REVIEW OF LITERATURE
DEFINITION

Encephalitis occurs when there is invasion of brain parenchyma by infectious agents. In such infections, meningeal involvement is almost invariably present, so that the disease called encephalitis is usually a meningo-encephalitis in which encephalitis symptoms predominate. It can be divided into primary and post-infectious or parainfectious forms and the disease may be sporadic or epidemic. The primary form of disease occurs when the encephalitis is the presenting form of the disease and is infectious agents within the CNS. The term postinfectious or parainfectious is used to describe encephalitis that follows or occurs in combination with other viral illness or administration of certain vaccines. The cause of the encephalitis in such case is believed to be hypersensitivity reaction. If the infection may extend to the spinal cord, the term encephalomyelitis is used. Encephalitis may be focal, multifocal or diffuse and may involve all elements of the brain parenchyma or restricted to specific cell population or anatomic locations.

AETIOLOGY

The term 'neurotropic virus' was formerly used to describe minute pathogenic agents which attack the nervous system.
Many significant contributions have been made in the field of discovery of virology neurotropic viruses. A large number of these viruses have been isolated as causative agents and the search for others is in progress.


CLASSIFICATION OF PRIMARY NEUROTROPIC ENCEPHALITIS

A. Proved Viral Etiology

1. Arthropod : tick born encephalitis(Flavi virus)
   (Formerly group Arbovirus).
   a. Russian (Spring summer) encephalitis.
i. Central European encephalitis.

ii. Louping ill encephalitis.

b. Colorado tick fever.

   a. Group A: Alpha virus (formerly group A arbovirus).
      i. Western equine encephalitis.
      ii. Eastern equine encephalitis.
      iii. Venezuelan equine encephalitis.
   b. Group B: Flavi virus (formerly group B arbovirus).
      i. St. Louis encephalitis.
      ii. Japanese encephalitis.
      iii. Murray valley encephalitis.
      iv. West Nile encephalitis.

3. Polio-encephalitis - Picorna virus (Enterovirus).

4. Rabies encephalitis (Lyssa virus).
   - Post vaccination encephalomyelitis.

5. Haemorrhagic encephalitis.

6. Herpes simplex encephalitis.

7. Coxsackie disease.

8. Echovirus encephalitis.

B. Suspected virus Etiology

1. Epidemic encephalitis (Von-Economo).

2. Iceland disease.

3. Dawson's inclusion body encephalitis.
EPIDEMIOLOGY

Although encephalitis occurs in all countries, and in all seasons, many of the agents associated with them have a definite seasonal incidence. Encephalitis caused by arthropod born viruses and enteroviruses is most common in late summer and early fall except for Colorado tick fever which occurs in late spring or early summer. Encephalitis associated with lymphocytic choriomeningitis is most common during the winter and early spring. Mumps encephalitis usually occur during out breaks of epidemic parotitis between January and May. Although sporadic cases occurs throughout the year.

Encephalitis may also follow exposure to reservoirs of specific infectious agents. Meningo-encephalitis virus may follow exposure to infected mice.

Rabies is almost always acquired from an animal bite, although the incident may be remote in time and forgotten at the time of presentation.

PATHOPHYSIOLOGY

Infectious agents may reach the CNS by haematogenous dissemination from an extracranial source by neurotropic spread or by direct passage across the cribiform plate.

The haematogenous route is by far the most common. In poliomyelitis and encephalitides due to echovirus and coxsackie virus, the infectious agent is
acquired by ingestion and replication Peyir's patches and intestinal lymphatic to produce viremia and CNS involvement.

In the arthropod borne encephalitides and in Rocky mountain spotted fever, the infectious agents enters the circulation by cutaneous inoculation and replicates in vascular endothelial cells.

Several viruses may also reach the CNS by neurotropic spread along the schwann cell sheath surrounding nerves or by retrograde movement within axons. Rabies virus enters nerve fibres at the site of an animal bite or, rarely, in the nasal mucosa and travels within peripheral nerves or the olfactory nerve to reach the spinal cord and brain.

Herpes-virus similar may reach the nervous system by neurotropic spread from a bite. Herpes simplex viruses type 1-2 also capable to neurotropic spread.

The Pathologic consequences of encephalitis are tissue destruction, inflammation and oedema. These pathologic changes may be so slight as to produce no symptoms or may produce fulminant illness and rapid death. Virtually all non-viral encephalitides, as well as many of viral origin, are characterized by involvement of an element of the brain parenchyma. In these infectious necrosis of brain tissue often occurs, and if it is extensive, as in herpes simplex encephalitis, may be accompanied by haemorrhage.

In certain infection, such as Rocky mountain, spotted fever or certain case of tuberculosis, necrosis
is not the result of actual invasion of the brain by the organism, but rather the consequences of vascular involvement, with thrombosis of vessels and subsequent infarction.

Certain viral infections are restricted to specific cell population, such cellular specificity occurs in infections caused by poliomyelitis virus or, occasionally other enteroviruses, in which motor neurons within the spinal cord and brain-stem are commonly involved. In mumps encephalitis, extensive involvement of ventricular ependymal cells may occur. Infections may also involve specific anatomic regions. The most important examples of such anatomic specificity is herpes simplex encephalitis, in which there is preponderant involvement of the orbitofrontal cortex and temporal lobes.

In all encephalitis, inflammation is accompanied by cerebral oedema when the infection is extensive, cerebral oedema may have as a mass lesion and produce death from brain herniation.

**CLINICAL PRESENTATION**

Encephalitis may be sudden in onset or develops insidiously over a period of hours to days. Fever is usually, but not always, present. Headache photophobia and signs of meningeal irritations are common. The most characteristic feature of encephalitis is impairment of mental status. Intellectual impairment may be subtle early in the infection, but stupor and coma often develop
as the infection progresses. Focal neurologic abnormalities are frequently evident and may include hemiparesis, visual field defects, aphasia, and sensory neglect or abnormalities or cortical sensation. Injury to basal ganglia may result in choreoathetosis or in parkinsonian symptoms of cogwheel rigidity or bradykinesia. Cerebellar ataxia may be seen. Cranial nerve palsies may occur secondary to actual invasion by the infectious agent but are more usually due to compressive entrapment of nerves within inflamed meninges.

Focal or generalized seizures may be the presenting features of encephalitis or may occur at any time during the infection.

Myoclonus is common in severe encephalitis but has a little localizing significance. Signs referable to temporal lobe olfactory or gustatory seizures, receptive dysphasia, inferior quadrantanopia, or loss of short-term memory should always suggest the possibility of herpes simplex encephalitis.

**Epidemic Encephalitis: Japanese Type B, St. Louis Type, and Murray Valley Type**

These varieties of epidemic encephalitis, one occurring in Japan and other Asian countries, another in United States, and third in Australia.

These diseases are all caused by viruses which measure 40-70 nm in diameter. They used to called arboviruses (meaning arthropod born) (Johnson, 1982).
The natural reservoirs of these viruses are mammals or birds, and the virus is usually transmitted to man by the bite of a mosquito or tick. The St. Louis virus is found in wild birds in the Western USA but more often in Culux mosquitoes breeding on stagnant water with high organic contents, in the urban midwest. Urban epidemics of encephalitis occur in thought years because of poor drainage, while rural epidemic are more often associated with high rainfall (Johnson, 1982).

Japanese encephalitis type B is caused by virus which was first transmitted to monkey by Hayashi. Kawamura and his colleagues transmitted the virus to mice and monkeys (Inada, 1937) and showed that it was immunologically distinct from the virus of the St. Louis epidemic which was also transmitted to monkeys and mice by Muckenfuss, Armstrong and McCordock (1933) and Webster and Pite (1935). Russian autumnal encephalitis is now generally regarded as identical with Japanese type B encephalitis while the Murray Valley type which occurs in Australia and New Guinea is clinically indistinguishable from the Japanese variety and is due to a very similar but nevertheless distinctive virus. West Nile encephalitis, and louping-ill (which is the only disease of this group to occur in Great Britain) (Webb, Connolly, Kane, 1968).

First epidemic of viral encephalitis occurred in Japan in 1871. In India the first outbreak of
encephalitis was reported by Chatterji (1945) from Calcutta, although sporadic cases have been observed in Agra in 1956, Bombay and other places. The biggest epidemics was reported in 1954 Jamshedpur, followed immediately by outbreak in Bilsapur and Nagpur in M.P., Mysore, Monghyr and Patna in Bihar, Herdoi, Allahabad, Kanpur and Bareilly in U.P., Panipat, Sonepat and Ambala etc. in Punjab and also Delhi is covering a wide area of the northern India hence called as Northern India Epidemic of encephalitis.

The pathological picture in the three diseases is virtually identical except that Japanese observers described areas of softening in the brain which were not observed in the American epidemics, and in the Japanese B and Murray Valley types selective damage to purkinje cells is seen. All levels of the nervous system may be affected and severe inflammation is always found in the brain-stem, the basal ganglia, and the white matter of the hemispheres. The inflammatory changes are diffuse, involving the basal pons, the entire medulla, the cortex and white matter of the cerebellum, the basal ganglia and also cerebral cortex (Lowenberg and Zbinden, 1936; Robertson, 1952). There is neuronal degeneration, diffuse microglial and macroglial proliferation and perivascular cuffing (Reyes, Gardner, Poland and Monath, 1981).

Characteristic features of Japanese encephalitis have been described as a syndrome consisting of altered
sensorium masked like facies with tremors and symmetrical paresis without sensory loss. Ocular tremors are uncommon among Indian patients (Sen Gupta et al., 1974).

Laboratory diagnosis depends upon the recognition of complement fixing and neutralizing antibodies which appear at about the seventh day (MacCallum, 1967; Hannoun Shiraki and Osetowska, 1970).

EASTERN AND WESTERN (EQUINE) ENCEPHALITIS

These forms of encephalitis have been known in the United States for many years. In 1931 it was first discovered by virus belong to the togavirus group. These viruses, though similar, are immunologically distinct, and are known as the Western and Eastern Strains (Baker, 1942).

It has been shown that various species of bird constitute a reservoir of infection, that a woodtick also harbours the virus, and that mosquitoes transmit it to man (David, 1940).

Clinical onset is sudden, with generalized headache, nausea, elevation of temperature and lethargy. Focal sign of nervous involvement are usually absent, but in overt cases there are stiffness of the neck, muscular weakness and diminution of tendon reflexes. The CSF shows a moderate, predominantly mononuclear pleocytosis. Patient make a complete recovery in a week or two but mental defect, epilepsy, and spastic palsies have been observed (Finley, 1958; Aguilar, Calanchini and Finley, 1968).
POLIOENCEPHALITIS

Poliomyelitis was characterised as a distinct clinical entity only in late 19th century. Some of the historical landmarks are: the experimental transmission of the disease to monkeys (Land Steiner et al, 1909). The adoption of the virus to cotton rats are mice (Armstrong et al, 1939), the discovery that polioviruses can be grown in primate, non neuronal tissue (Fuders et al, 1941).

Paralytic poliomyelitis was recognised in India only in 1947 when one of the most severe epidemics occurred in the Andman Island. In 1949, it was noted in Bombay and since then, the number of cases appears to be rising progressively in different parts of the country. The virus spreads from human to human through polluted water or food, the most important source of contamination being human faeces.

In Bombay, seasonal incidence is marked 60 per cent of cases are recorded during June to September as evident from ICMR (1975), recent studies in Poliomyelitis.

The virus of poliomyelitis consistently involves the cerebral hemispheres, producing meningitis, mesoderma glial reaction and neuron damage. The meningeal reaction is invariably mild and implicates all cortical areas; however, the posterior portion of the frontal lobes are by far the most commonly involved. The neuronal changes are strikingly localized to the large and giant
pyramidal cells of layer 5 and the medium pyramidal cells of layer 3 of the motor cortex. These nerve cells reveal chromatolysis, swelling fragmentation and pyknosis. Relatively extensive inflammatory changes present in the motor area consist of diffuse and focal areas of inflammatory cells. Glial nodules are few (Baker and Buggs et al., 1954).

In the "Paralytic poliomyelitis (polioencephalitis) paralytic stage it is almost impossible to differentiate these cases from the cases of viral encephalitis besides those caused by the polio virus as both these syndromes have almost the similar type of presentation along with the signs of encephalon involvement. Although in the polio infection limb pain and tenderness will be prominent finding in the limb usually later on weakened in the paralytic stage. This may raise the suspicion in the mind but the diagnosis of these cases in preparalytic stage is confirmed only by virus isolation of poliomyelitis. Those cases which pass on to the manifestation of paresis or paralysis of the limb or limbs with persisting or residual evidence of brain substance injury, are easier to diagnose clinically. Viral studies show that fewer than 40% of the cases of nonparalytic poliomyelitis are actually this disease.

Commenting upon the age incidence of poliovirus affection Brain has described that infants under the age of one year are rarely attacked. In country where hygiene
is poor most sufferer are between the age of 2 and 4. After the age of 25 disease is very rare. Male suffers some what frequently than females.

Meyer et al (1953-58) separately grouped 144 cases under the syndrome of "paralytic poliomyelitis". Eighty percent of these cases have been virologically proved to be cases of poliomyelitis. Some of the cases clinically diagnosed as aseptic meningitis and encephalitis were virologically proved of polio-virus affection. Thus its similarity clinically with other two syndromic obvious.

Agarwal et al (1954) reported 53 cases from Allahabad. Seventy five percent of the cases were below 5 years of age. Thirteen cases had the involvement of brain stem and 4 of them died of respiratory complications. Bulbo encephalitis form was observed in 3 patients which showed equivocal signs of encephalitis with involvement of spinal and brain stem. One boy of 15 years presented with headache, semicoma, coarse tremors of limbs, restless, besides fever. He was diagnosed to be a case of polio encephalitis with involvement of brain stem and respiratory muscles but recovered completely.

**RABIES ENCEPHALITIS**

The history of rabies is indeed ancient forming a part of the natural history of animals. From the earliest period, the disease had been associated with mad dogs whose bites could transmit the virus to other animal
and humans through the saliva (Bell et al., 1964). The efforts of many to transmit the disease from man to animal culminated in Pasteur's classical studies and he is ultimate success in 1886 of treating cases of dog bite. In 1903, Negri discovered certain bodies, the well known Negri bodies which he considered, to be the etiological agent, supposedly a protozoan. This has proved to be in-correct. However, electron microscopy has shown that these bodies contain virus particles of rabies.

The virus of rabies belongs to the family rhabdoviridae in the group Lyssavirus. The concept of rabies virus as a single antigenic species, was challenged and now it has been shown to be a member of serologically related viruses which can be distinguished readily (Shop et al., 1976).

Rabies had a world-wide distribution. In India, it has been endemic for thousands of years and shows an alarming increase in incidence. It is the most common form of encephalitis in India. Like Japanese encephalitis, rabies is also a zoonosis involving different wild and domestic animals. In India, where the stray dog population remains unrestricted, dog have been responsible for 89.2 percent and Jackals for 6 percent of the 44,869 persons who underwent treatment with vaccine (ICMR, 1973). On the other hand, a variety of animals including foxes, skunks, raccoons and bats have been involved in rabies epidemiology in countries where
dog rabies is generally controlled (Winkle, 1974; Parker et al., 1966; WHO expert committee report, 1973).

In India, only one case was noted following the bite of a bat (Veeraraghavan et al., 1955). Mottcwhick and Gregg (1975) have illustrated statistically accordingly, if a rabid wolf bites more than one person within a short period of time, and if at least one of them dies of rabies, the probability is that about 60 percent of the bitten individuals will develop clinical rabies. In the case of a severe bite by a proved dog, only 32 percent of infected persons will developed fatal rabies. The figures will be reduced if they receive effective treatment after exposure.

A serious problem raised is the possibility of developing disease through bites of apparently healthy dogs who remain healthy during the period of observation. This question of latent and abortive rabies has been reviewed by Bell et al. (1964). In India, there was a report of a normal looking dog who showed virus in the saliva at intervals of 14 occasions between 75 to 180 days after biting a person who developed fatal rabies. The saliva was found to be negative when followed for another 34 months (Veeraraghwan et al., 1969).

The usual incubation period of rabies varies between 20 to 60 days. It is shorter (34-48 days) with head bites than with bites on the extremities (46-78 days) (Ahuja et al., 1950).
Prodromal symptoms of pain and tingling at the site of the bite or anxiety and restlessness with anorexia, headache and fever are followed in 2-10 days by the neurological syndrome. This consist of hallucination, disorientation, convulsions, neck stiffness and paralysis. Short bouts of excitement with psychomotor activity, running and thrashing of limbs, may characterize this phase. These last a few minutes and then the patient become quiet and cooperative by anxious. Pharyngeal and generalized spasms characterize this phase. These pharyngeal spasms are brought on by attempts to swallow, water and later even by the mere sight of water (Ahuja et al., 1950). The patients begins to fear water and gets disturbed by noise or excess of light. The paralysis may be diffuse and symmetrical or ascend as in the Guillain Barre syndrome until there is respiratory paralysis followed by unconsciousness and death (Dupont et al., 1965).

Diagnosis is possible through actual isolation of virus by inoculation of experimental animals or through visualization of Negri bodies (Johnson et al., 1964). The fluorescent antibody technique provides a rapid and reliable method for identifying rabies antigen in tissues of infected animals (Goldwasser et al., 1958). Other methods include serum neutralization testes (Lennette et al., 1971). The indirect fluorescent rabies antibody test (Thomas et al., 1963).
HERPES SIMPLEX ENCEPHALITIS

It is caused by DNA virus in the family Herpatoiridae, genus Herpes virus. The virus has two distinct serotypes, type 1 being mainly associated with encephalitis (Gupta et al, 1972). It is a common cause of sporadic acute encephalitis and has a world-wide distribution.

There is an acute onset of fever, headache, apathy and convulsions; loss of consciousness usually occur by the sixth or seventh days of illness while rhythmic movements of the larynx and pharynx are very common. Evidence of rising intracranial tension deepening unconsciousness and papilloedema often demand surgical decompression.

The CSF shows elevation of proteins with increase in lymphocytes. Millipore filter examination of the CSF may reveal large eosinophilic cells with intranuclear inclusion (Gupta et al, 1972). The EEG shows diffuse slowing widespread, periodic stereotyped sharp and slow wave complexes, bilaterally over both hemispheres or transient episodes of active unilaterally. These are similar to those found in SSPE but with shorter periodicity and only in the acute phase of the illness. In addition the EEG may show a localized sharp and slow waves abnormality in 66 percent of proven cases (Gupta et al, 1975).
KYASANUR FOREST DISEASE (KFD)

KFD virus is an RNA virus placed in the family Togaviridae genus Falviviruses i.e. the same group B of arboviruses as the JE virus. In this group, it belongs to the subgroup known as the Russian spring summer encephalitis viruses, most of which are known as to be transmitted by bites of ticks.

The disease was first reported in monkey and men from the Kyasanur forest (Shimoga District, Karnataka State, S. India) (ICMR, 1973, Research in rabies).

Recently the virus has also been isolated from human in N. Canara District (Karnataka states) (Winker et al, 1974). Apart from these two areas in Karnataka state KFD has been reported only in laboratory workers (Wadia et al, 1975).

The initial illness characterized by fever, headache, myalgia, sore throat, cough, abdominal pain and diarrhoea lasts for a 8 or 9 days. After a period varying from 10–12 days of normal temperature, the fever reappears. It is in this stage that the CNS may becomes affected. Headache and vertigo are complained of an abnormal deep reflexes with equivocal plantar responses, meningeal signs and mental disturbances are observed (Webb et al, 1961).

The CSF shows a polymorph or lymphocytosis with normal chemistry. However, the EEG may be abnormal in the first phase of the illness (Wadia et al, 1975).
POST INFECTIONS ENCEPHALITIS

The encephalomyelitis complicating varicella, rubella and variola are known to be result of an immunological reaction within the brain involving principally the white matter. However, the measles virus has been isolated from the brain itself and it is possible that measles encephalitis could be a result of invasion of the brain by the virus together with an early development of antibody response of the host (Webb et al, 1964).

Indian reports give the incidence of measles encephalitis to vary between 2-20 percent children under three years are most liable to this complication. Mumps encephalitis appears to be more infrequent and may occur following only an orchitis, by itself or following the parotitis. Agarwal et al (1971) found antibodies in CSF to adenovirus in 22, mumps in 11, and measles in 13 of 59 patients suffering from virus encephalitis.

Following a skin rash and high fever, or an enlargement of the parotid gland, at an interval varying from 2-14 days. These may be either a sudden convulsion, with loss of consciousness or a more gradual and progressive drowsiness passing into stupor and coma, preceded by irritability, headache and signs of meningeal infection. Involuntary movement, hemiplegia, ataxia, and speech disturbances may occur.

The CSF usually shows an elevation of lymphocytes and proteins, with normal sugar and chloride
and quadriplegic, with pyramidal and extrapyramidal signs. The jerks persist till a late stage of illness. The course lasts about 18 months.

The CSF may show a paretic colloidal gold curve. The EEG is characteristic, stereotyped repetitive complexes (which are superimposed in a given channel) occur on a background which shows progressive slowing. The origin of these discharges is probably within deep brain structures. There are numerous case reports in the Indian literature (Gupta et al, 1975; Singhal et al, 1974; Saeed et al, 1975).