NeuroAIDS: A worrisome issue

Neuropsychiatric complications contribute ~15% of world's total disease burden.[1] Addiction, dementia, epilepsy, mood disorders, schizophrenia, etc. are some of the most common neuropsychiatric complications reported in general population. At present, neuropsychiatric complications have been reported with higher incidences among HIV patients compared to non-HIV individuals. Some of the most common neuropsychiatric disorders among HIV seropositive patients are HIV-Associated Dementia (HAD), HIV-Associated Encephalopathy (HIVE), etc. Various neuropsychiatric symptoms in HIV patients have been grouped as "neuroAIDS". An increase in incidences of neuroAIDS may be due to an increase in the life-span of HIV seropositive patients. This is one of the reasons for neuroAIDS becoming a new and emerging health concern among long-term HIV/AIDS survivors. The question remains, "Is neuroAIDS really such a serious health issue that needs immediate attention?" It is difficult to answer this question, but its significance can be realised with the fact that >50% HIV seropositive patients show signs and symptoms of neuroAIDS at later stages of HIV infection.[2]

The first case of HIV infection was reported among gay men from Los Angeles, USA in 1981, as they were diagnosed with *Pneumocystis carinii* pneumonia (PCP).[3] Usually, PCP has rare occurrence in general population, and is known to present with higher incidences among immune-deficient patients. Later, these patients were confirmed with HIV infection, as it was identified by Luc Montagnier of Pasteur Institute, Paris, France.[4] The UNAIDS (2009) report suggested that >34 million people are living with HIV, out of which >2 million are children below the age of 15 years. Even though various effective measures are adopted to control HIV infection, it is surprising to mention that >2 million people get new HIV infections on an annual basis [Table 1]. The situation is worsening day by day due to the addition of new cases to the existing pool of HIV seropositives. Apart from new infections, the burden of HIV infection is increasing due to an increase in average life-span of HIV seropositive patients, because improved antiretroviral drugs are effective in reducing HIV replication significantly. Annual addition of more than 2 million cases over and above 34 million existing cases has raised an alarming situation for a chronic and fatal disease like AIDS.[5]

AIDS is the final outcome of HIV infections, with certainty of death. Previously, a high incidence of mortality was reported among HIV patients, which has been significantly reduced due to advancements in antiretroviral treatments. On one hand, Highly Active Antiretroviral Treatment (HAART) is the latest strategy for AIDS treatment, which has improved the health of HIV patients as well as increased their life-span post-infection. On the other hand, HAART has its own drawbacks too, that a majority of antiretroviral drugs do not cross the blood brain barrier (BBB); therefore, the brain serves as a good reservoir for HIV replication.

In fact, the benefits and drawbacks of HIV medications act as a double-edged sword. Anti-HIV drugs help to increase the life-span of HIV seropositive patients, while these drugs can also lead to the development of various neuropsychiatric complications. With time, immune-competency decreases in the long-term HIV seropositive patients; therefore, they become vulnerable to various opportunistic infections like PCP, pneumonia, Kaposi's sarcoma, etc. Certainly, these infections also act as contributing factors for different neuropsychiatric complications. These neuropsychiatric complications are not new to AIDS patients, because initial cases of AIDS were also presented with symptoms like PCP. Unfortunately, these complications failed to attract requisite attention in those initial cases, because the priority at that time was to control the spread of HIV infections. At present, HIV seropositive patients who have access to improved antiretroviral drugs can live for >20 years post infection; therefore, these patients can now live longer, even though they remain infected with HIV. Now these patients have to face new emerging complications known as neuroAIDS.

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Table 1: HIV/AIDS epidemic till 2008: A summary*

	Living with HIV	New infection†	Death†
Adults			
Men	15.70	1.15	0.85
Women	15.70	1.15	0.85
Children	02.00	0.43	0.28
Total	33.40	2.73	1.98

*Adapted from UNAIDS Report, 2009; †Annual estimate; Figures are in millions

At this moment we can say that this is the cost that HIV seropositive patients have to pay for their longer life-span.

The question still is: "Is neuroAIDS an alarming clinical condition among long-term HIV seropositives?" The answer for this can be judged with the fact that as per some estimates, >50% long-term HIV seropositive patients may end up showing signs and symptoms of neuroAIDS at some point of time in their life. Such a high prevalence of neuropsychiatric complications indicates that in near future, we should expect large numbers of HIV patients living with neuroAIDS. Continuous accumulation of long-term HIV seropositive patients is expected to increase the burden of neuroAIDS on daily basis. This fact gets its strength from UNAIDS Report (2009) estimates, which suggest that only ~5,500 people die every day with HIV/AIDS, while ~7,400 people get newly infected on a daily basis. This means that ~1,900 new patients are added every day to the existing pool of HIV seropositive patients, which could translate into ~0.7 million patients annually.

Long-term HIV seropositive patients will show signs and symptoms of neuroAIDS at later age, and it should be considered as an important health issue due to various reasons: (i) addition of new patients in the existing pool on daily basis, (ii) onset of neuroAIDS occurs in the age range of ~35-45 years, which is considered as the prime age for human productivity, (iii) antiretroviral medications already incur high cost towards HIV medication, (iv) addition of expenses towards medication for neuropsychiatric complication, (iv) patients with neuroAIDS become least productive in their life, so there is a loss of either individual or family income, (vi) need for a caretaker or caregiver to HIV patients again add up to the cost of living for neuroAIDS patients, (vii) hiring a professional caregiver will certainly add an enormous expenditure towards the cost of maintenance for the patient. These are some of the compelling reasons to recognise the adverse impact of neuroAIDS as an emerging complication.[6]

Neurotoxicity in the central nervous system (CNS) is the foremost reason for the emergence of neuropsychiatric symptoms among HIV seropositive patients. HIV infection to CNS or brain is still a mind boggling issue for biomedical scientists and clinicians, because CNS/brain is one of the most protected organ-system of body. CNS is separated from rest of the body by BBB, which acts as a protective barrier to regulate entry of foreign substances to the brain. However, HIV infection in brain was reported from cadaver cases.

Apart from brain being the most protected organ system and a majority of cell types present in brain also do not express primary receptors, *i.e.,* CD4 for HIV infections; therefore, it is difficult to explain HIV infections to the CNS. Neurons are also not known to express CD4 receptor till date.[7] So far, a majority of evidences suggest that the main contributing factor for neuroAIDS is neurotoxicity rather than direct HIV infection. Neurotoxicity undoubtedly plays an important role in neuronal loss. But the question still remains: "What are the causes of neurotoxicity?" Some of the strong possibilities are under active consideration, *e.g*, (i) Is HIV itself responsible for neuroAIDS? (ii) Is neuroAIDS a secondary complication evolved due to long-term antiretroviral treatments? (iii) Low or negligible penetrance of antiretrovirals in brain, (iv) Are low levels of persistent and chronic HIV infections contributing towards development of neuroAIDS?, or (v) Is it a combined effect of all these possibilities? The present understanding of neuroAIDS and its causes are still not very clear.[8]

Improved antiretrovirals help lower HIV replication to below detection limits, which means that a very low level of viral replication continues in HIV patients eventhough they are under treatment. This low level of viral replication could lead to chronic accumulation of different virotoxins, pro-inflammatory cytokines, and inflammatory cytokines. Accumulation or consistent production of these biomolecules could be a reason to alter the physiology of BBB. A possible alteration in physiology of BBB may support the entry of virotoxins, cytokines, HIV alongwith infected T cells, and monocytes, which are present in the peripheral circulation. Although neurons are the most common cell types present in the CNS, but CNS harbours other cell types like astrocytes, oligodendrocytes, microglia, and perivascular macrophages as well.[9] In general, neurons are the most susceptible cells to any alteration in CNS, which results in neuronal death. Recovery of neuronal loss is impossible due to inherent characteristics of the neuron, *i.e.,* their inability to regenerate. Microglia and perivascular macrophages are the only cells of CNS that express primary receptors for HIV infectivity, *i.e.,* CD4; therefore, these cells could serve as a reservoir for HIV. Unfortunately, HIV can remain latent for longer periods in these cells; thus, these cells may have barely minimal level of HIV replication. But at some point of time, HIV replication may be triggered in these cells; therefore, these cells may serve as major source of HIV replication in brain. Still, the causes and factors for the induction of active HIV replication in these cells are not clear. But a low level of HIV replication in latently infected microglia and perivascular macrophages is considered as one of the major reasons for chronic neurotoxicity in CNS. Chronic neurotoxicity could be responsible for neuronal loss. Neuronal loss in CNS could be a pathological condition, leading to neuroAIDS. During late stages of HIV seropositive patients' life-span, an active HIV replication could accelerate neuroAIDS progression. Therefore, various underlying mechanisms at cellular and molecular levels can induce, maintain, and worsen neuroAIDS. These facts and rationale necessitate the need for thorough studies to understand the mechanism of neuroAIDS. A better understanding of the mechanism will pave the path to control the menace of neuroAIDS before it worsens further.

The major obstacle for better understanding of neuroAIDS is unavailability of any suitable model either for *in vivo* or *in vitro* systems. Unavailability of any suitable model is also a major hurdle to (i) study underlying causes of neuroAIDS, (ii) molecular mechanism of neuroAIDS, and (iii) test the efficacy of drugs for neuroAIDS. Under these circumstances, there is a need to pay more attention on researches to control neuroAIDS, if not to minimise its clinical symptoms.

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