are the cells responsible for the maintenance and production of myelin. Clinically, PML develops insidiously and evolves relentlessly until the patient's death in about 6 months or more. The centrum semiovale is frequently affected with extension into the cortical and subcortical areas of the cerebral hemispheres with a predilection for the parietooccipital areas. This involvement may help explain many of the neurologic symptoms seen with PML such as visual loss, aphasia, hemiparesis, ataxia and other focal findings.

  The T2-weighted MR images are more sensitive than CT or the T1-weighted images in detecting the extent and number of white matter lesions. PML lesions usually do not enhance. PML should be considered in any patient with AIDS who has focal high intensity intracerebral lesions on the T2-weighted scans. Contrast is frequently helpful in PML patients because this lesion does not enhance and can be distinguished from toxoplasmosis which does enhance.

  Cytomegalovirus (CMV) is a member of the herpes virus group which often causes CNS abnormalities in immunosuppressed patients. The infection is frequently asymptomatic, although ventriculitis and/or focal, multifocal or diffuse encephalitis may occur. CMV has a predilection for involvement of the ependymal or subependymal regions. Magnetic resonance imaging shows both gray and white matter disease, ventriculitis and cortical atrophy. Studies done postmortem show focal hyperintense lesions without mass effect on the T2-weighted images. These lesions most frequently represent necrosis or infarction often associated with CMV infections. The high rate of infarction is believed due to infection of the endothelial cells causing occlusion of the vascular lumen.
SUMMARY

- The most commonly involved brain areas in herpes encephalitis include
  - Cingulate/limbic lobe cortex
  - Insula cortex
  - Anterior temporal cortex
  - Orbital frontal cortex
  - Basal ganglia
  - Periventricular

- Pathological changes is more commonly cortical

- Cortical and gyral enhancement is very common in the acute stage.

- Hemorrhage, in herpes encephalitis, takes the form of petechial hemorrhagic spots rather than gross hemorrhage and that is why it is more commonly seen pathologically and much less commonly seen radiologically. When hemorrhage is gross, and large enough, it is readily seen by CT scan and MRI.

- Edema, secondary to the associated vasculopathy, is the underlying pathological phenomenon of the demonstrated CT scan and MRI abnormalities.

- All the associated CT scan and MRI abnormalities, being secondary to vasogenic edema, are reversible by proper antiviral treatment.

- Following resolution of the encephalitic process, persistent MRI/CT scan abnormalities represent brain infarctions, astrogliosis or encephalomalacia.

Addendum

- A new version of this PDF file (with a new case) is uploaded in my web site every week (every Saturday and remains available till Friday.)

- To download the current version follow the link "http://pdf.yassermetwally.com/case.pdf".
- You can also download the current version from my web site at "http://yassermetwally.com".
- To download the software version of the publication (crow.exe) follow the link: http://neurology.yassermetwally.com/crow.zip
- The case is also presented as a short case in PDF format, to download the short case follow the link: http://pdf.yassermetwally.com/short.pdf
- At the end of each year, all the publications are compiled on a single CD-ROM, please contact the author to know more details.
- Screen resolution is better set at 1024*768 pixel screen area for optimum display.
- For an archive of the previously reported cases go to www.yassermetwally.net, then under pages in the right panel, scroll down and click on the text entry "downloadable case records in PDF format"
References


11. Behan PO, Kennedy PGE: Immunological aspects of viral infections of the nervous system. EOS journal of Immunology and Immunopharmacology 8:180-185, 1988


46. Metwally, MYM: The acyclovir responsive herpes simplex encephalitis, definition of its radiological features, correlation with the clinical picture and CSF. Ain-Shams medical journal, Vol 51, No 1,2,3, pp 269-293, 2000

