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Altered structural brain changes and neurocognitive performance in pediatric HIV

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ABSTRACT

Pediatric HIV patients often suffer with neurodevelopmental delay and subsequently cognitive impairment. While tissue injury in cortical and subcortical regions in the brain of adult HIV patients has been well reported there is sparse knowledge about these changes in perinatally HIV infected pediatric patients. We analyzed cortical thickness, subcortical volume, structural connectivity, and neurocognitive functions in pediatric HIV patients and compared with those of pediatric healthy controls. With informed consent, 34 perinatally infected pediatric HIV patients and 32 age and gender matched pediatric healthy controls underwent neurocognitive assessment and brain magnetic resonance imaging (MRI) on a 3 T clinical scanner. Altered cortical thickness, subcortical volumes, and abnormal neuropsychological test scores were observed in pediatric HIV patients. The structural network connectivity analysis depicted lower connection strengths, lower clustering coefficients, and higher path length in pediatric HIV patients than healthy controls. The network betweenness and network hubs in corticolimbic regions were distorted in pediatric HIV patients. The findings suggest that altered cortical and subcortical structures and regional brain connectivity in pediatric HIV patients may contribute to deficits in their neurocognitive functions. Further, longitudinal studies are required for better understanding of the effect of HIV pathogenesis on brain structural changes throughout the brain development process under standard ART treatment.

1. Introduction

Acquired immunodeficiency syndrome (AIDS) is caused by human immunodeficiency virus (HIV) and is characterized by the progressive failure of the immune defense resulting in the life threatening complications such as infections and cancers (Frisch et al., 2000; Kumarasamy et al., 1995). The global burden of pediatric HIV remains a challenge around the world with ~3.4 millions children living with HIV (Global Burden of Disease Pediatrics Collaboration et al., 2016). Perinatal transmission of HIV is the primary source of HIV transmission in children during pregnancy, delivery and breast feeding periods. Pediatric HIV patients showed neurodevelopmental delay and subsequently cognitive impairment including visual, language, attention, memory, learning and hearing disabilities (Le Doare et al., 2012; Van Rie et al., 2008; Belman et al., 1988).

Histological studies have demonstrated tissue injury in cortical and subcortical regions in the brain of HIV patients (Kibayashi et al., 1999; Gelman, 2015; Lang et al., 1989). Magnetic resonance imaging (MRI) has been used to measure these changes *in vivo* non-invasively. Though numerous MRI studies investigated structural and functional changes in the brain of adolescent and adult HIV patients only few studies reported these changes in pediatric HIV patients (Hoare et al., 2012; Cohen et al., 2016). Previously, altered metabolites level in the brain of pediatric HIV patients is quantified using proton MR spectroscopy and correlated with $CD4^+$ counts and cognitive functions (Keller et al., 2004; Lu et al., 1996). Neuroimaging technique such as diffusion tensor imaging depicted reduced fractional anisotropy and increased mean diffusivity in multiple brain regions in pediatric HIV patients as compared to healthy controls

Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; ELISA, enzyme-linked immunosorbent assay; FLAIR, fluid attenuation inversion recovery; FSPGR, fast spoiled gradient echo; TR, repetition time; TE, echo time; FA, flip angel; FOV, field of view; RAKIT, revised Amsterdamse kinder intelligence; GAT, graph-theoretical analysis toolbox; ROIs, regions of interest; C, clustering coefficient; L, characteristic path length; SW, small-world index; TBM, tensor based morphometry.

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(Hoare et al., 2012; Cohen et al., 2016). A recent study depicted global reduced gray matter and white matter volumes in pediatric HIV patients using volumetric based approach (Cohen et al., 2016). Since multiple cortical and subcortical brain regions are involved in the normal brain functioning and neurocognitivity by evaluating the *in vivo* changes in these structures may improve understanding of the neurobiology of pediatric HIV patients.

In the current study, we measured cortical thickness, subcortical volume, and structural connectivity in perinatally infected pediatric HIV patients and compared with those of healthy controls. Additionally, neurocognitive test scores were quantified and correlated with the brain structural changes. We hypothesized that changes in cortical thickness and subcortical volumes will affect the brain connectivity and cognitive performance in pediatric HIV patients.

2. Materials and methods

2.1. Participants

Thirty four perinatally infected pediatric HIV patients (mean ± SD, 10.2 ± 1.7 years) and 32 (mean ± SD, 11.2 ± 2.9 years) pediatric healthy controls of similar socioeconomic and ethnic group were included in this study. HIV assay was performed as per the national HIV testing protocols *i.e.* screening by HIV enzyme-linked-immunosorbent-assay (ELISA)/Rapid test followed by confirmation with 2 further HIV rapid tests of higher specificity. All subjects underwent clinical assessment including neuropsychological test and brain MRI. Informed consent was obtained from all participants or their nearest kin prior study. Institutional Ethical Committee approved the study protocol.

2.2. Magnetic resonance imaging

Brain MRI was performed on a 3 T clinical Scanner (GE Healthcare Technologies, Milwaukee, WI, United States) using a 32-channel head coil. T_2-weighted, T_1-weighted and fluid-attenuated inversion recovery (FLAIR) images were acquired to assess any gross brain pathology, such as tumor, cyst, or any other mass lesion. Presence of such anomalies and poor image quality due to motion artifacts were used as exclusion criteria. The inclusion criteria for pediatric HIV patients were infection of HIV in fetal or neonatal period and were on the antiretroviral treatment. For healthy controls, inclusion criteria were similar demographic, socioeconomic and educational status. For the structural analysis, high-resolution 3D T_1-weighted brain images were acquired using a fast spoiled gradient echo (FSPGR) BRAVO pulse sequence with following parameters: repetition time (TR) = 8.4 ms, echo time (TE) = 3.32 ms, inversion time = 400 ms, flip angel (FA) = 13°, matrix size = 512 × 512, field of view (FOV) = 240 × 240 mm^2, slice-thickness = 1.0 mm.

2.3. Neuropsychological examination

Neuropsychological examination was performed in all subjects using well-established Indian adopted Revised Amsterdamse Kinder Intelligence Test (RAKIT), which contains a battery of 9 subsets that assess language, memory, learning, visual, motor coordination, concentration, mental speed, and attention. The RAKIT test battery includes- Closure test; this is a cognition and perception test that consists of 50 presentations, Exclusion test; this cognition test consists of 50 presentations, Memory-span test; this memory test consists of 36 items, Verbal-Meaning; this is based on the knowledge of concepts and verbal conceptualization and consists of 60 items, Mazes; this is a visual-motor coordination, planning and foresight speed test and consists of 14 items, Learning-names; this memory test contains 12 items, Quantity; this is a perception based test containing 65 items, Discs; this test tells about the spatial orientation and speed of spatial visualization and it contains 18 items, hidden-figure; this test is used for the transformation of visual field and convergence/flexibility of closure and it consists of 45 items (Yadav et al., 2010).

2.4. Data processing and measurements of cortical thickness and subcortical volumes

FreeSurfer (v. 5.3.0) was used to quantify cortical thickness and subcortical volumes using high-resolution T_1-weighted images in all subjects as described in detail elsewhere (Dale et al., 1999; Fischl et al., 1999). The processed data were examined for quality and to make sure that non-brain areas were omitted from analysis. Similarly, all boundaries (gray, white, and pial) were visually evaluated, and if needed, minor edits were performed to correct the misidentified areas.

Regional changes in cortical thickness between pediatric HIV patients and healthy controls were performed on smoothed gray matter surface maps. Smoothing was performed using a Gaussian kernel (full width at half maximum, 15 mm) (Yadav et al., 2015). In the analysis, regional cortical thickness was modeled as a function of groups, and age and gender were included as covariates in the model. Monte Carlo simulations with 10,000 iterations were applied to correct for multiple comparisons using a cluster-wise threshold of $p < 0.05$. Brain sites that survived after correction for multiple comparisons are depicted on the cortical thickness maps. For structural identification, clusters with significant difference between groups were overlaid onto averaged inflated cortical surface maps.

2.5. Network analysis

2.5.1. Network construction

Graph-theoretical analysis toolbox was used for the analysis of global and regional network properties (Hosseini et al., 2012; Rubinov and Sporns, 2010). FreeSurfer parcellated 84 regions of interest (ROIs) from cortical and subcortical areas were used for the network construction. Inter-regional ROIs correlations metrics for both groups were generated using Pearson correlation coefficient.

2.5.2. Global network

To detect differences in the global network topology between groups, we measured clustering coefficient (C) and characteristic path length (L) of the network at different densities from 0.27 to 0.50 with interval of 0.02. The C and L of both groups were compared with the corresponding mean values of a random graph with the same number of nodes, total edges, and degree distribution (Sporns and Zwi, 2004; Maslov and Sneppen, 2002). The small-world index (SW) was computed as (C/Crand)/(L/Lrand), where Crand and Lrand are the mean C and L of the random network (Bassett et al., 2006). The characteristics of SW networks are: C must be significantly higher than that of cluster random networks (C/Crand ratio > 1), and L should comparable to path length of random networks (Hosseini et al., 2012) (L/Lrand ratio close to 1). We also measured the nodal characteristic (betweenness) of the structural networks at threshold density of 0.27 to detect anatomical or functional connections.

2.5.3. Network hubs

The network hub is a node with central module that has higher degree than average node and considered as a crucial regulator of effective information flow in the brain (Rubinov and Sporns, 2010). We considered a node to be a hub if its degree was higher than or equal to two standard deviations of mean network degree (Hosseini et al., 2012; Bassett et al., 2008).

2.5.4. Structural network comparison

For measuring the network difference between pediatric HIV patients and healthy controls, a non-parametric permutation test with 100 repetitions was performed. In each repetition, cortical and subcortical volumes (84 ROIs) were randomly reassigned to each individual