

Editorial

Pathology and Diagnosis of Central Nervous System Infections

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Infections of the central nervous system (CNS) are important because of the many pathogens, the emerging and reemerging of new infections, and the heavy burden they impose on health care system. The most formidable challenge is the increasing number of people at risk of developing CNS infections due to acquired immunodeficiency syndrome (AIDS) and the recipients of hemopoietic and solid organ transplantation and other causes of immunosuppression. There have been significant developments in the last few decades in understanding the biology of disease process by the application of new technologies. Advancements in brain imaging and newer diagnostic modalities have achieved early diagnosis helping patient management with new therapies. The pathogenetic factors contributing to neurovirulence of the pathogens have been elucidated by the use of molecular biological techniques.

The infections are caused by wide variety of organisms including bacteria, parasites, fungi, and viruses. The clinical course may be acute, subacute, or chronic depending on the pathogen, location, and immune status of the host. The clinical manifestations are protean.

The normal brain is a highly complex and specialized organ. It is protected by bony encasement of skull and thick dura mater. However, this encasement limits its capacity to swell in case of inflammation. Another important defense for brain is in the form of blood brain barrier (BBB), made up of a system of tight junctions in capillaries that resist the entry of the inflammatory cells, pathogens, and macromolecules into the subarachnoid space. The brain has a rudimentary lymphatic system. The microglia and perivascular macrophages have much lower expression of major

histocompatibility complex (MHC) molecules. This helps the pathogen by poor antigen presentation to body's immune system and greater survival.

The exact mechanisms to breach the BBB by certain pathogens are poorly understood, for example, rabies virus and herpes simplex virus travel within peripheral nerves to enter CNS, whereas encapsulated bacteria and fungi enter from the blood stream and possess surface components that allow them to traverse the capillary tight junctions. The natural CNS parasites (*Naegleria fowleri*) infiltrate and infect the CNS of healthy host by targeted attacking of the BBB's endothelial cells. The opportunistic CNS parasites (*Toxoplasma gondii*) infect the CNS in immunocompromised patients when the body is unable to effectively resolve inflammation of the BBB's endothelial cells, increase the permeability of the BBB, and allow large molecules and parasites to cross BBB and enter the brain.

Owing to the limited space and involvement of vital areas, CNS infections are associated with high morbidity and mortality. Rapid diagnosis and emergent interventions are necessary to improve outcomes of these patients. The laboratory diagnosis of CNS infection is essential for optimal therapy. However, it is most challenging and appropriate that the use and selection of laboratory tests requires close interaction between clinician and laboratory personnel. A timely cerebrospinal fluid (CSF) examination can give wealth of information. Apart from cell count, the CSF can be subjected to Gram's stain, fungal stains and culture of bacteria, fungi, and mycobacteria. Moreover, viral meningitis and encephalitis can be diagnosed by CSF serology, viral DNA markers, and polymerase chain reaction (PCR). Tissue diagnosis depends

upon location of the infectious focus and possibility of a biopsy from the site. Histopathology almost always gives a clue to the underlying infectious agent with the help of special and immunohistochemical stains for various types of organisms. The diagnostic yield can be further improved by the application of PCR and other molecular techniques.

Brain abscess is a focal suppurative process within the brain parenchyma, commonly caused by bacterial, fungal, and parasitic pathogens. Despite advances in diagnostic and surgical methods and advent of new antibiotics, brain abscess continues to be a serious medical problem. The predisposing factors vary in different parts of the world. Because of improvements in the treatment of ear, sinus, and orofacial infections over the last 50 years, there is decreasing incidence of brain abscess due to otogenic infections in developed countries when compared to developing countries. However the frequency of brain abscess increased in patients with AIDS and in patients using broad spectrum antibiotics, corticosteroids, or immunosuppressive agents.

V. Lakshmi et al. in a review of 352 brain abscess samples in 24 years from a developing country like India observed that otogenic infections and sinus infections by contiguous spread constitute the commonest source for brain abscess. There were only 4 patients who were immune suppressed, and two of them had mycotic abscesses. Cryptogenic brain abscesses constituted 23.3% of abscesses. *Staphylococcus aureus* was the most common isolate. The authors observed a change in the trend of the causative organisms in the later half of the study period when unusual organisms like *Burkholderia pseudomallei*, *Salmonella typhi*, *Nocardia spp*, *Cladosporium bantiana*, *Fonsecaea pedrosoi*, *Entamoeba histolytica*, and *Acanthamoeba* were isolated. There were 8 brain abscesses due to mycobacterium tuberculosis, 3 *Nocardia spp* and 5 mycotic organisms and 2 amoebic abscesses. The diagnosis of these group of brain abscess was complemented by histological studies. Tuberculous brain abscess is essentially a histological diagnosis wherein the wall of the abscess lacks granulomas, and the central necrotic material contains acid fast bacilli.

The factors for a favorable outcome for brain abscess include being male, having a Glasgow coma scale score >1.2, and being sepsis-free and having positive culture. Identification of microorganisms in the aspirated material depends on the prompt examination of smear and appropriate culture techniques. The mortality and morbidity and long-term sequelae of brain abscess are due to persistent release of proinflammatory mediators by activated microglia, astrocytes, and infiltrating inflammatory cells along with disruption of BBB. Anti-inflammatory drugs along with specific antimicrobial agents help in minimizing damage to the adjacent brain parenchyma.

Most protozoal infections except cerebral malaria are uncommon and are restricted to particular geographical regions. Because of increasing international travel, parasites that were previously limited to tropical regions pose an increasing infectious threat to populations at risk for acquiring opportunistic infection, especially people with human immunodeficiency virus (HIV) infection or individuals who have received a solid organ or bone marrow transplantation.

Though CNS is an immunologically privileged site, the parasites try and gain access to the CNS due to a variety of factors which include easy access to nutrition and the ability to avoid much of the body's normal immune response. Though CNS may be one of the many systems involved, CNS involvement indicates a poor prognosis in the protozoal infections.

Though only a relatively limited number of parasites can penetrate and infect the CNS, the parasites employ a variety of techniques to evade and suppress immunity and exploit the milieu for survival. Understanding the host parasite interactions and pathogenesis helps develop efficacious treatment strategies. Detailed neuropathological studies with application of molecular biological methods helps in this direction. The awareness of endemicity and geographical distribution of parasites is necessary for proper planning of the laboratory tests. Serological tests, culture and molecular methods, are very useful in the diagnosis of parasitic infections. L. Chimelli in her paper stressed the importance of morphology of the parasites on tissue in establishing the diagnosis. She stressed the changing patterns of some protozoal infections of CNS after the institution of highly active antiretroviral therapy (HAART). The diagnosis remains a problem in many patients despite all the available tests and examination of brain at autopsy may become inevitable in making a diagnosis.

Fungal infections of CNS are being increasingly reported in the last few decades due to increase in the number of immunosuppressed individuals. A variety of fungi cause infections of CNS either an acute or chronic meningitis or space occupying lesion. Yeast fungi predominantly cause meningitis, and mycelial fungi cause mass lesions of brain. The type of pathology and clinical syndrome is determined by the morphology and size of the fungus and the host immune status. In the patients with intracranial mass lesions, direct extension from colonized paranasal sinuses or ear canal is more common than by hematogenous dissemination from lung, gastrointestinal tract (GIT), or skin. *Aspergillus sp* is the most common agent to cause intracerebral granuloma or abscess.

C. Sundaram and J. M. K. Murthy reviewed intracranial aspergillus granulomas and observed that most of the reported large series are from countries with temperate climate like India, Pakistan, Sudan, and Saudi Arabia. The spread is often from paranasal sinuses by direct extension and in immune competent hosts. The lesions are often extracerebral granulomas, characterized by dense fibrosis. Rare intraparenchymal granulomas were reported. The importance of histochemical stains like Gomori methenamine silver in the diagnosis is stressed. Environmental factors like temperate climate humidity favor the growth of the fungus. The aerolized spores during ploughing or construction activity are colonized in the sinuses or lungs. Dissemination to CNS occurs due to local altered immunity and mucosal invasion. The dense fibrosis does not allow effective penetration of antifungal agents thus necessitating radical surgery.

Following HIV infection, especially with HIV encephalitis, variable degree of demyelination is found in the brain, especially the subcortical white matter of the frontal and temporal lobes. This is further accentuated by coinfection with

JC virus causing progressive multifocal leucoencephalopathy, involving the white matter fiber tracts, basically infecting the oligodendroglia. S. Surendran et al. in their earlier molecular studies showed the presence of human aspartoacylase in oligodendroglia taking part in myelin synthesis. Altered levels of aspartoacylase/aminoacylase (ASPA) and abnormality in the metabolic pathway have been found to induce oxidative damage and participate in the evolution of Canavan's disease and Parkinson's disease. In a brief report in this issue, they described depletion of immune labeling for ASPA protein in the white matter in cases of HIV encephalitis. This indicates that an aberration in ASPA pathway participates in the demyelinating pathology seen in cases of HIV. More in depth study with larger autopsy sample size is needed to further validate the observations and suggest a pathogenetic role.

With transformation of the world into a global village with primitive to advanced modes of transport, old infective conditions are emerging in new places, and some diseases are manifesting with varied clinical features confounding the infectious disease specialist and the laboratories. Many of them are turning out to be zoonoses of well-recognized or newly discovered viral infections, jumping the species barrier and infecting the human beings. This is further facilitated by the economic necessity of close proximity of the domesticated animals and the human beings, afforestation leading to migration of the animals into human habitat. K. T. Wong and K. C. Ong have provided a brief review of an encephalitis, glomerulonephritis, bronchitis, and bronchiolitis caused by Hendra virus and Nipah virus originating in the Eastern World. The viral infection has spread to humans essentially by contaminated oropharyngeal secretions and urine from infected domestic animals. The intermediate host is essentially determined by the proximity to the human habitat and domestic animal rearing habit of the villages involved. The person-to-person transmission in Bangladesh and India by the henipaviruses reflects high human density in a restricted area and aerosol spread like the recent mutated influenza virus epidemic. The clinical features of Hendra virus has not been well characterized while Nipah viral infection is very well studied and recorded.

With henipavirus infection, probably viral persistence is responsible for recurrent and recrudescing encephalitis, similar to a few of the arboviral infections. The site of latency of the virus is not clear. The pathology of henipavirus is diffuse parenchymal vasculopathy, endothelial cell syncytia, and encephalitis. In Nipah virus infection CNS vasculopathy is more prominent, thus highlighting variable pathologies in henipavirus group of infections. Similarly the susceptibility of the experimental animals is also variable, modulating the spread of infection in the natural habitat. Curiously in case of Nipah viral infection, role of peripheral nerves in the viral transmission to CNS had been suggested only in pigs.

The formation of neuronal syncytia indicates the activity of fusion viral protein, a feature of paramyxoviruses. Sharing the same viral receptor on the cell membrane of both humans and animals (ephrin B₂ and ephrin B₃), especially the vascular endothelium explains the evolution of clinico-pathological features and CNS involvement. With changing

ecology following the expansion of human habitat and associated domesticated animals, disturbing the environment and homes of pteroid bats in developing countries, future outbreaks of henipavirus can be anticipated. This calls for evolving treatment strategies and vaccination policies.

In Asian countries rabies viral infection continues to be a public health problem with no reliable cure in sight. WHO estimates 50,000 deaths every year worldwide, nearly 60% of them occurring in India alone. Humans and canines, the common mammals infected, acquire the disease following the bite of a rabid animal. On entering the nervous system by a receptor-mediated mechanism, the virus replicates and spreads widely in the CNS with a fatal end. Clinically rabies infection manifests either as furious (encephalitis) or paralytic form, two thirds of the subjects suffering from the aggressive, hydrophobic, and furious form. Most of the studies evaluating the pathogenesis of rabies have been carried out in laboratory animals using laboratory-adopted virus strain (CVS), while the natural infection by the nonattenuated "street virus" in humans and canines is not well worked out.

In addition to cytopathic effect of the viruses, altered neurotransmitter activity resulting in deleterious CNS physiology have been incriminated as the cause for acute morbidity and mortality following infection with neurotropic viruses like rabies. Apoptosis, which is essential for the programmed cell death and embryogenesis, has been observed in a multitude of viral infections, and the number of correlations between viral pathogenesis and apoptosis continues to grow. Some of the viruses promote noninflammatory apoptotic mechanism to induce cell death and escape into the interstitium to infect another healthy cell. On the other hand, other viruses cleverly exploit the high regulated apoptotic pathway by blocking it within the cells they reside, thus evading the host surveillance mechanism and promote their survival. RNA viruses multiply rapidly to produce many virions before the host mounts effective immune surveillance to contain them. Observation of apoptosis in mouse neuroblastoma cells when infected with highly neurotropic challenge virus standard (CVS) of rabies virus leads to the impression that neuronal damage and loss in rabies is mediated by apoptosis. Subsequent workers as well, using the laboratory passaged CVS strain and animal models, have suggested that apoptotic neuronal cell loss was an early event correlating with disease severity. Though apoptosis is well recognized in animals infected with laboratory-adopted-rabies virus, whether the same mechanism is operative in natural infection by rabies virus present in nature remained a moot point.

The neuronal apoptosis following rabies infection is found to be age dependent, being evidence in suckling mice infected with CVS strain, but not in weanling and adult mice.

In the present issue, in an original study, M. S. Suja et al. evaluated the role of apoptosis in rabies encephalitis in humans, canines, and rodents infected with wild-type street virus and compared with a rodent model infected with laboratory-passage and -attenuated rabies virus, inoculated by different routes. They also studied the age-dependent expression of apoptosis in mice when infected with CVS

strain. Rabies viral load and encephalitic pathology were more evident in the human and canine brain in contrast to rodents infected with wild type of virus, but absence of neuronal apoptosis was common. On the contrary, as observed by other researchers, apoptosis was recorded in suckling mice infected with CVS strain, more evident by intracerebral inoculation and rarely in wild-type street virus-inoculated rodents. Interestingly the apoptotic cell signal was noted only in inflammatory cells, but was distinctly absent in neurons and glia. It is suggested that apoptotic cell loss only in inflammatory cells but not in neurons, could be a natural adoptive mechanism by the rabies virus to facilitate the survival of the virus, its propagation in stable population of neurons. It is also evident that the apoptotic cell damage is not responsible for the evolution of clinical features and terminal mortality following rabies infection. This also could account for long incubation period and long-term survival of the rabies virus in the host. It is not yet clear in which of the neuroanatomical areas in the mammalian system the virus resides dormant in latency to get activated in opportune moment. Further studies on molecular, cytokine/chemokine pathways, and neurotransmitter pathways coupled with investigating aberrant neurophysiology may offer clues to bimodal clinical manifestation and fatality from rabies virus. Among the four types of Prion disease, Creutzfeldt-Jakob disease (CJD), sporadic CJD (sCJD) is the commonest form arising from random mutation or posttranslational modification of the PrP gene. On the contrary, the new type of CJD, namely, the variant CJD (vCJD) manifests in young (mean age of 23 yrs) has longer duration of illness (12–24 months), with psychiatric presentation and absence of characteristic EEG changes. This form of CJD is causally linked to oral ingestion of meat from cattle infected with bovine spongiform encephalopathy. Neuropathologically CJD is characterized by spongiform change of cortical neuropil in cerebral cortex, cerebellar molecular layer, diencephalic nuclear areas and brainstem, neuronal loss, and reactive astrocytosis. Fairly distinct differences in the pattern of prion protein distribution recognized by immunohistochemistry are described. In sCJD, the deposition of PrPSc occurs in a synaptic pattern, distributed along the cortical ribbon and the neuropil of nuclear areas reflecting diffuse degenerative change in the presynaptic terminals and relative failure to aggregate. In the case of vCJD, the PrPSc deposits take the form of classic mature plaques of Alzheimer's disease (AD) with dense central core and less compacted halo of deposit around, and diffuse deposits (fine feathery diffuse deposits akin to immature plaques in AD) floridly.

These morphological variations appear to reflect differential distribution of the prion protein in different anatomical areas corresponding to the evolution of pathology spreading along relatively distinct axonal pathways reaching the cortical lamina and other nuclear areas. In other neurodegenerative disorders (β amyloidopathies, taupathies, and synucleinopathies) like in AD, Lewy body dementia, Pick's disease the density distribution of the pathological change in cerebral cortical ribbon varies across the different cortical lamina. This probably reflects laminar spread and distribution of the pathological changes corresponding to

degeneration of specific anatomical pathways having their neurons of origin or presynaptic axonal termination in particular cortical lamina. To an extent, this laminar distribution gives insight into neuroanatomical progression of the proteinopathies in the cerebral cortex and corresponding clinical cognitive and motor abnormalities during the disease progression.

In this issue, R. A. Armstrong from Birmingham evaluated the laminar distribution of the pathological changes in sporadic and variant CJD by rigorous quantitative morphometry in well-characterized samples. The cases of sCJD were homozygous for methionine at codon 129 with Type 1 PrPSc (M/M). All the cases of vCJD were also methionine/methionine (M/M) homozygotes at codon 129. Thus, the cases analyzed had relative genetic homogeneity to compare. The cases of sCJD revealed diffuse spongy change in the cortex affecting all the cortical lamina, more surviving neurons in upper layers of the cortex and neuronal depletion in lower layers, classical synaptic pattern of prion protein deposition, and gliosis in the lower layers. On the contrary, in cases of vCJD, the spongy change was more evident in the upper layers corresponding to subpial spongy change and presynaptic targeting axonal pathology. This was further corroborated by florid and diffuse deposits of prion protein in upper cortex. The astrocytosis in vCJD was essentially similar to sCJD, more evident in the lower layers, probably as a late event to neuronal and axonal degeneration. Similar though labour intensive, study in some of the neuroanatomical areas like cerebellum, brainstem, and diencephalic nuclei leading to neo cortex probably can offer insight into temporal evolution and neuroanatomical spread of prion pathology and contrasting features with other protein misfolding neurodegenerative disease.

In conclusion, the various articles in this issue address the pathology, pathogenesis and diagnosis of infections of CNS.

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