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Proceedings from the NIMH symposium on “NeuroAIDS in Africa: Neurological and neuropsychiatric complications of HIV”

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Abstract

Despite major advances in HIV-1 treatment, the prevalence of HIV-associated neurocognitive disorders (HAND) remains a problem, particularly as individuals on suppressive treatment continue to live longer. To facilitate discussion on emerging and future directions in HAND research, a meeting was held in Durban, South Africa in March 2015 as part of the Society of Neuroscientists of Africa (SONA) conference. The objective of the meeting was to assess the impact of HIV subtype diversity on HAND and immunological dysfunction. The meeting brought together international leaders in the area of neurological complications of HIV-1 infection with special focus on the African population. Research presentations indicated that HAND was highly prevalent and that inflammatory cytokines and immune-activation played important roles in progression of neurocognitive impairment. Furthermore, children on antiretroviral therapy were also at risk for developing neurocognitive impairment. With respect to the effect of HIV-1 subtype diversity, analyses of HIV-1 clade C infection among South Africans revealed that clade C infection induced cognitive impairment that was independent of the substitution in HIV-1 Trans-Activator of Transcription (Tat; C31S). At the cellular level, a Zambian study showed that clade C infection resulted in reduced brain cell death compared with clade B infection suggesting clade specific variations in mediating brain cell injury. Furthermore, *ex vivo* Tat protein from clade CRF02_AG, prevalent in West/ Central Africa, exhibited reduced disruption of brain endothelium compared with clade B Tat protein. Discussions shed light on future research directions aimed at understanding biomarkers and disease mechanisms critical for HAND.

*To whom to address correspondence.

Conflict of Interest

This work was written as part of Dr. Jeymohan Joseph's official duties as a government employee. The views expressed in this article do not necessarily represent views of NIMH, NIH, HHS or the United States Government.

Keywords

Human immunodeficiency virus (HIV); HIV-associated neurocognitive disorders (HAND);
NeuroAIDS

Introduction

Increased availability of antiretroviral therapy (ART) has significantly improved survival rates of HIV-infected individuals (Maschke et al., 2000, Sacktor et al., 2002, Gray et al., 2003, McArthur et al., 2003). Paradoxically however, increased survival rates in these individuals consequently resulted in an undesirable increase in the prevalence of neurocognitive impairments (Heaton et al., 2011) collectively referred to as HAND (Antinori et al., 2007). To address HIV subtype variations in HAND pathology globally, participants from all over the world gathered in Durban, South Africa to attend the 12th International Conference of the Society of Neuroscientists of Africa (SONA). The meeting brought together clinicians and basic neuroscientists under one roof to showcase research advances in various neuroscience research fields (<http://www.sona2015.com/>). Symposium #7 was dedicated to neurological consequences of HIV infection running under the title: “NeuroAIDS in Africa: Neurological and neuropsychiatric complications of HIV”. With Jeymohan Joseph (NIMH) and Shilpa Buch (UNMC) as co-chairs, this plenary covered topics including inflammatory cytokines, neuroimaging and effects of HIV subtypes on neurocognitive functions. Summaries of each of the six presentations are as follows:

Neurological and neuropsychiatric complications

Dr. Jackie Hoare presented data evaluating white matter damage in cART-treated HIV-positive children in South Africa (Hoare et al., 2015) and use of diffusion tensor imaging (DTI) techniques to study neurocognitive impairment in HIV-positive children who are cART naïve “slow progressors” (Hoare et al., 2012). She showed that 45.35% of HIV infected children from Cape Town had neurocognitive disorders. Using DTI, Dr. Hoare and colleagues found damaged neuronal microstructures in HIV-infected children (n=75) compared to HIV-uninfected individuals (n=30). Furthermore, children with HIV encephalopathy (HIVE) exhibited increased levels of white matter damage when compared to ART treated, HIVE negative children. DTI also revealed significant loss of myelin in ART-naïve children when compared with ART-treated control group. Similarly, ART-naïve “slow progressors” performed poorly compared to the control group on verbal tasks and tests of memory, executive function and visuospatial processing. “Slow progressors” also exhibited abnormal white matter microstructure in corpus callosum and superior longitudinal fasciculus compared to controls suggesting significant disruption to primary brain pathways (Hoare et al., 2012). These findings suggest that regardless of ART, children remain at a risk for developing CNS disease. This risk also extends to physically healthy ART-naïve slow progressors.

Prevalence of HAND, status of immune cell activation and cytokine levels

Dr. Noeline Nakasujja from Makerere University presented preliminary data revealing that HAND was prevalent among ART naïve HIV-positive people in rural Uganda. Using Frascati criteria to determine HAND staging as normal, asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND) and HIV-associated dementia (HAD) as previously described (Antinori et al., 2007), the study found that 12.8% of study participants showed normal neurocognitive function (10 of 78); 16.7 % with ANI (13 of 78); 42.3 % with MND (33 of 78), and 28.2% had HAD (22 of 78). Furthermore, persons with CD4<200 (n=38) had significantly higher levels of inflammatory cytokines (IL-12, IL-5, IL-4, IL-2, GM-CSF) in CSF compared to those with CD4>350. Individuals with either MND or HAD had increased levels of IFN- γ in CSF compared to persons in the normal or ANI staging. These differences in CSF cytokines suggest that inflammation plays an important role in the progression of neurocognitive impairment in HIV-infected adults.

Dr. Jibreel Jumare presented data on markers of activation of monocytes and macrophages based on a project seeking to identify ‘correlates of monocyte-associated virus in HIV neurocognitive impairment’ in Nigeria. The study found evidence of neurocognitive impairment in 22.7% of 176 HIV-infected ART naïve participants. ANI was found among 15.3%, while 7.4% had MND. None had HAD. Mean level of soluble CD14 (a marker of monocyte activation) was higher among those with MND or ANI compared to unimpaired individuals. Similarly, the mean level of neopterin (a marker of immune activation) was higher for those with MND when compared to those without impairment. There was also a trend among women with MND to have higher levels of soluble CD163 and TNF- α when compared to unimpaired women. These findings strengthen the existing evidence on the vital function of monocyte activation in HAND pathogenesis, and indicate a possible interaction of gender and immunological processes on neurological outcomes.

Effects of HIV subtype diversity on HAND

Dr. Robert Paul’s presentation focused on the effects of HIV subtype diversity on impairment of cognitive functions based on recent studies his team conducted in South Africa; a country where HIV-1 subtype/clade C is predominant. Intriguingly, more than half of all HIV infections worldwide are caused by HIV-1 subtype C, with large percentages of individuals residing in India and Sub-Saharan Africa (Wainberg, 2004, Sacktor et al., 2007). One of HIV proteins (Tat) has been implicated in CNS disease. Tat from Clade C virus has a polymorphism at C31S (Ranga et al., 2004). However, prevalence of this Tat polymorphism in samples isolated from South Africa was not as highly conserved as samples from India (Rao et al., 2013). This unique characteristic of the virus in South Africa allowed for a direct comparison of cognitive and imaging outcomes among individuals with or without the Tat defect. The work presented by Dr. Paul identified significant impairments in cognitive function in HIV-positive individuals compared to HIV-negative individuals independent of the Tat mutation (C31S). In contrast, cognitive performance was not significantly different between seropositive individuals with intact Tat sequence (C30C31 motif, n = 128) and those with defective Tat (C30S31 motif, n = 46) (Paul et al., 2014). Preliminary data also

exhibited no significant differences by Tat status on neuroimaging outcomes (Paul *et al.*, submitted manuscript).

Based on studies carried out in Zambia, Dr. Victor Mudenda's presentation highlighted the effects of HIV-1 clade C on HAND pathology and HIV-1 viral RNA distribution within the brain, cerebrospinal fluid and peripheral blood compartments. Microgliosis and astrogliosis was found reduced in a cohort of 17 end-stage, ART naïve HIV-1 clade C-infected cases when compared with HIV-1 clade B infected cases. In addition, while multi-nucleated giant cells were not observed in these subjects, HIV-1 p24 and viral RNA positive cells were observed in perivascular areas. Opportunistic infection-associated pathology was also not readily observed thus ruling out possible interfering factors. With regard to viral RNA distribution, HIV viral sequences obtained from 4 of these subjects were distinct in the central nervous system (CNS) versus the blood compartments, but were similar in the brain and CSF thus suggesting lack of viral compartmentalization within the CNS.

Dr. Kanmogne presented preliminary data on comparative analysis of Tat proteins derived from HIV-1 clade B (Tat-B), the main HIV subtype in Western countries, and those derived from recombinant HIV-1 CRF02_AG (Tat-AG), the main viral subtype common in West and Central Africa. Data revealed that Tat-AG had marginal effects on the blood-brain barrier, whereas Tat-B induced transcriptional upregulation of proinflammatory chemokines, complement components C3, C7, and factor-B, matrix metalloproteinases (MMP)-3, MMP-10, MMP-12; and also increased the activity of these MMPs in a dose-dependent manner (Woollard *et al.*, 2014). Additionally, preliminary data also showed increased replication and transactivation of HIV-1 CR02_AG in macrophages that was associated with increased acetylation of histone proteins and histone acetyl transferase activity (Bhargavan *et al.*, 2016). More studies in HIV infected individuals from Cameroon are underway to shed light on the effects of HIV subtype on viremia and neurocognitive impairment.

Discussion

Drs. Buch and Joseph led discussions focused on future directions on HIV-associated complications of the CNS in Africa and summarized symposium outputs. Studies presented from five countries (South Africa, Zambia, Cameroon, Uganda and Nigeria) demonstrated that HAND was prevalent in all these countries. HIV-1 clade C infection in South Africa revealed significant functional cognitive impairment that was independent of Tat (C31S) mutation, suggesting thereby that HIV-1 clade C could cause cognitive impairment similar to other HIV clades. These results highlighted the fact that similar to other viral clades, individuals infected with HIV-1 clade C, are also candidates that would require mental health care (Paul *et al.*, 2014). However, longitudinal studies on neuropsychiatric evaluations of Clade C infected individuals are necessary to substantiate and draw conclusions related to the role of Tat dicysteine motif in cognitive outcomes.

Similar to discussions at a previous 'NeuroAIDS in Africa' meeting (Robertson *et al.*, 2010) and a 'Global NeuroAIDS Roundtable' (Joseph *et al.*, 2013), this symposium also reiterated an urgent need in the field for development of standardized neurocognitive assessment tools. Such standardized methods will enable comparisons across studies and further clarify

relationships between HIV clade diversity and the development of associated neurological disorders.

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