NEUROMICROBIOLOGY

Aditi Singh, Shailendra K. Saxena, Niraj Mishra & Asha Mathur

Introduction

The neuromicrobiology, which emerged as a sub branch of neuropathology, has now become an independent branch of medical sciences dealing with the identification and characterization of microbes affecting the nervous system. Though the first institute in the country for neurology, National Institute of Mental Health and Neuro Science (NIMHANS) was established in 1954 at Banglore, the independent department of neuromicrobiology was started there in 1977. The main objective of this department is to aid neurology, neurosurgery and psychiatry in diagnosing the micribiological aspects of CNS infection. At the same time the National Institute of Virology (Pune) as well as various departments at different hospitals and medical colleges are also engaged in neuromicrobiology research in India. Recently the Department of Biotechnology (DBT), Government of India established a centre for brain research, named as National Brain Research Centre (NBRC) at Manesar near New Delhi. This centre is dedicated to provide infrastructure to work at the frontiers of neurosciences including neuromicrobiology and could be one of the few institutes in the world solely focussed on understanding the brain in a unified manner.

Infections of the CNS can be broadly of three types:

Acute infection: Acute infections of the nervous system are among the most important problems in India. These clinical syndromes include bacterial and viral meningitis, encephalitis (viral, tuberculour or cysticerial) and systemic infection caused by *Salmonella*, Gram-negative bacteria or *Brucella* etc.

Sub acute infection: This syndrome overlaps that of chronic infection e.g. partially treated pyogenic brain abscess, fungal infections, meningitis, neurocysticercosis, neurosyphilis etc.

Chronic infection: These infections include tuberculosis meningitis, neurocysticercosis and complications of systemic infection (fungal infection). Chronic viral infections are of three types:

In Persistent infection, virus is readily apparent and frequently shed e.g. congenital viral infections due to cytomegalovirus, HSV type II, rubella and HIV-I. Enteroviruses also cause a chronic central nervous system infection. In *Latent viral infection,* viruses are not demonstrable but periodically reactivate and intermittently shed e.g. herpes family. Herpes simplex virus (HSV) type I causes neural latency in sensory neurons at the trigeminal ganglia, HSV type II, Epstein-Barr virus (EBV) and Varicella zoster virus (VZV) latently infect sacroganglia,

lymphocytes and satellite cells of multiple sensory ganglia respectively. In *Slow virus infection,* viruses in the brain have a long incubation period due to slow growth, often incomplete and partially controlled by host defenses. These agents can be conventional viruses and unconventional agents referred to as prions.

Main routes of CNS invasion by microbes can be either haematogenous or through cranial or olfactory nerves. Blood-borne invasion is the commonest (e.g. Polio virus and Meningococcus), while invasion via peripheral nerves is less common (e.g. HSV, VZV, rabies viruses). Varieties of infectious agents can cause neurological disorders. They may be virus, mycoplasma, rickettsia, bacteria, fungi, chlamydia and parasites (Figure-1 and Table-1). But the most common are viruses, e.g. Polio, meningitis, and encephalitis etc.

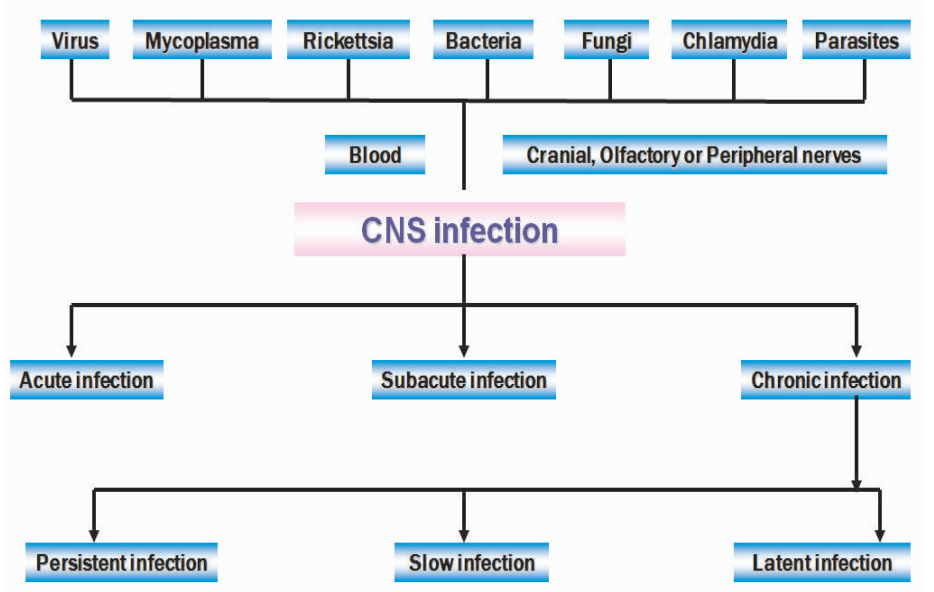

Figure 1 Categories of infectious agents and classification of infection on the basis of severity. Bacteria, Chlamydia, Fungi, Mycoplasma, Parasites, Rickettsia and Viruses cause infection of CNS. They get the entry and travel to the CNS by blood, cranial or peripheral nerves. The infection depending on severity and duration can be classified in three main categories, acute infection, subacute infection and chronic infection. Chronic infection can also be divided in three categories persistent, slow and latent infection.

Table 1: Overall view of different neural infection in India

Type	Neural Infection	Agent
Viral	**Japanese encephalitis**	*Japanese encephalitis virus*
	West Nile encephalitis	*West Nile virus*
	Chikungunya (CHIK) virus	*Chikungunya virus*
	Dengue	*Dengue virus*
	Herpes simplex encephalitis	*Herpes simplex virus*
	Subacute sclerosing panencephalitis	*Measles virus*
	Rabies	*Rabies virus*
	Kyasanur forest disease	*Kyasanur forest disease virus*
	Nipah encephalitis	*Nipah virus*
	Hepatitis Hepatic encephalopathy	*Hepatitis virus*
	Acquired Immunodeficiency syndrome	*Human immunodeficiency virus*
	Poliomyelitis	*Polio virus*
Bacterial	**Neurotuberculosis**	*Mycobacterium tuberculosis*
	Acute Bacterial Meningitis	*Pneumococci*
		Salmonella
		Meningococci
		H. influenzae
		Citobacter
		Pseudomonas
		Bacillus anthrasis
		S. pneumoniae
		H. Influenzae
		Cryptococcus
		Salmonella
	Tubercular bacterial meningitis	*Mycobacterium tuberculosis*
	Neural Leprosy	*Mycobacterium leprae*
	Brucellosis	*Brucella*
	Botulism	*Clostridium botulinum*
	Leptospirosis	*Leptospira icterohaemorrhagiae*
	Brain abscess	*Clostridium*
		Prevotella melaninogenicus
		Bacteroides preacutus
		Fusobacterium nucleatum
		Peptostreptococcus spp
		Burkholderia pseudomallei
		Angiostrongylus cantonensis
		Pseudomonas
		Scedosporium apiposporium
		Salmonella entritidis
		Salmonella typhi

Fungal	**Meningitis**	*Cryptococcus neoformans*
		Candida albicans
		Aspergilius
		Nocardia asteroids
		Histoplasma-capsulatum
		Zygomycetes
		Penicillium marneffeiand
		Cladosporium bantianum
	Aspergilosis	*Aspergillus*
	Candidiasis	*Candida*
	Zygomicosis	*Zygomycetes*
Parasitic	**Neurocysticercosis**	*Cysticercosis cellulosae* larvae of *Taenia solium*
	Hydatidosis	*Hydatid larvae* of *Echinococcus*
	Leishmeniasis	*Leishmania donovanii*
	Brain abscess	*Paragonimus*
		Schistosoma
		Spirometra
		Trichinella
Protozoan	**Cerebral malaria**	*Plasmodium vivax*
	Toxoplasma encephalitis	*Toxoplasma gondii*
	Acanthamebic granuloma	*Acanthameb*
	Brain abscess	*Entamoeba histolytica*
		Toxoplasma
		Acanthamoeba
Prion	**Creutzfeldt-Jacob disease**	*CJD-PrP*

Common viral infections

Viral infections of CNS depend on the neurovirulence and the neuroinvasiveness, which are governed by the combined effect of viral and host factors. Always there is continuous intraction between virus and host. Different viral factors tries to induce infection in animal same time host factors tries to protect the infection. After infection, there is complex interplay between different host susceptibility factors (genetic makeup of the host, age, sex, species and environment), immune-response (cytokines and chemokines, nitric oxide, proteases and co-infection) and infectious agents (LTR, co-receptor usage and variation in other genes). Neuropathology is the result of interaction of all the three factors (Figure-2). That is why some individuals are highly prone to certain type of infection and others are prone to different ones. The symptoms of the infection depend on the site and cell types of infection and changes in the cells e.g. alteration in the cells, differentiation in the cells, transformation in the cells and cell death. Acute viral encephalitis is the most common CNS infection.

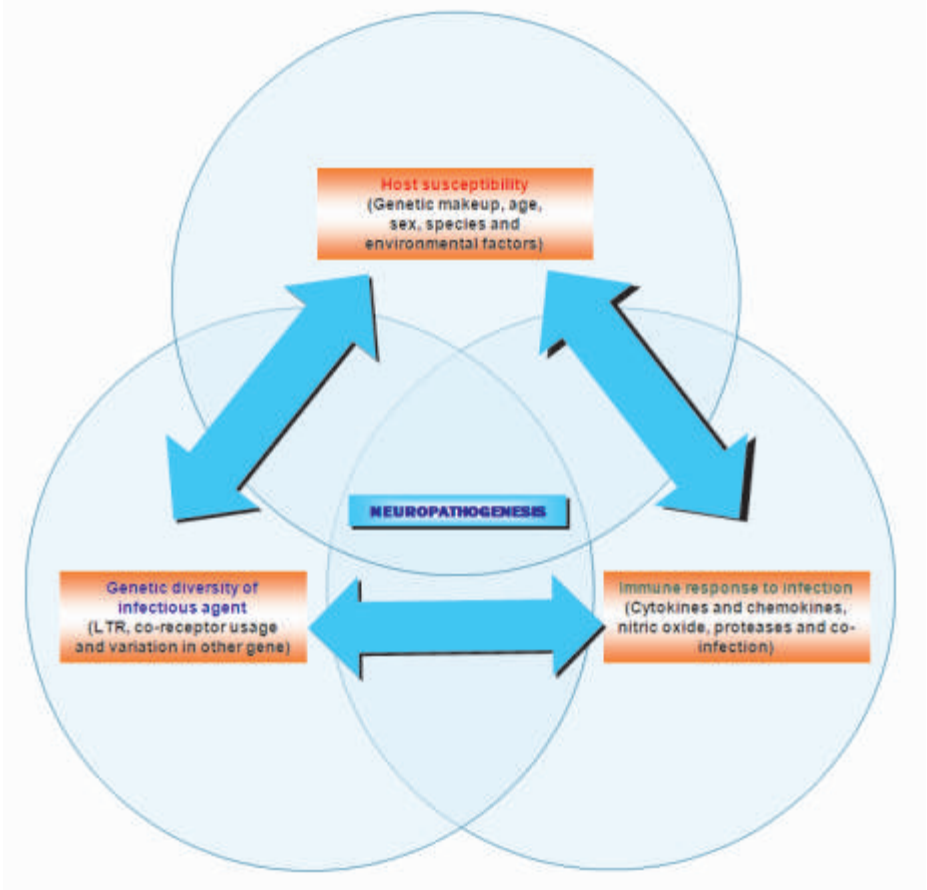

Figure 2: Determinants of neuropathogenesis. The chart suggests that three main components (genetic diversity of infectious agent, host susceptibility and immune response to the infection) involve in neuropathogenesis. The complex interplay between all the three components is very important to get the disease.

(A) Acute viral Encephalitis

Since its first detection in 1955 almost every year, the so-called 'mysterious diseases' known as encephalitis invade India and unfailingly claim thousands of lives. In India, although many encephalitis outbreaks have been reported in the years 1958, 1965, 1968, 1978, and 1983 etc., several of them remained undiagnosed. In the absence of a defined cause, these outbreaks were tentatively attributed to Reye's syndrome, dengue, chikungunya, Japanese encephalitis, measles, and so on. There were two major epidemic of encephalitis were reported in late 1950s known as "Nagpur encephalitis" and "Lucknow encephalitis.

The "**Nagpur encephalitis**" outbreak occurred with some regularity annually in eastern Maharashtra during late 1950s (Berry et al, 1959; John et al, 1978, 1983). It had been investigated for JE etiology which was ruled out. Later it was investigated for enterovirus etiology in 1968. Results clearly showed that the disease was an encephalopathy syndrome and not encephalitis as believed popularly until then (John et al, 1978, 1983). Tissue biopsy specimens confirmed to contain intracellular microvesicular fat accumulation, and thus the disease was found to be indistinguishable from Reye's syndrome (John et al, 1983). An Expert Group of the Indian Council of Medical Research (Technical Report vies 1970) mentions that the Nagpur encephalitis syndrome is an encephalopathy and this pyrexial illness is possibly due to some or many infectious agents, bacterial or viral, the manifestions being aggravated by the increase in ambient temperature.

The "**Lucknow encephalopathy**" was reported in 1958 (Gupta et al, 1959; Bajpai et al, 1960). From investigation of encephalitis, 59 cytopathogenic agents were isolated from 321 specimens. The indentified strains were Polio-virus 1, ECHO 11, ECHO 7 and Coxsackie B 3, and two o f Coxsackie B 5. Their isolation rate was 17%, which was reported by Gupta et al (1963).

Viral encephalitis is an acute infection and inflammation of brain. A clinico-epidemiological study was done by Das et al (2005) in the children of West Bengal on acute viral infection of brain and reported aseptic meningitis, encephalitis, and meningo-encephalitis as the cause. The over all mortality was 45.5%. Characteristically, there are signs of cerebral dysfunction such as abnormal behaviour, seizures, and altered consciousness often with nausea, vomiting and fever. Although viruses are the most common cause of encephalitis, such as Japanese encephalitis (JE), human immunodeficiency virus (HIV), rabies, West Nile, chickungunya, measles, mumps, etc.; bacteria, fungus and parasites may also be responsible for infection.

1. Japanese encephalitis (JE)

It is one of the most important mosquito-borne viral encephalitis in India. It is caused by Japanese encephalitis virus (JEV), a member of the family *Flaviviridae*, affecting all age groups with highest incidence of disease among children. JE

accounts for 50,000 acute illness per year. Fatality rate is 25-50% (Gourie-Devi 1984) and approximately two-third of the survivors develope neurological sequelae. The risk factors in fatal outcome during JE have been the presence of virus in CSF (Mathur et al 1990) and detection of autoantibodies to neural antigens in the CSF of the JEV patients (Desai et al 1994). Man is a dead end host, while pig acts as an amplifying host.

The virus spreads in the form of epidemics, although several endemic areas of JEV activity are known. The disease has been recognized in India since 1945 and has become endemic in several parts of the country (Mohan Rao 1983, Prasad et al 1993, Mathur et al 1982 and Saxena et al 2006). At present JE is not only endemic in many areas, it is also spreading in naïve, non-endemic zone. The nucleotide sequence analysis of the virus isolated from India, shows that two completely different strains, one GP78 isolate (Mathur et al 1982) close to SA41 from China and the other Vellore P20778 close to Beijing 1-1 isolate, are in circulation (Vrati et al, 2000). The disease presents with a prodromal stage, an acute encephalitic stage with coma, convulsion, and variable neurological deficits and a convalescent stage. JEV infection during first and second trimesters of pregnancy can cause fetal death and abortion (Chaturvedi et al 1980), which has been experimentally demonstrated in mice also (Mathur et al 1981, 1982). In some of the JE patients in whom the clinical course is prolonged, subacute form of the disease is seen. JEV can establish persistent and latent infection in humans and recurrence of the symptoms has been reported in some children more than a year after the acute encephalitic phase (Sharma et al 1991). Desai et al (1995) have demonstrated persistence of JEV in cerebrospinal fluid up to 110 days post infection along with high titres of IgM and neutralizing antibodies in 5% of children. Development of hydrocephalus in humans (Ravi V. personal communication) as well as experimental mice has been established (Mathur et al 1986). Involvement of the peripheral nerves following JEV infection has been reported, and Ravi et al (1994) have demonstrated that JEV infection may predispose to Guillain-Barre syndrome in the endemic areas. Parasitic infestations enhance the probability of viral invasion through modulation of the host-defense mechanisms. It has been shown that the co-occurrence of the cysticercosis with JE results in poor outcome of the patients (Desai et al 1997).

A rapid diagnosis of JE is necessary as number of conditions such as acute meningitis, cerebral malaria, Reye's syndrome, and other viral encephalitis mimic the clinical picture of JE. CSF pressure is raised with mild elevation in protein level and marked pleocytosis. The electroencephalogram (EEG) is abnormal and shows diffuse slowing of background activity with asymmetry in hemispheres and dysthermia (Gourie-Devi & Deshpandey 1982). Brain echo, computed tomographic (CT) scan and magnetic resonance imaging (MRI) are useful tools in diagnosis of JE. MRI is more sensitive than CT scan in revealing changes in thalamus, basal ganglia, substantia nigra, brain stem and may be helpful in the diagnosis of JEV especially in endemic area (Kalita & Misra 2000). Confirmatory diagnosis of JEV

should be carried out by virus isolation and serology. CSF, plasma and brain tissue (post-mortem) collected early in the illness can be used for virus isolation while CSF and paired serum samples are necessary for antibody estimation. Haemagglutination inhibition (HAI), complement fixation (CFT) and neutralization tests (NT) were used for the diagnosis, but they are cumbersome and cross-react with other flaviviruses, so they are now being replaced by a number of other sensitive tests for the rapid diagnosis of JE such as an indirect immunofluorescence (IIF) test for the detection of cell bound JEV antigen in CSF (Mathur *et* al 1990), rapid micro-neutralization test (MNT) for the detection of neutralizing antibodies to JEV in CSF (Desai et al 1994), rapid IgM capture ELISA (JEV-Chex) for CSF and serum samples (Ravi et al 2006) and reverse transcriptase polymerase chain reaction (RT-PCR).

Host defense mechanism is mediated probably through soluble, non-cytotoxic, inhibitory factors. During JEV infection macrophages produce a neutrophil chemotactic macrophage-derived factor, MDF (Khanna et al 1991). MDF plays a protective role in the host defense against JEV, by inhibiting the JEV replication through production of reactive oxygen intermediates (Srivastava et al 1999) in neutrophils and reactive nitrogen oxide species (Saxena et al 2000; 2001) in macrophages, and consequently degrading the virus protein and RNA.

There is no specific treatment available for JE. Although therapeutic role of diethyldithiocarbamate (A*ntiJEd*) have been demonstrated during JEV infection (Saxena et al 2003). The most effective control measure besides control of mosquitoes is vaccination of affected population. A mouse brain-derived formalin-inactivated vaccine is available for immunization against JE. Limitations in terms of safety, availability, and cost, have resulted in a number of approaches towards the development of effective vaccines in India. Attempts are being made to develop improved vaccine using the recombinant DNA technology (Kaur & Vrati 2003) and oral immunization using conventional immunogens (Ramakrishna et al 1999).

2. West Nile virus (WNV)

West Nile encephalitis (WNE) is an arthropod-borne flavivirus and belongs to the JEV antigenic complex. The virus is maintained in nature in a bird-mosquito cycle. It is highly prevalent in India, showing presence of WNV infection in different parts (Rodrigues et al 1981). Usually it causes mild infection (Paul et al 1970), but has been reported to cause encephalitis also (Paramasivan et al 2003; Gajanana et al 1995). The virus was reported for the first time in mid fifties (Banker 1952; Smithburn et al 1954). Subsequently WNV antibodies have been detected in human sera collected from Tamilnadu, Karnataka, Andhra Pradesh, Rajasthan, Maharashtra and U.P. (Chaturvedi et al 1970; Banerjee 1996; Thakare et al 2002). WNV has been isolated from the sporadic cases of encephalitis (George et al 1984; Paul et al 1970). In humans with neuroinvasive disease, IgM antibody is detected in CSF and serum in acute stage of illness. An immunofluorescence assay or RT-PCR

could be used in detection of virus. Serum samples are not always positive. The interference of cross-reactions of closely related virus has been reported. At present no vaccine is available for the control of WNV infection in the humans though there are two candidate vaccines under laboratory trial.

3. Chikungunya virus (CHIKV)

CHIKV is a rare cause of meningoencephalitis in India and is transmitted by the bite of an infected *Aedes aegypti* mosquito. The symptoms are most often clinically indistinguishable from those observed during dengue infection. Evidence of dual infection with Chikungunya and Dengue virus from the same patient has been reported (Myers & Carey 1967) and so CHIK meningoencephalitis should be suspected in the presence of the concurrent Dengue infection. CHIK virus (CHIKV) has caused numerous large out breaks in India. This virus was first isolated in Kolkatta in 1963 (Shah et al 1964). After that, there have been several reports showing presence of virus in different parts of country (Jadhav et al 1965, Dandawate et al 1965a). Since the outbreak of CHIKV in 1971, there were no reports showing presence of the virus for a long time (Pavri 1986). After a gap of more than 25 years, CHIKV has re-emerged by causing several long scale outbreaks in various parts of the country as Andhra Pradesh, Karnataka, Maharashtra and Orissa (Saxena et al, 2006, CDC report 2006, WHO bulletin 2006, Ravi 2006). A widely circulating low virulent CHIKV is a possible explanation for the epidemiological pattern of the CHIKV disease in this region (Mourya et al 2001).

Isolation and identification of the virus from the clinical specimens gives a definite diagnosis of the viral infection of the nervous system. The detection of the antiviral antibodies in the CSF and paired sera samples is the most widely employed method for the diagnosis of CHIKV infection and PCR has proved to be helpful in viral nucleic acid detection.

4 Dengue virus

This viral infection in human may be associated with hemorrhagic manifestation and encephalopathy. In the study of the cases of encephalopathy, detection of IgM antibodies, predominantly of Dengue viral antigen has been demonstrated (Thakare 1996). An outbreak of acute encephalitis of unknown origin with high fatality was reported in children from Andhra Pradesh state in southern India during 2003. Rao et al (2004) investigated and identified the causative organism as Chandipura virus. Cell lines and peripheral blood lymphocyte co-cultures were used to isolate the causative agent from clinical samples. Identity of the agent was established by electron microscopy and serological and molecular assays.

5. Herpes simplex encephalitis (HSE)

HSE is one of the serious neurological disease caused by herpes simplex virus. HSV type1 and type 2 are the members of the family Herpesviridae which

includes many viruses of medical importance such as Varicella- zoster virus (VZV), human cytomegalovirus (CMV) and Epstein Barr virus (EBV). The HSV causes cold sores and genital lesions and it is transmitted directly through human contact. Once inside the body, the virus travels through nerve fibres and can cause infection in the brain. The virus may also undergo a period of latency and reactivation can be due to emotional and physical stress. The mortality rate is very high if remained untreated. Serological studies have revealed antibodies to HSV in 40-85% of the population and it is reported that HSV-1 encephalitis constitutes very low (1.1%) proportion of acute viral encephaltis in eastern Uttar Pradesh (Gambhir et al 1999). HSV appears to be under diagnosed in India (Ravi 1992, Satishchandra et al 1996). With an upsurge of AIDS, HSV may perhaps emerge as an impotant OI in future.For the laboratory diagnosis of HSV, paired serum and CSF samples collected 10-20 days apart are suitable for antibody detection by ELISA, while CSF and brain tissue specimen collected at acute stage of illness are useful for virus isolation and antigen detection by immunocytochemistry, immunofluorescence tests and nucleic acid detection by polymerase chain reaction (Vani et al 1994). Rapid diagnosis can be made by screening inflamatory cells or by antiviral antibody detection in CSF or serum of patients (Sreedharan et al 1994).

6. Subacute sclerosing panencephalitis (SSPE)

It is a chronic and persistant neuro-degeneartive infection of CNS caused by measles virus. Number of studies from India detected antimeasles antibody in the CSF and serum of patients with SSPE, having significant morbidity and mortality (Singhal et al 1974, Broor et al 1979, Thakare et al 1987). Mathur et al (2000) demonstrated the presence of antimeasles antibody in the CSF and serum of patients with encephalitis. Ravi et al (1992) at NIMHANS, Bangalore studied 1223 laboratory confirmed cases of measles infection, out of which 828 turned out as SSPE. From a tertiary care center, clinical profile for adult onset of SSPE was investigated and compared with the juvenile onset patients by Prashant et al (2006). Diagnosis was based on clinical and electroencephalographic findings and raised anti-measles antibody titres in cerebrospinal fluid. According to them, SSPE in adults poses diagnostic challenges for clinicians. A high index of suspicion and appropriate investigations are necessary for early diagnosis. High vaccination coverage rates and the administration of second dose of measles vaccine have resulted in a significant decline in the incidence of SSPE in many countries. However, in India incidence of SSPE remains high. The risk of SSPE after measles vaccination has been estimated at 0.7/million doses. There is a report of developing SSPE presumably as a result of delayed effect of measles, mumps, and rubella (MMR) vaccine (Belgamwar et al 1997).

The serum and CSF of healthy and infected (central demyelinations, subacute sclerosing panencephalitis, Guillain Barre Syndrome and cerebrovascular accidents) person was studied for CSF albumin quotient, IgG index and synthesis rate (Prabhakar et al 1990). Progressive rubella panencephalitis (PRP), SSPE

and PML are due to the rubella virus, measles virus and opportunistic JC papovavirus infection respectively. But majority of cases is now due to HIV-1 infection. The symptoms are hemaporesis, visual loss, aphasia, seizures, dementia, personality changes, gait problems and less commonly cerebellar, brain stem, and spinal cord features. Death is the last destination. Neuroimaging shows a very characteristic white matter lesion most commonly posteriorly in the parietal occipital area without enhancement or mass effect.

7. Rabies

Rabies is a severe, highly fatal viral encephalomyelitis caused by rhabdovirus. It is primarily a zoonotic disease of warm-blooded animals, specially the canines (dogs, cats, wolves, jackals, bats) that account for 99% of all human rabies. Veeraraghavan et al (1965, 1966) had reported case of rabies in bat bitten human in Kaviti village India. It is endemic in India and continues to occur with considerable magnitude with an estimated 3 per 1, 00,000 cases per year and the annual human mortality rate is 25,000 with three million people receiving post-exposure prophylaxis. Man is infected by the bite or lick of the rabid animal. Veeraraghavan and Balasubramanian (1958) detected the presence of the rabies virus in submandibular glands in dogs, which were positive for the rabies infection during laboratory diagnosis. They also isolated the virus from submandibular glands, but were unable to isolate it from the encephalon. Pasteur Institute, Coonoor, India reported five serial cases with unusual chronically infected dog, which transferred the infection to the human. This dog after the death of patients was kept under observation from 1966-1970. Rabies virus was isolated from the saliva of dog with and without giving the course of prednisolone. Bur Rabies virus was not isolated from dog's brain, spinal cord or salivary gland after the postmortem even after getting positive results for fluorescent antibody staining to rabies antigen in brain and spinal cord. No antigen was found in the dog's blood at any time. This was extremely interesting and unusual serial-reports as seronegative dog transferred the virus to human (Veeraraghavan et al, 1972, 1987). Cortieosteroids are reported to be beneficial for the improvement of conrplicaations following antirabies vaccine (Veeraraghavan1955). Protective role of ACTH during rabies and receptor-destroying enzyme of V. cholerae was also demonstrated (Veeraraghavan and Balasubramanian, 1954a, 1954b). The evaluation of different rabies vaccine was done Pasteur Institute, Coonoor, India. The importance of antirabies serum and vaccines were analysed in exposed and unexposed individuald (Veeraraghavan and Subrahmanyan, 1963a, 1960, Veeraraghavan, 1954c), antigenic value of lyophilized phenolized antirabies vaccine (Veeraraghavan and Subrahmanyan, 1961) and in retreatment value of booster doses of vaccine was also done (Veeraraghavan and Subrahmanyan, 1963a and 1963b).

Sandhyamani et al (1981) have studied the brain pathology of rabies in detail and reported characteristic intracytoplasmic three types of inclusion body (Negri body) in neurons. Suja et al (2004) reported rabies encephalomyelitis caused

by bite of a rabid wild fox (*Vulpes vulpes*). Immunostaining using polyclonal antibodies to the rabies viral nucleocapsid antigen and to the whole virion demonstrated high viral load within neurons with extensive spread along axonal tracts. Genomic sequence analysis demonstrated close homology with canine virus strain with only minor variations. A sensitive, specific and rapid simple enzyme immuno-assay (EIA) has been developed to detect rabies antigen in the brain specimens of animals and humans. (Vasanth et al, 2004). Diagnosis can also be made by detection of viral antigen by immunofluorescence observations on skin biopsies, corneal impression smears or brain biopsy. Characteristic intracytoplasmic inclusions (Negri bodies) are seen in neurons. Virus could be isolated by intracerebral inoculation in newborn Swiss albino mice (Rathor et al 2001). More specific and sensitive immunoperoxidase test for the diagnosis of rabies was developed as an alternative to fluorescent antibody test (Kotwal et al 1985).

The study of negri body of rabies in human and mouse brain (Veeraraghavan, 1951) had shown that nucleocapsid virions are emerging and accumulating in Negri body (tubular/bullet shaped thought to be viral). The post exposure treatment of class three bite cases, as recommended by the World Health Organization, must involve the administration of human rabies immunoglobulin as soon as possible and up to the seventh day of start of anti rabies vaccination to ensure passive immunization. If the risk is definitive, active immunization should start with killed diploid cell-derived rabies virus vaccine (Goel et al 2003). Chhabra et al (2005) have demonstrated that purified chick embryo cell vaccine (PCECV) is safe and highly immunogenic in Indian subjects when administered intradermally as 0.1 mL/site using the "2-2-2-0-1-1" post-exposure regimen. Nervous tissue vaccine is still used in India because of its low cost, but there is problem of neuroparalysis. This occurs due to an immune mediated demyelination induced by myelin protein in vaccine. Acquisition of spongiform encephalopathies in India through sheep-brain rabies vaccination was studied by Arya (1991).

8. Kyasanur forest disease (KFD)

Tick-borne Kyasanur forest disease (KFD) is febrile hemorrhagic illness caused by highly pathogenic flavivirus Kyasanur Forest Disease virus (KFD). First cases of KFD were diagnosed in 1957 at Kyasanur Forest, Shimoga district Karnataka, India. Thus it was named as KFD. KFDV is genetically closely related to tick borne encephalitis viruses Russian spring summer encephalitis (RSSE) virus group, but produce hemorrhagic fever instead of encephalitis (Banerjee, 1977). Although some serologic surveys suggest that the virus is active in other parts of country since 1970 but till date virus is only isolated in Karnataka, India (Bhat, 1983; Sarkar and Chatterjee, 1962; Padbidri et al, 2002). Fatality rate associated with KFD is only 2–10% (Pattnaik, 2006). The exact reason of the sudden emergence of KFDV in India during the late 1950s and the subsequent localization

to Karnataka state alone are not clear. Since 1957 different outbreaks were reported and every year there is increase in the infection (Chin, 2000; Pattnaik, 2006).

Most cases in men are reported during dry season. Rural grazers living in epidemic areas are more prone to the infection (Upadhyaya et al, 1975a, b). But cases were also reported in laboratory personnel (Pavri, 1989). Epidemics generally start by infection in monkeys. High mortality in monkeys was reported (Sreenivasan *et al.,* 1986) and Epizootiology of KFD in wild moneys of Shimoga, specifically the death of monkeys in dry seasons (February and March) correlates well with human cases of KFD (Goverdhan et al, 1974). However, in nature monkeys are not supposed to be the reservoir of the virus. *Suncus murinus*, *Rattus blanfordi*, porcupines, and squirrels are suppose to be the natural reservoir of KFDV as virus has been isolated as well as and the presence of neutralizing antibodies is also confirmed. Monkeys, *P. entellus* and *M. radiata*, are amplifiers of the virus. Man and cattle are accidental hosts. (WHO,1985). Infection is transmitted by the bite of *Haemaphysalis spinigera* tick as its larvae and nymphs parasitize birds and monkeys. The adult tick feeds on cattle. *H. spinigera* nymphs attach themselves to humans, and transmit the virus (Varma, 1989). Intensity of the infection is directly correlates with the density and infected number of vector (Banerjee and Bhat, 1977). Unfed nymphs are highly anthropophilic and transmit the disease to humans by bites. Ticks also transmit the virus transovarialy. Experiments suggests that an infected adult tick shows a high titre virus and virus can be detected for as long as 245 days after infection (Bhat et al, 1978).

The clinical symptoms include sudden onset of fever, anorexia, cephalalgia, insomnia and myalgia. On third or fourth day, diarrhea and vomiting start. Prostration, palpable cervical and axillary lymph and papulovesicular lesions on the palate are common symptoms during infection. Hemorrhagic manifestations are very common in poor and malnourished agricultural workers with other co-infection. IgE has also been implicated as a cofactor, lymphocytosis, interferonemia is concomitant with the viremic phase in the immunopathology of KFD (Pavri, 1989, Sathe et al. 1991). Parenchymal degeneration of the liver and kidney, haemorrhagic pneumonitis, moderate to marked prominence of the reticuloendothelial elements in the liver and spleen, with marked erythrophagocytosis (Lyer et al, 1959). Prominent thrombocytopenia, neutropenia and leukopenia is common (Chatterjee et al, 1963) and bradycardia and hypotension are prominent signs. The fever lasts for 6-11 days. After an afebrile period of 9 to 21 days, patients faces second phase of pyrexia combined with neurological symptoms such as abnormal reflexes, mental confusion, stiffness of the neck and tremors (Webb and Rao, 1961; Wadia, 1975). Phagocytosis of erythrocytes and nuclear material was observed in peripheral blood. It is assumed that the nuclear material came from leukocytes that had been destroyed (Webb and Burston, 1966).

The only molecular information available is the nucleotide sequences of genes encoding the vital structural proteins (Venugopal et al, 1994) Homology

modeling (Pattnaik et al, 2004). Presence of KFDV specific neutralizing antibodies in fed blood has no effect on survival of KFDV in the ticks (Singh et al, 1965). Different vaccines were made and trials were performed Aniker et al, 1962; Mansharamani et al, 1965; Dandawate et al, 1965b; Mansharamani et al, 1967a, b; Banerjee et al, 1969; Anderson and Singh, 1971, Bhatt and Anderson 1971; Bhatt and Dandawate, 1974; Thind, 1981; Kayser et al, 1985, Upadhyaya et al, 1979). Formalin-inactivated vaccine produced in chick embryo fibroblasts proven to be most effective (Dandawate et al, 1986). But despite of routine vaccination, during 1999 to 2004 increase in the number of KFD cases have been reported in Karnataka.

9. Nipah virus (NiV)

During early 2001 an outbreak of febrile illness associated with altered sensorium was observed in Siliguri, West Bengal, India. Patients were positive for NiV-specific IgM and IgG ELISA and NiV specific reverse transcription–polymerase chain reaction. Sequence analysis also conformed the same and also provided the evidenced that the NiV strain is more closely related to NiV from Bangladesh isolates than Malaysia isolates. This is the first report of Nipah virus infection in India (Chadha et al, 2006).

10. Hepatitis virus induced hepatic encephalopathy

Hepatitis A virus is more frequent in India but its infections are self-limiting with low rate of fulminant hepatic failure (FHF). In India Hepatitis B and Hepatitis E is main cause of acute liver failure (Aggarwal, 2007; Acharya et al, 2000). Superinfection with Hepatitis E virus in patients with underlying CLD causes severe liver decomposition that is frequently complicated with hepatic encephalopathy (Monga et al, 2004). The prevalence of IgG anti-HEV antibodies among the adult population in endemic regions is only 33%- 40%. More than 80% of chronic liver disease (CLD) patients lack these antibodies. Acute hepatic failure and FHF in India is always present with encephalopathy within four weeks of the onset of acute hepatitis. Most of the FHF were caused by presumptive non-A, non-B viral infection. The cause and rapidity of the onset of hepatic encephalopathy in patients with FHF have been reported as important prognostic predictors of Hepatitis E infection (Monga et al, 2004; Acharya et al, 1996). Acute liver failure due to acute Hepatitis E infection in pregnant woman has high mortality especially in those women who have high grade of encephalopathy (Banait et al, 2007). During hepatitis infection opportunistic infections like fungus and gram-negative bacteria cause sepsis and cerebral odema (Acharya et al, 2000). Drug induced hepatitis associated with hepatic encephalopathy is sometimes seen during tuberculosis treatment (Gupta and Tekchandani, 1994).

11. Human immunodeficiency virus (HIV)

HIV-1 and HIV-2 is the causative agent of Acquired immunodeficiency syndrome (AIDS). It is a lentivirus (slow virus), belonging to the group of retroviruses, having a positive single stranded RNA genome. The first case of HIV was reported from Bombay in 1982. Now India is one of the most affected country by HIV and as the cases of AIDS are increasing, the cases of neurological disorders are increasing (UNAIDS report, 2006). According to the reports, 40-50% of patients at the later stages of HIV infection usually develop neurological problems and in 10% of the cases the first sign of this may be neurological illness. HIV-1 subtype C is prominent in most of the cases of AIDS in India. The exact numbers of the AIDS patients are not available due to social stigma, illiteracy, and unavailability of the proper diagnosis. In autopsy, nearly 82% of HIV infected individuals are suffering with the neurological problems like peripheral neuropathy (most common), opportunistic infections (OIs), encephalitis and lymphomas (Shankar et al 2005). The viruses were recovered from the cerebrospinal fluid (CSF), spinal cord, and brain (Ho et al 1985). The higher IgG level in the CSF compared to serum also characterizes the CNS infection in HIV patients. During the early course of the disease, the polyclonal hypergammaglobulinemia induced by the virus results in demyelinating diseases of the central and peripheral nervous systems (CNS and PNS). As the HIV infection progresses, the direct toxic effects of the virus unfold, directly damaging the CNS and PNS, resulting in protean clinical manifestations (Deshpandey & Patnaik 2005). HIV replication results in a decrease in the number of circulating CD4+ T-helper cells and persistent viral replication, which results in immunologic decline leading to opportunistic infections and neoplasms.

HIV does not directly invade nerve cells but it affects their functioning leading to the symptoms like confusion, forgetfulness, behavioral changes, severe headaches, progressive weakness, loss of sensation in the arms and legs, stroke, cognitive motor impairment or damage to the peripheral nerves, spinal cord problems, lack of coordination, vision loss, gait disorders, destruction of brain tissue, and coma (Deshpande & Patnaik 2005). The three top order opportunistic infections associated with HIV in India are cryptococcal meningitis, cerebral toxoplasmosis, and tubercular bacterial meningitis (TBM). Cryptococcosis is a common fungal brain infection of patients with AIDS and usually presents as meningitis or meningioencephalitis (Shankar et al 2005; Wadia et al 2001). In a study of ten HIV positive individuals from Bangalore, 9 had evidence of neuro- AIDS, in which Cryptococcal meningitis (CM) was seen in five cases with disseminated systemic cryptococcosis in two (Santosh et al 1995). Lanjewar et al (1998) had also studied the spectrum of neuropathological brain lesion in HIV/AIDS cases in Mumbai. The autopsy study revealed that opportunistic infections (OIs) were present in 39% of the cases, of which cryptococcosis was present in 8%. Prevalence of fungal meningitis amongst HIV patients was demonstrated in 15 (3.1%) of 483 AIDS cases. 12 of them had CM, while 3 were infected with Candida albicans (Jaiswal et al 2002). In two studies conducted in HIV positive patients in Mumbai and Chennai,

CM has been reported as the most common opportunistic infection of the CNS with HIV and accounted for 2-4.7%of opportunistic infections (Kumaraswamy et al 2003; Vajpayee et al 2003). Diagnosis of CM is based on demonstration of organism in CSF (India ink smear), a positive blood culture and CSF antigen latex agglutination test.

Several reports indicate rising trend of visceral leishmaniasis (VL) and HIV co-infection. Both VL and HIV tend to lower the cell-mediated immunity (CMI) resulting in poor drug response and other OIs. Diagnosis of such co-infected cases is quite difficult. Tests like nested PCR, rk39 immunochromatographic test etc., can be of help. Other common opportunistic infections prevalent in India are aspergillosis, candidiasis, *Nocardia asteroides*, *Histoplasma capsulatum* causing meningoencephalitis, zygomycosis, *Penicillium marneffeiand*, *Cladosporium bantianum*, herpes family [primarily cytomegalovirus (CMV) and less frequently VZV and HSV] and papova virus. Lesions which were studied by Santosh et al (1995) using autopsy and biopsy material, showed that 90% of the HIV positive patients were suffering from neuro-AIDS and 80% were found suffering from OIs like CM, tuberculous lymphadenopathy, toxoplasma encephalitis, acanthoamoeba, meningococcal meningitis, *Pseudomonas septicaemia*, *Pneumocystis carinii* pneumonia and HIV leukoencephalopathy. The incidence of PML caused by JC virus has increased along with the high incidence of HIV/AIDS, though very few proven cases have been reported from India. By specific immunohistochemical staining of biopsy tissues of diffuse white matter lesion of HIV positive individuals, Yasha et al (2005) have established the diagnosis of PML caused by JC virus. The histological examination revealed intranuclear, basophilic inclusion bearing oligodendrocytes and cytoplasmic positivity of the astrocytes. Infections like *Cryptosporidium* and *Plasmodium* (protozoans) are also seen in HIV-1 infection.

The era of highly active antiretroviral therapy (HAART) has led to a considerable decline in the HIV disease progression rates and HIV-1-related OIs especially in developed countries. It needs to be given for management of HIV infection along with treatment of other OIs (Sinha et al 2005). With the incidence of patients infected with HIV increasing in India, the CNS manifestations of the disease will be seen more frequently. Unfortunately due of cost concern, antiretroviral treatment is not available for high number of HIV-infected population. Although a number of studies have shown uniform impact of HAART on disease progression; its effect on treating HIV infection of the brain and its manifestations, such as AIDS dementia complex (ADC), remains unclear, along with the reasons why AIDS dementia complex continues to be a problem in the era of HAART (Saksena 2005).

(B) Poliomylitis

Polio continues to be a serious threat to children in South- East Asia. 40% of the confirmed cases of Poliomylitis and 60% of “wild” Polio virus isolated world

wide are contributed from India (CDC, MMWR 2000). Poliomylitis was endemic in India with isolated epidemics reported from some parts of the country (Dave 1960, Gujaral et al 1971). The endemicity has been shown by serological studies and isolation of viruses (John et al 1970, Chaturvedi et al 1971). There are very few reports of intra-typing of Polio virus isolates from India. A study done on South Indian population shows that out of 607 Polio virus intratyped, 573 were found to be wild type (Deshpande & Dave 1991). Another study done in 1996 reported absence of wild Polio virus isolates from healthy children of the same area; although most of the stool samples were collected from children who were recently vaccinated (Deshpande et al 1996).

In 1980 the annual number of the polio patients was estimated to be 4,48,000, the time represents true pre-vaccination era (Basu 1981). Although oral polio vaccine (OPV) was available for use in India from 1980, but most of the target population was unvaccinated till 1990. Only after 1990, the incidence of poliomylitis had declined rapidly due to high vaccine coverage. Currently poliomylitis cases have shown a major decline (only 141 wild polio virus confirmed cases in 2001 have been reported) which is attributed to the use of OPV. Oral Polio vaccination will only be stopped, when the eradication of the wild polio virus has been documented convincingly; however the extensive use of live polio virus vaccine results in circulation of mutated vaccine virus arising due to inter and intra-human passage (Li et al 1996). Since 1997, surveillance of acute flaccid paralysis (AFP) was established in India to support polio erradication programme (Bannerjee et al 2000). In 2004, India reported the lowest number (66) of polio cases on record with transmission limited to key districts in parts of UP, Bihar and Mumbai. But in 2006 again a surge in the number of cases of polio occurred with more than 258 cases till September 2006 (Mudur 2006).The greatest barrier to successful prevention of polio virus transmission in India remains the difficulties in reaching the final 10% of the children in these key high-risk districts. Another high risk connected with the polio is the improper maintainance of “cold-chain”.

The cases of AFP due to wild polio virus infections are of primary importance to the polio erradication programme; so non-polio enteroviruses isolated from the cases are normally not studied further (Deshpande et al 2003). Even though polio virus is the common etiological agent for AFP in Northern India, non-polio enteroviruses such as Echo viruses (30 serotypes), Coxsackie viruses Group A (23 serotypes) and Group B (6 serotypes) and numbered Enteroviruses (Enterovirus 68-71) are also emerging as important pathogens for this condition (Sokhey et al 1996). Coxsackie B viruses (serotype 1-6) are implicated in severe acute and chronic diseases (Kapoor et al, 2001). Echovirus 7 and 11 isolates are found to be more frequent in cases of encephalitis (Madhavan & Sharma,1969).

(C) Prions

Prions are the infectious proteins that are devoid of nucleic acid and degeneration of CNS. **Creutzfeldt-Jacob disease (CJD)** is a rare and invariably fatal neuro-degenerative disorder. The first report of CJD in India was in 1968 at NIMHANS, Bangalore and since then few more cases have been reported from there (Shankar & Satish Chandra). Recently 10 cases of CJD were detected in North India (Mehndiratta et al 2001).

Bacterial infections of CNS

Bacteria can cause acute infection of CNS by haematogenous dissemination or local invasion from infected ear, sinuses or local injury or via neurotoxins produced at other site of infection and carried to the CNS. The organism most commonly responsible for acute bacterial meningitis is *Streptococcus pneumoniae* in adult and *Haemophillus influenzae* in infant and children, while meningitis by *Meningococci* is of low prevalence. The most important cause of subacute and chronic CNS infection is *Mycobacterium tuberculosis.*

1. Neurotuberculosis

It is one of the major causes of CNS infection in India. Incidence of tuberculosis is increasing mainly as a consequence of the increasing prevalence of HIV infection. The types and extent of the lesions depend on the host immune response. Tandon et al (1988) observed that in immunized tuberculin negative monkeys intracisternal infection of live tubercle bacilli resulted in diffuse meningitis, while in BCG vaccinated animals the meningitis is localized to the site of infection. In a study carried out to find the humoral and cell mediated immunity in patients with tuberculous meningitis (TBM), Kamat et al (1999) have observed hypergammaglobulenemia of IgG, IgM and IgA with a decrease in the total T cells and a lower T_H:T_s cell ratio indicating a deficiency or a defect in immune system of patient infected with TBM. Incidence of neurotuberculosis in hospital based studies in sixties and seventies reported that 2-5% of all pediatric admissions in India suffer from TBM. 5-10% of all adult admissions in Neurology department of AIIMS are cases of neurotuberculosis (Prasad & Menon 1997). The protective role of BCG vaccination against TBM is controversial in India, largely due to the presence of the other predisposing factors such as age, nutritional and socio-economic status and household contact (Kumar et al 2005). In a study done between 1972-1992 at the TB clinic, Institute of Child Health, Madras, Somu et al (1994) have observed the occurrence of TBM in the ratio of 1:3 among BCG vaccinated and non-vaccinated children. The different forms of neurotuberculosis are tubercular meningitis, which is the most prevalent form of neurotuberculosis in children (Karande et al 2005), intracranial tuberculoma, tuberculous encephalitis, tuberculous brain abscess and tuberculous arachnoiditis. TBM is mostly secondary to tuberculosis elsewhere in body. Though in majority of cases the primary focus is

difficult to identify, widespread hematogenous spread is common with TBM (Maniar 1994).

Since mid-fifties, significant contributions had been made in the field of neurotuberculosis (Tandon 1973, 1978; Gourie-Devi et al 1981). There have been many studies from India where various prognostic factors affecting the outcome during TBM have been evaluated. In a study conducted in Government general hospital in Kakinada, India, (Jakka et al 2005) have shown adverse neurological outcome in childhood tuberculous meningitis associated with increased cerebrospinal fluid adenosine deaminase levels. Younger age, tonic posturing, papilloedema, focal neurological deficit and stage at presentation have been shown to affect adversely in the prognosis of children with tuberculous meningitis by Mahadevan et al (2002). The level of LDH rises sharply in complicated cases and rising titre indicates neurological sequelae. Estimation of myelin basic protein (MBP) in CSF indicates host response to neurotuberculosis [normal values indicate a good prognosis and high level of MBP severe neurological complications (Moharana 1998)]. Clinical profile of bacteriologically confirmed 107 cases of tuberculous meningitis were studied and it was observed that mortality during the first month of illness was 22%, while some of the cases presented acute neurological illness (Thilothammal et al 1995).

Neurotuberculosis may present in a variety of atypical forms: appearance of intracranial tuberculoma (Ira 2005), unilateral thickening of the meninges (Praharaj et al 1997), tuberculous radiculomylitis or arachnoiditis (Phadke et al 1994), Guillian – Barre syndrome (Rama Rao 1983), tuberculous abscess of the brain (Chandramukhi et al 1981) and intramedullary tuberculoma (Shaharao et al 2004). Intravenous drug addicts with AIDS are at higher risk of CNS tuberculoma and tuberculous brain abscess, which may develop without meningeal involvement. The diagnosis of TBM is often presumptive and is based on the clinical and CSF findings, whereas radiological and bacteriological findings add-up to the post-test probability of the diagnosis. Ahuja et al (1994) have described a set of diagnostic criteria for the diagnosis of TBM using clinical, CSF, bacteriological and radiological findings. Newer techniques based on molecular biology tool like DNA probes, monoclonal antibodies and a battery of purified mycobacterial antigens help in accurate immunodiagnosis on a large scale.

The characteristic CSF picture consists of lymphocytic pleocytosis, raised protein and moderately low or normal sugar. Protein above 1 gm% is seen in severe and advanced cases. ESR is usually raised (Prasad & Menon 1997). The confirmatory tests based on detection of *Mycobacterium* include CSF smear examination and CSF culture for acid-fast bacilli (AFB), tests based on the mycobacterial products/ constituents are detection of CSF 3-(2- ketohexyl) indoline and *M. tuberculosis* antigen in CSF by ELISA, RIA and *M. tuberculosis* DNA by PCR with 100% specificity (Kulkarni et al 2005; Srivastava et al 2006). There are tests based on the detection of host response such as CSF lymphocyte

transformation assay, anti-BCG secreting cells in CSF, antibody to *M. tuberculosis* in CSF, leukocyte migration inhibition assay, T-cell immunoblotting, adenosine deaminase (ADA), floating tubercles in CSF cytology and bromide partition test. But the accuracy of a diagnostic test is best determined by its sensitivity and specificity. Various workers have studied the sensitivity and specificity of these tests like ELISA has been evaluated by a number of workers (Desai et al 1993; Shankar et al 1991).

Research on tuberculosis at Central Drug Research Institute (CDRI), Lucknow has aimed at finding new drug. This area has been supported by search of new, efficient and non-hazardous screening system (Srivastava et al 1998), identification of new drug targets, rapid and early diagnosis of tuberculosis with help of *M. tuberculosis* specific DNA sequences (Prasad et al 2001). A repetitive sequence specific to *M. tuberculosis* was isolated from a lambda-gt11 library of *M. tuberculosis* by DNA : DNA hybridization using genomic DNA of the bacteria as probe followed by subtractive hybridization with cocktail of other *M. tuberculosis* DNA. This leads to identification of 1291 bp fragment of *M. tuberculosis* containing repetitive sequences, which produced positive hybridization signal with *M. tuberculosis* DNA with in 30 minutes.

2. Acute Bacterial Meningitis (ABM)

ABM constitutes an acute neurological disorder associated with significant morbidity and mortality in developing countries. The infection of the meninges is often associated with septicemia but rarely the primary source of infection could be the respiratory tract, ear, infected meningocele or cephalhematoma (Ghai 1993). Studies on pyogenic meningitis carried out in different parts of country, demonstrated predominant etiological agent as *Pneumococci* (Gogate & Deodhar 1984; Ayyagiri et al 1984). The other bacteria to cause bacterial pyogenic meningitis have been shown to be *Salmonella* (Ayyagiri et al 1985), *Meningococci*, *H. influenzae*, *Citobacter, Pseudomonas* (Ghosh et al 2000), and *Bacillus anthrasis* (Chandramukhi 1982).

Hospital outbreak of neonatal meningitis by *Salmonella* has been shown to be due to serotype *Worthington* (Ghadage & Bal 2003; Ayyagiri et al 1990; Udani et al 1999). A retrospective analysis of childhood ABM from a tertiary care hospital in Bangalore revealed a winter clustering of cases and an absence of typical signs and symptoms in 40% cases of patients with *Staphylococcus aureus* (10%) and coagulase negative *Staphylococcus* (9%) being the most common etiological agent (Pulickal et al 2005). The burden of invasive *H. influenzae* type b (Hob) is substantial with the incidence of Hib meningitis estimated to be 50-60 cases / 10,000 children below five years of age (John et al 1998). Chinchankar et al (2002) from Pune analyzed the profile of ABM in early childhood and have found *Streptococcus pneumoniae* (39%) to be the predominant microbe. In another study, 35% emergence of drug resistant *Pneumonococcal* meningitis has been observed

followed by *H. influenzae* type b (26%) by Vashishtha (2000). In a prospective surveillance study of acute infection caused by *H. influenzae* conducted in six referral Indian hospitals during 1993-1997, it is shown that 75% of the patients who had *H. influenzae* were below five years of age and 62% of the patients had meningitis (IBIS Group of International Clinical Epidemiology Network 2002). Sahai et al (2001) have analyzed 100 cases of ABM in children aged between one month and twelve year and shown that the overall case fatality ratio was 25%. *S. pneumoniae* had a higher case fatality rate than Salmonella group B and *H. influenzae* (50% vs.17% vs. 12%). Another study carried out by Seetha et al (1999) had reported that the percentage of bacterial isolates was highest in infants and children where as *Cryptococcus* species was isolated from adult patients.

Acinetobacter meningitis following head injury has been reported by Venkataraman et al (1999). Clostridia rarely cause meningitis infection. Treponema involving CNS is usually those causing neurosyphilis (Srinivasan & Ranganatha 1977). Iatrogenic meningitis is a rare complication of lumbar puncture (LP). Pandian et al (2004) have studied all cases of iatrogenic meningitis occurred 24 hours to 21 days after LP, managed in the Department of Neurology of two referral hospitals at Ludhiana, India between 1984-2002. In the study, the organisms isolated from CSF were *Pseudomonas aerugenosa, Staphylococcus aureus, Acinetobacter spp., M. tuberculosis* and apsergillosis. Infection following CSF shunt has been reported by Upadhyaya (1985) and Bhatnagar (1983), whereas incidence of post-operative meningitis at NIMHANS between 1978 and 1988 was 2.18% (Chandramukhi 1989).

Basic studies of CSF including routine biochemical methods and microneurological studies such as gram staining, culture, antigen detection by latex agglutination test and C-reactive protein detection are the most important aspect of laboratory diagnosis of meningitis. The diagnosis of bacterial meningitis based on direct microscopy is quick but lacks sensitivity. Culture takes at least 24 hours and is very often negative to prior treatment with antibiotics. Newer techniques based on immunological methods or gene amplification hold great promise for diagnosis of infections caused by organisms that are difficult to culture or present in small number. Pandit et al (2005) and Sharma et al (2002) have documented that PCR based assays are useful adjuncts to conventional bacterial culture and antigen detection methods in establishing the bacterial etiology in meningitis in settings where substantial number of specimens are culture negative. Molecular diagnostic methods, though expensive, are justified in developing countries like India. PCR is a sensitive and specific diagnostic tool that may be valuable in a population with high pre-hospital antibiotic usage (Singhi et al 2002).

3. Tubercular bacterial meningitis (TBM)

TBM is less common than cryptococcal meningitis and toxoplasmosis in Indian patients, despite the prevalence of pulmonary and extra pulmonary tuberculosis. Wadia et al (2001) observed that tubercular meningitis is present in

18%, amongst a large number of patients with neurological complications. Nexus of infections (tuberculoma of brain, pulmonary tuberculosis and visceral leishmania) with human immunodeficiency virus in an individual in Bihar has been reported (Pandey et al 2005). There are certain differences between HIV positive and HIV negative patients of TB meningitis. In HIV patients there is reduced and atypical inflammatory response, extensive vasculopathy and cognitive dysfunction is more common. Mortality is also high in such patients. In the CT scan of HIV patients, there would be absence or minimal meningeal enhancement and absence of communicating hydrocephalus.

4. Brain abscess

Brain abscess is a serious, life threatening complication of several diseases. Immediate treatment is necessary for reduction in mortality. Recently, an increasing proportion of brain abscesses are not caused by classic pyogenic bacteria; but rather by fungi and parasites, including *Entamoeba histolytica, Toxoplasma, Acanthamoeba, Paragonimus, Schistosoma, Spirometra,* and *Trichinella*.

In a study of 406 cases of brain abscess, both anaerobic and aerobic microbes were isolated. In over 85% of cases, the predominant anaerobic gram-negative bacilli were bacteroides, fusobacteria while anaerobic gram-positive cocci were *Clostridium* (Chandramukhi, 1989). Number of other workers has also shown that the anaerobic organisms are the major causative agents in brain abscess (Gupta et al 1986; Koshi & Lalitha 1982). In an investigation of brain abscess, identification and antimicrobial susceptibility of anaerobic strains were performed by conventional methods and the newer RapID ANA II panel and E-test methods, respectively. Characterization of the anaerobic isolates was done by RFLP in 18 cases of brain abscess. Anaerobic or aerobic organisms alone were recovered in 16.6% and mixed (aerobic and anaerobic both) in another 16.6% patients. The predominant anaerobes were *Prevotella melaninogenicus*, *Bacteroides preacutus*, *Fusobacterium nucleatum* and *Peptostreptococcus spp.* (all Gram positive cocci). All the anaerobic isolates were susceptible to metronidazole, except few isolates of *P. melaninogenicus*, which were resistant to penicillin. These findings indicate the microbial complexity of brain abscess and the need to target antimicrobial therapy against both the anaerobic and aerobic components of infection (Chaudhary et al 1998).

CNS melioidosis is a rare phenomenon and caused by *Burkholderia pseudomallei*, leading to brain abscess and has been reported by Lath et al (1998). *Angiostrongylus cantonensis* abscess in the brain was studied by Prakash et al (1992). Cerebral abscess caused by chromogenic fungus *Cladosporium trichoides* has been reported by Vyas et al (2000). Reports on human actinomycosis documented by culture have been infrequent particularly from India, though Koshi et al (1981) have reported cases of actinomycosis of brain confirmed by culture.

The commonest cause of brain abscess is chronic suppurative otitis media followed by compound injuries as demonstrated by Gupta et al (1990). In majority of the cases, the causative organism was *Pseudomonas.* Brain abscess with chronic suppurative otitis media caused by *Scedosporium apiposporium* in a non-immunocompromised child has been reported by Acharya et al (2006). The association of brain abscess with congenital heart disease was investigated by Ghosh et al (1990). Headache was the predominant clinical feature and anaerobic *Streptococci* were the commonest pathogen involved in the brain abscess. Other route of infection in the brain is hematogenous spread from distinct foci. Bonvin et al (1998) have reported a case of brain abscess caused by *Salmonella entritidis* in a previously healthy man, who spent 2 weeks in North India. Intracranial abscess and subdural abscess due to *Salmonella typhi* had been reported by Mahapatra and Bhatia (1987). The evaluation of the clinical profile, treatment and outcome of adult and pediatric patients presenting with intracranial abscess of otogenic origin was done and the advantages of concurrent craniotomy and mastoidectomy in abscess was studied. Children were found more commonly affected than adults, and there was a male preponderance. Meningitis was the most frequent intracranial complication, followed by cerebellar abscess (Kurien 1998). Early diagnosis of etiological agents in cases of brain abscess by conventional methods including CT scan and newer rapid tests is of paramount importance.

5. Neural Leprosy

Leprosy is a slowly progressive chronic infectious disease caused by bacillus *Mycobacterium leprae*. Bacilli localize preferably in the skin and peripheral nerves and have a propensity to cause nerve damage (Khanolkar 1964; Dastur et al 1973 a and b). The spectrum of clinical and pathological manifestations of the disease ranges from lepromatous to tuberculoid depending upon host T- cell mediated response. Pure neuritic leprosy (PNL) is difficult to diagnose and nerve biopsy is necessary to establish the diagnosis (Lalitha et al 1977).

A study conducted by Kumar et al (2004) observed that PNL constitutes a significant proportion of cases in India. Of the total 1542 leprosy patients seen between 1993 and 2003 at PGI, Chandigarh, 42% had PNL. Majority of the patients presented with involvement of two or more nerves, while mononeuritis was seen in 40% of the PNL patients. The study of leprosy in children by Sehgal and Joginder (1990) has indicated an incidence of 10% amongst all leprosy patients. The bacteriology was largely unproductive by slit-skin smears. They have also suggested that the diagnosis of leprosy should primarily be based on clinical features. In Mumbai, a population survey of 22287 industrial workers was done for leprosy and 270 leprosy cases were detected (PR 12/1000), however only 13 multibacillary cases (P.R. 0.5/1000) could be unearthed (Revankar et al 1989). An increasing incidence of Leprosy in low endemic area at Delhi has been observed, indicating urbanization and movement of people in search of employment etc. as the causative factors (Misra et al 1989).

Laxmisha et al (2004) came across a rare presentation of PNL presenting with multiple nerve abscesses. The biopsy of left radial cutaneous nerve showed granulomatous infiltrate of epitheloid cells, lymphocytes and caeseation necrosis of nerve. No bacilli were demonstrated with acid-fast stain. The co-existence of leprosy with neurofibromatosis is a rare finding, which has been reported by Grover et al (2005). In a follow-up study of patients with PNL, Suneetha et al (2005) have studied the development of cutaneous lesions and concluded that leprosy primarily affects the nerve and that a neuritic phase precedes the development of visible cutaneous lesions. In a disability pattern study of leprosy in Gorakhpur, it was found that disability was most commonly seen in lepromatous leprosy. Disability index was higher in males and was found to increase with increasing age of patient and duration of disease (Girdhar et al 1989).

6. Brucellosis

Neurobrucellosis is a rare but serious manifestation affecting CNS and peripheral nervous system caused by bacteria *Brucella melitensis*, *B. abortus*, *B. suis*, and *B. canis*. The clinical symptoms of infection mimic closely to diseases like tubercular meningitis, viral encephalitis, aseptic meningitis, cerebral malaria and viral encephalopathy. Since June 1997 to May 2003, 175 cases of Neurobrucellosis are reported in Bikaner, Rajasthan (Kochar et. al., 2007). In Indian patients, pulmonary manifestations of brucellosis was also observed which is again very rare (Kochar et. al., 2003). Serum and CSF testing for *Brucella* antibody titre is must to diagnose the infection and blood culturing of the suspected samples are not ideal to test the infection due to low yield if the bacteria from culture and longer time required for growth. High degree of cure rate can be achieved by treatment with combination therapy of doxycycline, rifampicin and streptomycin in a disease (Kochar et. al., 2000). Therefore Brucellosis is an important emerging zoonotic disease, which are often remains undiagnosed due to lack of proper diagnostics.

7. Botulism

It is Latin word means sausage. It is rare and lethal parasitic disease caused by botulin, the nerve toxin. Botulin blocks nerve function and leads to respiratory and musculoskeletal paralysis. The first case in India is reported in 1996. Food borne botulism generally associated with *Clostridium botulinum* was first detected in AIIMS. It has also been reported by Chaudhry et al (1998) and Agrawal et al (2004) in India.

8. Leptospirosis

It is an important occupational and sporadic zoonotic disease caused by the spirochaete *Leptospira icterohaemorrhagiae*. The disease becomes a major public health problem, particularly during the monsoon months. Clinical symptoms are fever, breathlessness, haemoptosis, bleeding, oliguria and icterus coma and

death. Leptospirosis was first isolated from Andaman Islands in 1931 (Taylor & Goyle 1931) and since then many workers have shown the seroprevalence of Leptospira from different parts of the country (Joseph & Kalra 1966). In 1993, a serosurvey of conservancy workers in Madras revealed a prevalence rate of 32.9% (Ratnam et al, 1993). In an outbreak of acute febrile illness with haemorrhagic manifestations and pulmonary involvement in North Andamans, 66% victims had significant titres of antibodies against Leptospira (Sehgal et al 1995). After severe flooding of Tamil Nadu in 1993, an epidemic of leptospirosis was noted with 80% patients of uveitis with Leptospira DNA and 72% positive for antibodies (Chu Kathryn et al 1998). Saravanan et al (1998) have shown 71% seropositivity in renal failure cases with clinical suspicion of leptospirosis in Chennai.

An outbreak of leptospirosis occurred in children living in slums following heavy rainfall and flooding in Mumbai and 32% of these children had acute leptospirosis (Karande et al 2002). In another study of sero-surveillance of leptospirosis in Pune, Ambekar et al (2004) have shown that it is maximum in sewer workers. Epidemic leptospirosis is increasingly being reported from North Kerala during monsoon months (Pappachan et al 2004). Prevalence of Leptospira has also been reported from eastern India (Basu et al 2003). There was an outbreak of leptospirosis after cyclone in Orissa (Sehgal et al 2002).

A study was carried out by Sharma et al (2006) to assess the seroprevalence of leptospirosis among the high-risk groups of Andaman Islands. They have shown that people engaged in activities such as agriculture, sewage cleaning, animal handling, animal slaughtering and forestry are frequently exposed to leptospirosis. Manocha et al (2004) have studied the frequency of leptospirosis in patients of acute febrile illness in Uttar Pradesh. Several isolates of Leptospira have been recovered over the years from Andaman Islands. Roy et al (2005) have shown in a recent study that 80% of the isolates were clonal in nature of strain *Leptospira interrogans sensu stricto* and study in animal population would help in understanding the transmission dynamics of this commonly circulating clone. Phylogenetic relatedness among leptospiral strains belonging to same serovar (serotype) but recovered from patients with different clinical syndromes was analyzed by using random amplified polymorphic DNA (RAPD) fingerprinting method, which has revealed five different genetic clusters (Natarajaseenivasan et al 2005). The disease is of profound importance because of its grave outcome, in its icteric form (Weil's disease) and may have mortality as high as 40% (Dutta & Christopher 2005).

Fungal infection of CNS

Infection to CNS by fungus is secondary infection that means the primary infection occurs at lungs or intestine and from here it reaches to CNS (brain and spinal cord). Generally fungal infections are due to suppressed immunity e.g. prolong chemotherapy or corticosteriod therapy (Asha et al 1986). The most common fungal infections are mucor, *Aspergillus*, *Candida*, *Cryptococci* and

Cladosporium. Cryptococcal meningitis (CM) is caused by *Cryptococcus neoformans,* most common fungal pathogen. In HIV, this is one of the most common OIs leading to memory loss, confusion, drowsiness and even death if remained untreated (Dismukes 1988; Oursler 1999; Shankar et al 2005). The infection can be identified through CT scan MRI, latex agglutination test (LAT, which is important in asymptomatic cases), staining with India ink, SF cytology by cytospin, CSF examination and culture method. The CSF of CM-positive cases revealed low levels of glucose, reduced cell count and high proteins (Khan et al 1996).

Parasitic infections of brain

Most common **parasitic infections** are neurocysticercosis and hydatid cyst of brain in India. At different centers of ICMR and different organizations like ASTRA research center Bangalore, the research for early and easy detection and vaccine development is going on.

1. Neurocysticercosis (NCC)

It is the most frequent parasitic infection of the central nervous system in India (Garg 2002). *Cysticercosis cellulosae* is the larva of *Taenia solium*. It may involve the brain parenchyma, the meninges or ventricles in form of meningeal racemose, parenchymatous, ventricular or mixed types of lesions. It may thus produce meningo-encephalitis, granulomatous meningitis, ependymitis, focal granulomas, solitary or multiple-parenchymatous cysts, hydrocephalous or a combination of these (Tandon 1983). Pathogenesis variation may result into different other complications like granuloma, residual fibrosis and calcification.

Clinically, it presents with focal or multifocal or generalized seizures (Sethi et al 1994; Singhi et al 2004; Garg et al 1998; Singh et al 2000; Mahajan et al, 2004). It can also present as focal mass lesion (Rajshekhar & Chandy 1997; Garg 2002). Coexistence of cysticercosis cyst and Japanese encephalitis has also been observed (Desai et al 1997; Singh et al 2001).

The diagnosis involves CT scan and immuunological skills (e.g. use of porcine cyst antigen, passive haemagglutination assay, complement fixation assay, ELISA and immunoscan), study of soft tissue calcification, subcutaneous nodule and stool examination. Immunoscan can also be used to localize cyst. The immunocytochemical study on cyst indicated the presence of cysticercal antigen in subtegumental cells and glycocalyx layer of bladder wall (Shankar et al 1994). Currently available international criteria (diagnostic criteria given by Del Brutto et al 2001) seems to be helpful for the diagnosis of NCC, however these criteria have been criticized for not being effective in differentiating several other infective and neoplastic diseases of central nervous system, like CNS tuberculosis from neurocysticercosis. These diagnostic criteria need to be modified so that they could be more suitable for Indian patients. However, because of the high prevalence

of several disorders with similar features, it is difficult to make reliable diagnostic criteria for neurocysticercosis, which are easy to use, and have a high specificity and sensitivity (Garg 2004).

2. Hydatidosis

In developing countries, hydatidosis, a cestode parasitic infestation, uncommonly involving the nervous system, presents with varied clinical manifestation, at times causing diagnostic dilemmas. Multiple intracranial and spinal hydatidosis is rare. Rumana et al (2006) have reported a series of 29 histologically confirmed cases of hydatidosis of neuraxis (intracranial and spinal) from South India and Dharkar (1977) has reported cerebral hydatid cyst from central India. **Echinococcus** This infection is rare in India. Thakur and Anand (1993) have reported echinococcal infection of brain in a patient with focal seizures from Pondicherry. The CT scan showed an isolated rounded lesion in the right frontparietal area. The blood eosinophil count was 25%. The indirect haemagglutination titre was more than 1:2048 for echinococcal protein and Casoni's skin test was strongly positive. Cerebrospinal **Acanthamebic** granuloma may also present with focal seizure (Velho et al 2003).

3. Toxoplasma encephalitis

It is one of the common CNS opportunistic infection in HIV positive patients. In a series of 135 hospitalized HIV infected patients from North India, cerebral toxoplasmosis was seen in 3.7% (Sharma et al 2004). Common causes of seizures in large number of patients with HIV infection are associated with cerebral toxoplasmosis (30.4%), along with other opportunistic infection as cryptococcal meningitis (17.3%), tuberculoma (13.4%), AIDS dementia complex in 4.3% and progressive multifocal leucoencephalopathy (PML) in 4.3% (Chadha et al 2000). Diagnosis of toxoplasmosis is based on CNS imaging demonstrating typical mass lesions. Serum antitoxoplasmosis antibodies have been used, though it has high (20%) false negative rate (Mathew & Chandy 1999).

4. Cerebral malaria

Different workers did the work on cerebral malaria at time to time (Verma et al 1976; Jhala et al 1992; Kamble et al 2002). The pathogens involved are *Plasmodium vivax* and *Plasmodium falciparum*. Cerebral and haemopoietic complications were the most common during the infection.

Conclusions and Future Direction

The emerging picture based on the present review exhibit complex interactions between functional characteristics of microorganisms and host central and peripheral nervous system. These interactions between microorganisms and host nervous system have been the subject of many classical studies that have now

progressed to the molecular level as well. However, several of these studies should also be viewed cautiously in light of regional differences in the genetic makeup of the human population and the circulating strains of microorganisms. There are many secrets to these interactions that must be discovered. It is hoped that further research in the context of ongoing prospective studies, using newer molecular and immunological techniques, will achieve this potential. As a better understanding of the host CNS response to microorganisms in the context of disease as well as drug/vaccine-induced protection becomes available, the ability to control the growing worldwide burden of neuro microorganisms will likely be improved.

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