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ORIGINAL PAPER

Correlating brain volume and callosal thickness with clinical and laboratory indicators of disease severity in children with HIV-related brain disease

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Abstract
Background Objective MRI markers of central nervous system disease severity may precede subjective features of HIV encephalopathy in children. Previous work in HIV-infected adults shows that brain atrophy was associated with low CD4 and with neuropsychological impairment. Significant thinning of the corpus callosum (CC), predominantly anteriorly, was also found in HIV-infected adults and correlated with CD4 levels. These findings have not been tested in children.
Purpose The aim of this study was to determine if brain volume and midsagittal CC linear measurements (thickness and length) on MRI in children with HIV-related brain disease correlate with clinical and laboratory parameters of disease severity.
Methods Retrospective MRI analysis in children with HIV-related brain disease used a volumetric analysis software and a semi-automated tool to measure brain volume and callosal thickness/length, respectively. Each measure was correlated with clinical parameters of disease severity including Griffiths Mental Development scores (GMDS), absolute CD4 counts (cells/mm^3), nadir CD4 (the lowest CD4 recorded, excluding baseline), duration of HAART, and decreased brain growth.
Results Thirty-three children with HIV-related brain disease were included. Premotor segment of the CC mean thickness correlated with age (p=0.394). Motor CC maximum thickness correlated significantly with general developmental quotient (p=0.0277); CC length correlated with a diagnosis of acquired microcephaly (p=0.0071) and to CD4 level closest to date of the MRI scan (p=0.04).
Conclusions Length of the CC and the "motor CC segment" may represent surrogate clinical biomarkers of central nervous system disease severity and with decreased level of immunity in HIV-infected patients that precede established HIV encephalopathy.

Keywords HIV · Encephalopathy · Corpus callosum · Neurodevelopment · Immunity · MRI

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Abbreviations

CC	Corpus callosum
TBV	Total brain volume
GM	Gray matter
WM	White matter
GMDS	Griffiths Mental Development scores

Introduction

HIV encephalopathy (HIVE) in vertically infected infants and children is AIDS-defining [1] and involves loss of brain growth, motor abnormalities, and cognitive dysfunction [2, 3]. An early biomarker of encephalopathy is needed [4] because early and intensive neuroprotective antiretroviral therapy may slow, halt, or reverse encephalopathy, improving neurocognitive outcome and survival in children with HIV dementia [3, 5, 6]. The aim of management, therefore, is to identify those HIV-infected infants that are at risk of CNS disease progression, early on [2]. MRI may have a role to play in this regard and may also play a role in predicting developmental outcome [7].

The most common imaging findings in children with HIVE are basal ganglia calcification and atrophy [1, 8, 9]. Studies in adults with AIDS have measured significant atrophy in the basal ganglia (specifically the corpus striatum), parietal gray matter, pericentral regions, cingulum, and white matter, including the corpus callosum (CC) [10, 11]. Brain atrophy in adults with HIV has been shown to be associated with low CD4 counts [10, 11] and with neuropsychological impairment [11].

Interpretation of standard structural MRI lacks the sensitivity to detect subtle volume and white matter abnormalities in HIV-related brain disease [11]. Volumetric techniques are therefore valuable for identifying subtler in vivo morphometric changes in the brain [12]. Ances and colleagues reported that brain volume assessment may be a more robust way of quantifying brain integrity in adults with HIV [6].

The areas of the brain most affected in HIV are those close to the ventricles. This is because there is easier viral penetration by HIV-infected mononuclear cells "trafficking" from the cerebrospinal fluid into brain and therefore a higher concentration of HIV toxins in these [6, 10]. The highest brain concentrations of HIV therefore are found in the caudate nuclei and CC [6, 10]. Ances and colleagues noted that decreases in brain volume in HIV-infected adults included a decrease in volume of the CC [6]. Chiang [11] and Dewey [12] also showed changes in CC volume in patients with HIV. Thompson and colleagues noted that white matter deficits might be easier to detect at the midline than globally [10]. They proposed the use of CC thickness as an MRI marker of white matter integrity in adults with AIDS [10]. These authors showed significant thinning of the CC involving predominantly the anterior three sectors (up to 25 % thinner than controls) in HIV-infected adults and significant correlation with CD4 levels [10]. This may be explained by the fact that severe immune deficiency results in greater HIV replication, which in turn results in HIV effects on the brain [13]. There are no such studies in HIV-infected children with suspected HIV-related brain disease.

The aim of this study was to determine if brain volume and midsagittal CC linear measurements (thickness and length) on MRI in children with HIV-related brain disease correlate with clinical and laboratory parameters of disease severity.

Materials and methods

In a cross-sectional study, brain volume and linear CC measures were derived retrospectively, from MRI, in children with laboratory-confirmed vertically acquired HIV. The children were imaged because they were diagnosed with HIV-related brain disease, over a 2.5-year period, at a referral hospital in South Africa. They were all part of a larger, prospective study, in which the current study is nested. Children had monthly assessments, including neurological examination and head growth monitoring. Comprehensive developmental assessment using Griffiths Mental Development Scales (GMDS) [14] was performed routinely at 12, 18, 30, and 42 months of age by one senior pediatrician specializing in pediatric developmental assessment as part of the prospective clinical study. All children were being treated on various antiretroviral therapy (ART) regimes at the time of imaging. All the children were from African and mixed races and hailed from a low socioeconomic background.

Inclusion criteria

To be included, children (≤13 years of age) with vertically acquired, laboratory-confirmed HIV infection (positive for HIV DNA PCR confirmed by plasma HIV RNA >1,000 copies/ml) had to have been referred for MRI because they were diagnosed with HIV-related brain disease during the study period.

Due to the development of criteria for the diagnosis of HIV encephalopathy before the highly active antiretroviral therapy (HAART) era [15], our clinicians referred children on ART who had HIV-related brain disease but did not meet the full criteria for encephalopathy to MRI. This is supported by the development of a category "HIV-related CNS compromise" in the classification of HIV-related CNS disease in children [16]. We used the following in-house criteria for HIV-related brain disease, using our experience of the performance of children attending our clinics on local neurodevelopment assessment tools—at least one of the following findings in the absence of a concurrent illness or environmental/social reasons that could explain the findings:

- Locomotor developmental delay:
  Confirmed on Griffiths Mental Development Scales: quotient drops of 15 (=1 standard deviation) or a locomotor quotient <80, which persists for at least 2 months; confirmed on Molteno Adapted Scale with ≥6 months delay persisting for at least 2 months
- Language developmental delay:
  Confirmed on Griffiths Mental Development Scales: quotient drops of 15 (=1 standard deviation) or a language quotient <80, which persists for at least 2 months, and with a normal hearing test; confirmed on Molteno Adapted Scale with ≥6 months delay persisting for at least 2 months
- Brisk reflexes fulfilling one of the following criteria:
  Spreads to other areas, sustained clonus, can elicit a reflex with a tap above or below tendon area

After excluding the following on history:

Birth hypoxia; opportunistic or other infection of the central nervous system; systemic CMV infection; severe illness requiring intensive care admission; gastroenteritis with hypernatremia; any near-death experience of documented event of prolonged hypoxia and/or hypotension that did not require ICU admission; prolonged hospitalization (>2 weeks) in the 3 months prior to the onset of symptoms; and lack of stimulation, social neglect, and possible lack of insight.

Of the patients considered, only those with available relevant clinical data were included which included Griffiths Mental Development Scales scores, assessment of brain growth (microcephaly) over serial measurements, time on HAART, and CD4 (count/percent and nadir CD4).

Exclusion criteria

Patients were excluded when MRI scans were unavailable, incomplete, or inadequate or later in the study whenever volumetric analysis (described below) did not result in adequate images for assessment.

MRI scanning was performed on a Siemens Magnetom Symphony 1.5 T (Erlangen, Germany). MRI parameters included the following: axial T2 (TE 103, TR 5460, slice 5 mm, gap 1.5 mm) and sagittal T1 (TE 14, TR 531, slice 5 mm, gap 1.5 mm). Axial T2 SE was selected because axial T1-weighted images are not routinely performed in the age group included.

Measurement instruments and data

Overall mean and maximum CC thickness Mean and maximum CC thicknesses were calculated in millimeters using a software developed in-house (by BS) by importing MRI data into a customized tool written in MATLAB (The Mathworks Inc., Natick, MA). A description of this method was published in 2012 [17] and is similar to another described method [18]. The operator (SA) selected the midline-sagittal, T1-weighted image, and dorsal (top) and ventral (bottom) CC contours were manually drawn using a point depositing system. This initiated the automated calculation of a third contour midway between these (referred to elsewhere as the CC diameter) [19]. The program then divided the midline contour into a number of segments through perpendicular spokes which intersected the dorsal and ventral contours. A maximum of 40 segments was chosen for this application to ensure that each segment still consisted of a contiguous strip of voxels across the CC. The system automatically plotted segment thickness as a function of distance along the midline CC contour. Segmental CC mean and maximum thicknesses were determined for each anatomic CC region as previously described [20–22] by including the thickness of all segment measurements within each region: "prefrontal" segment (anterior sixth), "premotor" segment (between the anterior sixth and the midpoint), "motor" segment (midpoint to posterior third), "sensory" segment (posterior third to posterior quarter), and "language"/"visual" segment (posterior quarter). CC length (from tip of rostrum midpoint to tip of splenium midpoint) was derived automatically.

Brain volume calculation Total brain volume (TBV), gray matter (GM) volume, and white matter (WM) volume were calculated from axial T2WI in each patient using MATLAB 7.3 (Works, Natick, MA) and Statistical Parametric Mapping software (SPM5, Wellcome Department of Imaging Neurosciences, University College, London) using voxel-based morphometric (VBM) analysis. This is a whole-brain technique for characterizing volume and tissue "concentration" differences in structural MRIs. The MRI scans were spatially normalized towards a template of normal pediatric MRI scans released by the Imaging Research Center, Cincinnati Children's Hospital Medical Center. The normalized images were then segmented into GM and WM and volumes in milliliters (ml) of each, derived using the automated volume calculation "Easy Volume." TBV was determined by summing the calculated GM and WM volumes. Use of the T2-weighted sequence for SPM segmentation and volume calculation has precedent in the work by Carone et al. [23] and von Bezing et al. [24].

Neuroimaging analysis was performed by the primary investigator (SA) who had over 14 years of pediatric neuroimaging experience at the time of the study.

Neurodevelopment Griffiths Mental Development scores (GMDS) determined closest to the time of MRI were used. Quotients (general quotient (GQ), locomotor sub-quotient, language sub-quotient) were obtained from raw scores or age equivalents using UK norms with a mean of 100 and standard deviation of 15 [14, 25]. Significant developmental delay was regarded as more than two standard deviations below the mean, i.e., quotients <70.

Clinical and laboratory data These included absolute CD4 counts (cells/mm^3), nadir CD4 (the lowest CD4 recorded, excluding baseline), duration of HAART, and the presence or absence of acquired microcephaly.

Data analysis

Data were summarized using mean and standard deviations for continuous normally distributed variables (age, CC thickness (mm), CC length (mm), TBV, GM volume, WM volume (ml), GMDS, CD4 (cells/mm^3), nadir CD4 (cells/mm^3), length on HAART (days)) and median and range when data were not normally distributed. Categorical variables (males/females and decreased brain growth (microcephaly)) were recorded as frequencies and percentages. Pearson correlations were used for normally distributed values and Spearman correlations for non-normally distributed values. Overall mean and maximum CC thicknesses, mean and maximum segmental thicknesses, and volume were correlated with GMDS GQ and sub-quotients (locomotor and language) as well as clinical and laboratory data in patients. Significance was considered if $p<0.05$.

Ethical issues

MRI studies were performed for clinical indications only. Two institutional ethics review boards approved the study (N07/09/208 and M110802).

Results

Out of a total of 56 children who had MRI scans for HIV-related brain disease and were considered for inclusion, only 48 had the relevant clinical data required. Exclusion criteria resulted in 4 patients being excluded because imaging was lost, and an additional 11 patients were excluded because of motion artifacts after the volumetric analysis. After applying the exclusion criteria, 33 patients remained as the study group. Patients' age ranged from 7 to 49 months (median 31 months; mean 30 months), and there were 16 boys and 17 girls. These were exclusively African and mixed-race children from impoverished backgrounds.

Table 1 Overall and segmental mean corpus callosum thickness

Variable	Mean thickness (mm)		
	n	Mean ± SD or median (IQR)	Min–max
Overall CC	33	5.54±0.64	3.9–6.9
Prefrontal CC	33	7.34±1.09	4.8–10.5
Premotor CC	33	5.53±0.66	4.4–7.3
Motor CC	33	4.1 (3.6–4.3)	2.6–6.5
Sensory CC	33	3.2 (2.6–4)	2.2–5.1
Visual CC	33	6.22±1.17	3.5–8.5

CC thicknesses are summarized in Tables 1 (mean) and 2 (maximum) and brain volumes are summarized in Table 3. Figures 1 and 2 demonstrate the midline CC slice used, the automated CC thickness measurements along the CC, and length measurement as well as representative slices of the segmented white and gray matter images used for volume assessment of the brain.

It was not possible to perform GMDS on two patients; thus, means were calculated from 31 patients. GMDS were performed at a mean age of 30 months (range 11–48 months), within a mean of 3 months time difference (range 4 days–6 months) from the neuroimaging date. Mean scores in patients fell into the low average range with a mean GMDS GQ of 84±6.97. The GMDS locomotor and language sub-quotients were 84±13.08 and 80±11.93, respectively.

Results of the other clinical and laboratory parameters including decreased brain growth (acquired microcephaly), time on HAART, nadir CD4, and CD4 closest to the time of the MRI are summarized in Table 4.

Significant correlations

Brain volume did not show any significant correlations with clinical or laboratory parameters. The closest to showing a

Table 2 Overall and segmental maximum corpus callosum thickness and CC length

Variable	Maximum thickness (mm)		
	n	Mean ± SD or median (IQR)	Min–max
CC length	33	48.9±2.7	41.3–54.7
Overall CC	33	9.3±1.2	6.6–11.6
Prefrontal CC	33	8.7±1.4	6.3–11.5
Premotor CC	33	7.5±1	5.9–10.4
Motor CC	33	4.6 (4.4–5.1)	3.5–6.9
Sensory CC	33	3.7±0.9	2.4–5.4
Visual CC	33	8.4±1.4	4.6–11.6

Table 3 Brain volume (TBV, GM, and WM) (ml)

Variable	Volume (ml)		
	n	Mean ± SD or median (IQR)	Min–max
GM	33	631.94±75.67	500–800
WM	33	354.85±45.12	257–430
TBV	33	986.79±93.29	820–1,184

GM gray matter volume, *WM* white matter volume, *TBV* total brain volume

correlation was total brain volume (TBV) with nadir CD4 (p=0.06). The only region of CC thickness that showed a significant correlation with a clinical parameter was the motor CC maximum (p=0.0277) which correlated with GMDS GQ. Specifically, CC thickness did not correlate significantly with time on HAART in our patients (the closest to a correlation was the prefrontal segment maximum p=0.0589). CC length correlated with decreased brain growth (acquired microcephaly) (p=0.0071) and with CD4 closest to the MRI scan (p=0.04). The only significant correlation with age was the premotor CC mean thickness (p=0.0413).

Discussion

The defining pathologically feature of HIVE is diffuse WM involvement which is more pronounced in the advanced stages of the disease [26]. It is stated that the pattern of CNS involvement in HIV-infected children differs from that in HIV-infected adults [27], and findings from adult studies cannot be extrapolated to children. The imaging correlate of HIVE is expressed in a study (from 1998), which showed that every child with a diagnosis of encephalopathy had a positive neuroimaging finding—either atrophy or basal ganglia calcification [9].

Neuroimaging has three specific roles in HIV-infected children [28]: (a) cerebral atrophy screening; (b) complication detection, e.g., tumor, vascular, and infection; and (c) treatment monitoring [29]. The screening role for MRI should be aimed at children who are at risk for developing encephalopathy, those with neurological symptoms, and those with neurocognitive dysfunction [30] and mainly involves the identification of brain atrophy. Cerebral atrophy and ventriculomegaly were reported to be present in 68 and 78 % (respectively) of HIV-infected children with symptomatic disease in one study [1]. Interpretation of standard

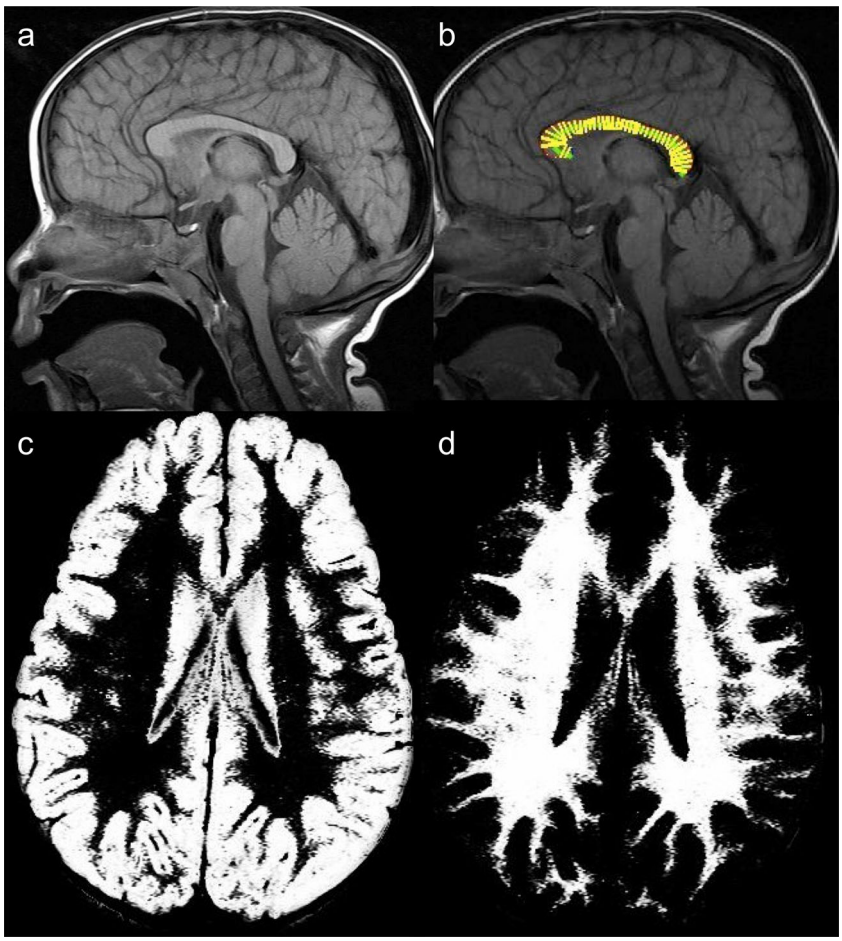

Fig. 1 A 1-year and 8-month-old boy with HIV-related brain disease and failure of brain growth that underwent corpus callosum thickness and length measurements as well as brain volume determination. **a** Midline sagittal T1WI MRI of the corpus callosum. **b** Midline-sagittal T1WI MRI of the corpus callosum indicating the 40 radial measurements of thickness produced by the custom semi-automated tool. **c** Gray matter segmentation for volume assessment. **d** White matter segmentation for volume assessment. (Mean CC thickness 5.9 mm; segmental motor CC thickness 4.1 mm; CC length 44.9 mm; brain volume 1,016 ml; gray matter volume 664 ml; white matter volume 352 ml; Griffiths general score 85; locomotor score 84; language score 77 (UK norm mean = 100; SD 15); length on HAART 86 days; nadir CD4 2,031 cells/mm^3; CD4 nearest the MRI scan 1,281 cells/mm^3)

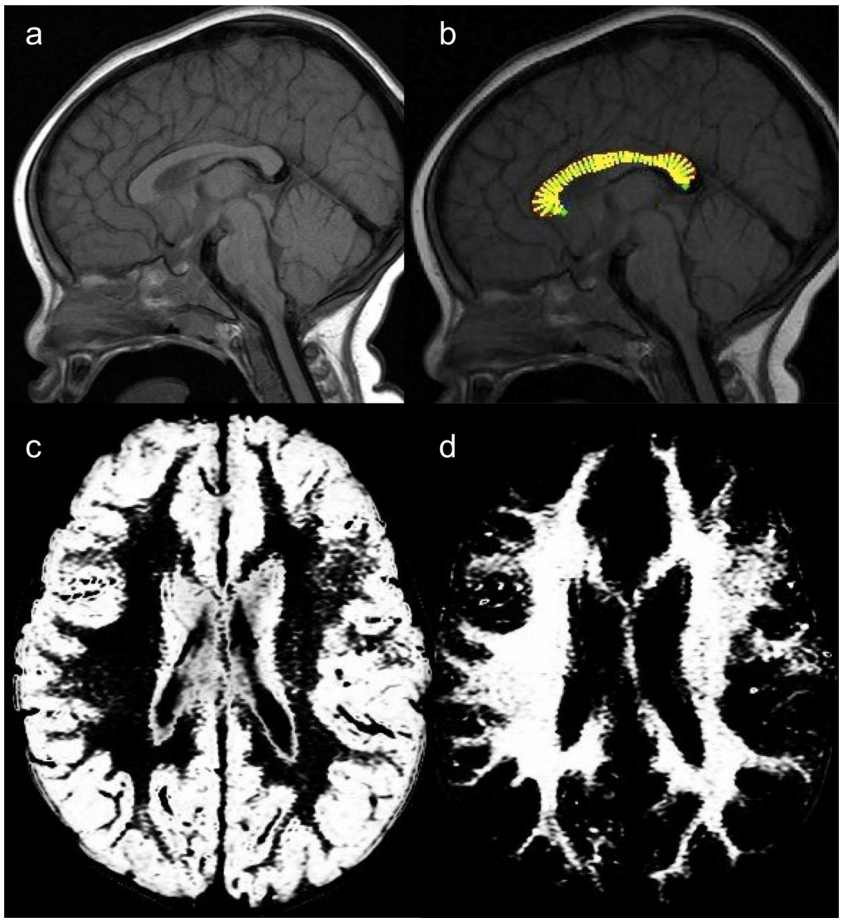

Fig. 2 A 2-year-old girl with HIV-related brain disease and normal brain growth that underwent corpus callosum thickness and length measurements as well as brain volume determination. **a** Midline sagittal T1WI MRI of the corpus callosum. **b** Midline sagittal T1WI MRI of the corpus callosum indicating the 40 radial measurements of thickness produced by the custom semi-automated tool. **c** Gray matter segmentation for volume assessment. **d** White matter segmentation for volume assessment. (Mean CC thickness 5.3 mm; segmental motor CC thickness 3.8 mm; CC length 46 mm; brain volume 894 ml; gray matter volume 605 ml; white matter volume 289 ml; Griffiths general score 92; locomotor score 105; language score 88 (UK norm mean = 100; SD 15); length on HAART 154 days; nadir CD4 358 cells/mm^3; CD4 nearest the MRI scan 1,907 cells/mm^3)

structural MRI, however, lacks the sensitivity to detect subtle volume and white matter abnormalities in HIV-related brain disease [11] and is also subjective. Volumetric techniques are therefore valuable for identifying subtler in vivo morphometric changes in the brain [12]. This is most accurately achieved through manual delineation by trained experts and is considered the gold standard. Automated techniques are preferred, therefore, because manual measurements are extremely labor-intensive and time-consuming [10, 11]. Ances and colleagues reported that brain volume assessment is a more robust way of quantifying brain integrity in adults with HIV [6]. Most researchers use Statistical Parametric Mapping (SPM, Wellcome Trust Centre for Neuroimaging, UK), which is partially automated and less labor-intensive but is obviously not automated enough for routine clinical use [10, 11]. This drives the ongoing search for clinically useful and quick surrogate methods reflecting brain volume and clinical parameters [10].

Hasan and colleagues used CC volume as a surrogate of brain volume [22] but again required a technically demanding volume determination making it a less likely clinical tool. Ances and colleagues noted that decreases in brain volume in HIV-infected adults included a decrease in volume of the CC [6]. Chiang [11] and Dewey [12] also showed changes in CC volume in patients with HIV. Thickness of the CC is affected by peripheral white matter loss, making it a useful surrogate for WM atrophy [10]. Thompson and colleagues made this important observation that white matter deficits might be easier to detect at the midline than globally [10]. These authors, understanding the need for clinical utility,

Table 4 Summary statistics of clinical and laboratory parameters

Variable	Number	Mean ± SD or median (IQR)	Min–max
Time on HAART (days)	33	107.78±45.52	24–199.4
NADIR CD4 %	33	21.4 (16.6–25.6)	12–35
NADIR CD4 count	33	1,099 (823–1,639)	268–3,055
CD4 % closest to scan	33	33.9 (29.9–40.2)	18.7–52.9
CD4 count closest to scan	33	1,403 (1,026–1,766)	644–3,558

proposed the use of CC thickness as an MRI marker of white matter integrity. Since 2007, seven studies of CC thickness have included children and adolescents, but there have been no previous reports of CC thickness in children with HIV infection [31–37]. Factors correlated with CC thinning have included hydrocephalus, mental retardation, sickle cell disease, spastic quadriparesis, fetal alcohol syndrome, neoplasia, preterm birth [35], periventricular leukomalacia, WM atrophy, motor performance, IQ [36, 37], ADHD [32], and fetal alcohol [31].

Even though Thompson and colleagues conceived using CC thickness as an MRI marker of white matter integrity in adults with AIDS [10], this has never been tested in children with HIV infection. We therefore decided to not only correlate brain volume with clinical and laboratory parameters of severity in HIV-infected children but also to correlate overall mean and segmental CC thickness with these. Importantly, this is a value (i.e., thickness) that can be generated by the radiologist at the clinical workstation through simple caliper placement.

The areas of the brain most affected in HIV are those close to the ventricles. This is because there is easier viral penetration by HIV-infected mononuclear cells trafficking from the cerebrospinal fluid into brain and therefore a higher concentration of HIV toxins in these [6, 10]. The highest brain concentrations of HIV therefore are found in the caudate nuclei and CC [6, 10]. Studies in adults with AIDS have measured significant atrophy in the basal ganglia (corpus striatum), parietal gray matter, pericentral regions, cingulum, and white matter, including the CC [10, 11]. The importance of this is that brain atrophy in adults with HIV has been shown to be associated with low CD4 counts [10, 11] and with neuropsychological impairment [11]. Thompson and colleagues went further to show significant thinning of the CC (predominantly at the anterior three sectors) of up to 25 % thinner than controls in HIV-infected adults and showed significant correlation with CD4 levels [10]. The explanation for this correlation of CD4 with CC thickness is the fact that severe immune deficiency results in greater HIV replication, which in turn results in greater HIV effects on the brain [13].

Maximum motor segment CC thickness in our patients correlated best with the GMDS GQ ($p=0.0277$). We also showed correlation of CC length with CD4 counts ($p=0.04$). Cohen et al. reported that adults with chronic HIV infection and episodes of severely impaired immunity (low nadir CD4) were at greatest risk for cerebral atrophy [13]. If this is the case, HAART may be unable to protect the brain from HIV-related degeneration [9, 13, 38]. Corpus striatum atrophy appears to occur despite treatment and is possibly dictated by an initial insult [38]. In addition, safety and dose of HAART has not been determined for children. Efavirenz may be neurotoxic [39] but is not for consideration in our study as it was not used in our patients. CC thickness did not correlate significantly with time on HAART in our patients (the closest to a correlation was the prefrontal maximum $p=0.0589$).

Limitations

There are several limitations related to the study. Firstly, patient subject numbers are relatively small. Fifteen patients were lost or excluded due to the inability to adequately assess brain volume calculations [12].

On the technical side, CC thickness measurements using our method have limitations:

(a) Selection of the midline is influenced by the thickness and number of sagittal slices. The thinner the slices, the more options there are for selecting the midline slice from, which would affect repeatability. The thicker the slices, the more chances there are that the slice selected is not the true midline sagittal but rather a parasagittal slice.
(b) Point deposition on the CC was operator-dependent both with regard to the number of points deposited and the site where these were deposited. There were no prescribed landmarks for depositing points. The following comments are also worth noting: the inferior CC margin and rostral edge were frequently indistinct, the union of the fornix with the CC may obscure the inferior margin, start/end points can be poorly defined, and the physical thickness of the marker dot can affect placement.

The customized tool used in our study differs to the one used by Westerhausen et al. by providing a maximum of 40 segments rather than 100 [34]. It was designed for use with Diffusion Tensor Imaging (DTI) where segments serve as seeds for fiber tracking and ensures that segments consist of a contiguous strip of voxels [17]. No DTI was used for this patient cohort and the software is intended for use in DTI imaging in future work.

Conclusion

Linear CC measurements on MRI may represent an early biomarker of HIV-related brain disease prior to establishment of brain atrophy. Where we expected brain volume to correlate with clinical and laboratory parameters of severity of HIV infection, we only showed a trend towards a relationship with nadir CD4. We did demonstrate, however, a statistical correlation of the degree of mental development with the motor segmental CC thickness and correlation of the CC length with the level of immunity and with acquired microcephaly. Linear

measurements are easy to perform and practical for the clinical radiologist who may be able to predict developmental outcome.

Planned further research includes fractional anisotropy and fiber number determination, using DTI, and correlating volume in patients with true atrophy and CC thickness.

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