White Matter Signal Abnormalities in Children With Suspected HIV-related Neurologic Disease on Early Combination Antiretroviral Therapy

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Background: The natural history and manifestation of HIV-related neurologic disease have been ameliorated by combination antiretroviral therapy (ART). We describe the characteristics of white matter signal abnormalities (WMSA) on magnetic resonance imaging in children with HIV-related neurologic disease.

Methods: We reviewed magnetic resonance imaging scans of children with suspected HIV-related neurologic disease despite early ART and correlated with clinical, neurodevelopmental data, virologic markers and time on ART. These children were also on the Children with HIV Early Antiretroviral (CHER) trial.

Results: Magnetic resonance imaging scans were performed at a mean age 31.9 months (range 8–54) on 44 children: 10 on deferred and 34 on early treatment arms, commencing ART at mean age of 18.5 and 8 weeks, respectively. Multiple high signal intensity lesions on T2/fluid attenuated inversion recovery were documented in 22 patients (50%), predominantly in frontal (91%) and parietal (82%) white matter. No differences in neurodevelopmental scores comparing children with and without WMSA were found. Neither lesion load nor distribution showed significant correlation with neurodevelopmental scores or neurologic examination. Normal head growth was more common in the WMSA group ($P = 0.01$). There was a trend for association of WMSA and longer time on ART ($P = 0.13$) and nadir CD4% ($P = 0.08$).

Conclusions: Half of children referred with HIV-related brain disease had WMSA on T2/fluid attenuated inversion recovery. Our findings of the association with normal head growth and duration of ART require further study. We suspect that WMSA can occur early and that initiating ART by 8 weeks of life may be too late to prevent HIV from entering the central nervous system.

Key Words: HIV-encephalopathy, HIV-related brain disease, developmental score, white matter signal abnormality, MRI, early antiretroviral therapy

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HIV-encephalopathy is an AIDS defining event,[1] which in its most severe form, presents with developmental delay and motor dysfunction.[2] However, with combination antiretroviral therapy (ART), manifestations are likely to be subtle and have not yet been well-described in children receiving early ART. It is critical to identify a good marker of HIV-related manifestations in the central nervous system (CNS)[3] as early treatment can slow deterioration and partially improve manifestations.[4,5] HIV-encephalopathy demonstrates white matter signal abnormality (WMSA), mainly hyperintensity on magnetic resonance imaging (MRI).[6] In adults treated with ART, resolution of WMSA mirrors clinical improvement.[7,8] The imaging findings in children with HIV-encephalopathy show basal ganglia calcification and atrophy. One limited study (21 children) antedating the availability of ART, demonstrated deep white matter hyperintensity sparing the subcortical U-fibers in a third of children.[9] Our aim was to determine the prevalence, distribution and characteristics of WMSA on T2/ fluid attenuated inversion recovery (FLAIR) sequences in a larger number of children initiating ART from an early age, but with suspected HIV-related neurologic disease. We also sought to correlate WMSA with developmental scores, clinical presentation and laboratory studies.

MATERIALS AND METHODS

We conducted a prospective study over 2.5 years (August 2007 to April 2010) at Tygerberg Children's Hospital, Cape Town, South Africa on HIV-infected children referred for neuroimaging by their infectious diseases clinicians because of suspicion of HIV-related neurologic disease (either poor head growth, long tract signs or neurodevelopmental delay).

The Children With HIV Early Antiretroviral (CHER) trial[10,11] took place in the same hospital and contributed all of the children referred for MRI. The CHER trial was a randomized 2-center study in which HIV-infected infants between 6 and 12 weeks of age and CD4 ≥ 25% were randomized to 1 of 3 strategies: ART deferred until indicated, early limited ART for 40 weeks or early limited ART for 96 weeks. Continuous ART was initiated in the deferred arm or in the early limited ART arms after interruption if the CD4% declined below 20% (25% for ART deferred in the first year of life). Other criteria for continuous ART were Centers for Disease Control (CDC) stage C or protocol-defined severe CDC stage B disease. The latter included bronchiectasis and severe lymphoid interstitial pneumonitis, nephropathy and cardiology. Additional criteria were failure to thrive not meeting CDC stage C, severe oral candidiasis, recurrent pneumonia and any condition considered severe enough for ART (with approval of the study team). A small group with CD4 ≤ 25% at baseline were recruited in parallel and also received early continuous ART on the recommendation of the study's data safety monitoring board. First-line ART was lopinavir-ritonavir, lamivudine and zidovudine. Many mothers had participated in the prevention of mother-to-child transmission program, which included zidovudine antenatally from 32 weeks and single dose nevirapine

at delivery. Mothers with CD4 count <250 cells per mm^3 received ART antenatally. Newborn infant received a single dose of nevirapine at birth and zidovudine for 7 days.

Children were in regular follow up[10,11] with clinical assessments monthly, including neurologic examination and head growth monitoring using CDC growth charts (<3 years) and World Health Organization percentile charts (>3 years). Poor head growth was defined as downward crossing of at least 2 major centiles on CDC charts and 1 centile line on World Health Organization charts. Neurodevelopmental screening assessment was performed every 6 months, and as part of a site-specific neurodevelopmental substudy, the Griffiths mental development scales (GMDS)[12] were performed at 12, 18, 30 and 42 months. GMDS quotients were obtained from raw scores or age equivalents, using the United Kingdom norms with a mean of 100 and standard deviation (SD) of 15.[12,13] Significant developmental delay was defined as >2 SDs below the mean (developmental quotient < 70).

Patients were excluded if evidence of current or previous opportunistic CNS infection; CNS neoplasm; neurologic disease caused by factors other than HIV; previous anoxic insults; persistent metabolic derangement or inadequate MRI scans (omitted sequences) were present. Post-gadolinium-enhancing lesions, such as focal, ring or solid enhancement, enhancement of the dura, meninges or cranial nerves, were excluded from the study. Baseline and clinical data were obtained from participants' medical records. Viral loads (VL) >750,000 copies/mL were assigned as 750,001 and those <400 copies/mL as 399. Mean VL at baseline from the CHER trial was calculated, and VL closest to scan was categorized as <or >400 copies/mL.

Scans were performed under general anesthesia (standard practice at our institution) on a Siemens Magnetom Symphony 1.5T. Sequences: Axial T2 spin echo, Axial FLAIR, Sagittal T1 spin echo, Sagittal T2 turbo spin echo, diffusion weighted imaging and post-gadolinium Axial T1 with a slice thickness of 5 mm. A pediatric neuroradiologist, blinded to clinical findings at time of referral, performed the MRI readings. Any nonenhancing WMSA was recorded according to anatomic regions of the brain and topographic white matter fiber involvement. Predefined criteria were used to describe the WMSA as pinpoint lesions, measurable lesions < 1 cm, measurable lesions > 1 cm or "larger" confluent lesions difficult to measure. The maximum diameter of the largest measurable lesion in each patient was determined on axial FLAIR sequences, using visual inspection to determine the slice. Diffusion-weighted imaging and apparent diffusion coefficient map were used to determine any diffusion abnormality relating to the lesions. "Lesion load" was arbitrarily determined by calculating the number of regions involved (divided into 17 zones: frontal, temporal, occipital, parietal left and right, corpus callosum, midbrain, pons, medulla, cerebellar hemispheres, cerebellar vermis, caudate, lentiform nucleus, thalamus), irrespective of the size and number of the lesions.

Quantitative cytomegalovirus (CMV) polymerase chain reaction was performed on stored plasma samples of all CHER subjects at screening in a separate substudy using the RocheCOBAS AmpliPrep/COBAS TaqMan CMV Test (Roche Molecular Diagnostics, Branchburg, NJ). CMV values ≥ 150 copies/mL were considered positive for exploring a potential relationship with WMSA.

For statistical analysis, 1-way analysis of variance (ANOVA) was conducted to compare continuous measurements between groups with and without WMSA. The χ^2 test was used to compare categorical variables (eg, gender) between the 2 groups. Spearman correlations were used to test for relationships between developmental scores and "lesion load" and also WMSA distribution. Two-way ANOVA was conducted to produce results corrected for gender. Ethics approval, N07/09/208, for the study was obtained from Stellenbosch University.

RESULTS

Forty-four HIV-infected children (22 boys) were studied. Age ranged from 8 to 54 months (mean 31.9 and SD 9.9 months). Average time between referral request and MRI scan was 2.2 months (SD 1.6 months). There were no exclusions because of image quality (motion artifact). MRI demonstrated WMSA on T2/FLAIR in 22 children, 50% of the sample. Demographic, immunologic and virologic data are shown in Table 1, which also shows comparisons in those with and without WMSA.

Prevalence and Distribution of WMSA

Sixteen children (73%) with WMSA had a combination of lesions (representative scan in Fig. 1A). Three children had only pinpoint lesions (Fig. 1B), 1 had only measureable lesions <1 cm and 2 children had confluent lesions. Lesion size ranged from 5 to 12 mm, with an average of 7.2 mm. In 12 children, the lesions were T1 isointense, 3 had T1 hypointense lesions and 7 had combinations of lesion intensity. None of the lesions demonstrated enhancement. Predominantly frontal (20; 91%; Fig. 1C) and parietal (17; 77%) distribution was noted in subcortical and deep white matter (Fig. 1D). Table 2 summarizes WMSA distribution. Other areas of involvement included the peritrigonal regions in 7 children (32 %), involving both right and left sides (unilateral in 1 child), left cerebellar hemisphere in 1 child (5%) and left lentiform nucleus in 1 child (5%). Of 22, 12 (54%) had WMSA in 4 or more zones. The maximum number of zones in a single child was 7.

Developmental Score

Assessments were performed at a mean age of 30 (range 11–48) months. Mean scores fell into the low average category with a mean general quotient (GQ) of 81.7 (range 67–101). The mean locomotor subquotient was 83 (range 50–116). The mean language subquotient was 79.7 (range 57–118). These mean scores are around 1 SD lower than previously described in HIV-uninfected children at 21 months of age, from this community[14] who had means of 95, 99.7 and 93.2, respectively, for GQ, locomotor and language. The time between GMDS and MRI ranged from 3.7 months before to 3.4 months after the scan. There was no difference between the groups (with and without WMSA) for time between scan and GMDS ($P = 0.87$) or mean age at GMDS assessment ($P = 0.46$).

Correlating Developmental Scores With Lesion Load and Distribution of WMSA

There were no differences in developmental scores in those with and without WMSA (Table 1). Lesion load also showed no correlation with developmental quotients (lesion load vs. GQ, $P = 0.99$; lesion load vs. locomotor, $P = 0.80$ and lesion load vs. language, $P = 0.50$). However, the child with the most sites involved (n = 7) also had the lowest overall GQ (67) and locomotor subquotient (50), both significantly delayed, with a language subquotient of 82, which is below average. This child, with a baseline CD4 of 13.4% and VL > 750,000 copies/mL at 9.4 weeks of age, received continuous ART. There were more boys in the group with WMSA (14 vs. 8), but no differences were found between the groups when controlling for gender on GMDS outcomes (2-way ANOVA results not shown).

Clinical Indications, Laboratory Tests and WMSA

For those with WMSA, significantly fewer (36%) had declining head growth as an indication for neuroimaging referral versus 64% without WMSA ($P = 0.01$). There was no difference

TABLE 1. Comparison Between Children With and Without WMSA

	WMSA Present (n = 22)	WMSA Absent (n = 22)	*P* Value	Effect size*
Male gender (%)	14 (64%)	8 (36%)	0.07†	Cramer's V = 0.27
Mean age at MRI (months)	32.8(9.4)	30.9(10.4)	0.53‡	0.2
Baseline (before 12 wks of age) mean (SD)				
CD4 absolute count (cells/mm^3)	1756 (778.2)	1859 (984)	0.70‡	0.12
CD4%	32.0 (11.9)	35.6 (9.6)	0.27‡	0.34
VL (copies/mL)	591931 (261,119)	571,449 (234,191)	0.79‡	0.08
Time on ART before MRI (wks) mean(SD)	115.6 (43.7)	94.4 (46.4)	0.13†‡	0.48
Mean age of ART initiation (weeks)	10	13.6		
Arms on CHER trial				
Baseline CD4 ≥ 25%	3	7	0.4	
ART-Def	7	7		
Early ART until W40	4	6		
Early ART until W96	5	2		
Early continuous ART§				
Baseline CD4 <25%				
Continuous ART	3	0	NS	
VL closest to MRI (%)				Cramer's *V* = 0.05
<400 HIV RNA (copies/mL)	48%	52%	0.86	0.04
>400 HIV RNA (copies/mL)	55%	45%	0.59¶	
Time between VL and MRI (days) mean (median)	88.5(56.5)	83.3 (50)		
CD4 count closest to MRI scan				
Absolute count (cells/mm^3)	1490 (819.6)	1441 (432.2)	0.81	0.08
CD4%	34.2 (8.1)	33.8 (9.2)	0.88	0.05
Time between CD4 and MRI (wks) mean (median)	35.1(18.5)	25.5(17.5)	0.53¶	0.18
Nadir CD4 closest to MRI				
CD4 count (cells/mm^3)	1184.3 (680.5)	1048.6(487.5)	0.45	0.23
CD4%	18.9 (6.5)	22.4(6.5)	0.08	0.55
Mean time between scan and nadir CD4 (wks)	89.0(54.4)	68.6(43.2)	0.18	0.43
CMV DNA positive at baseline‖	6 (75%)	2 (25%)	0.055	
CMV DNA negative at baseline	10 (37%)	17 (63%)		
Reason for MRI request: n (%)				
Developmental delay	19(51%)	18 (49%)	0.68	Cramer's V = 0.06
Poor head growth	10 (36%)	18 (64%)	0.01†	0.38
Increased muscle tone	5(42%)	7(58%)	0.50	0.1
Pathologic reflexes	14 (48%)	15 (52%)	0.75	0.05
Griffiths Mental Development Scales				
Age at assessment mean (SD) in months	31.0 (8.5)	29.0 (9.3)	0.46	0.23
Time between scan and GMDS in months	3.4 (3.0)	3.2 (4.2)	0.87	0.05
General quotient	83.2(7.4)	80.3(15.4)	0.44	0.25
Locomotor subquotient	81.5(11.9)	84.4(15.1)	0.49	0.22
Language subquotient	79.8(8.9)	79.5(13.1)	0.94	0.03

*Cohen's D unless otherwise specified.
†Significant *P* value.
‡F-test degrees of freedom 1,42.
§Received continuous ART although randomized to early limited ART.
¶Mann-Whitney *U* test
‖CMV ≥150 copies/mm^3; no CMV data for 6 with WMSA and 3 without WMSA
ART, combination antiretroviral therapy; ART-Def, ART deferred therapy; CMV, cytomegalovirus; NS, not significant.

in the frequency of developmental delay, increased muscle tone or pathologic tendon reflexes as a reason for referral between the children with or without WMSA.

There was no difference in baseline CD4 and VL pre-ART or CD4 and VL closest to MRI scan between the groups. Those with the lowest CD4% nadir showed a trend to more WMSA (*P* =0.08), which diminished when controlling for gender (*P* = 0.28 from 2-way ANOVA). We also noted a trend for CMV positivity and WMSA (*P* = 0.055).

Antiretroviral Therapy

Ten children in the deferred ART arm were referred for MRI. They had initiated ART at a median age 18.5 weeks because of immunologic and/or clinical decline and received ART for a median 114 weeks before the MRI. Three in this arm had WMSA.[10,11] Thirty-four children were in the early limited ART arms. They commenced early ART at a median age of 8 weeks and received ART for a median of 98 weeks. Of these, 2 children had not yet interrupted, 5 were in the ART interruption phase at time of neuroimaging and 17 had already restarted ART after a period of interruption. Ten children received early continuous ART. Seven with baseline CD4 ≥ 25% had already developed significant HIV-related disease (3 with failure to thrive and 4 with site-determined, HIV-related brain disease). The remaining 3 had a CD4% below 25% at baseline.

One child had changed to second line ART (didanosine, abacavir and nevirapine) for 6 months at 17 months of age (2 years before neuroimaging) and then changed back to first-line therapy; abacavir was added at 38 months of age (1 year before neuroimaging), because of virologic failure.

For those with a baseline CD4% ≥ 25% and initially randomized to early limited ART, there was a trend to more WMSA in those not interrupting ART compared with those who interrupted ART (*P* = 0.129, Fisher Exact 2-tail test).

There was also a trend for more WMSA with longer time on ART (in weeks) with mean (SD) 115.6 (43.7; *P* = 0.13 or *P* = 0.20

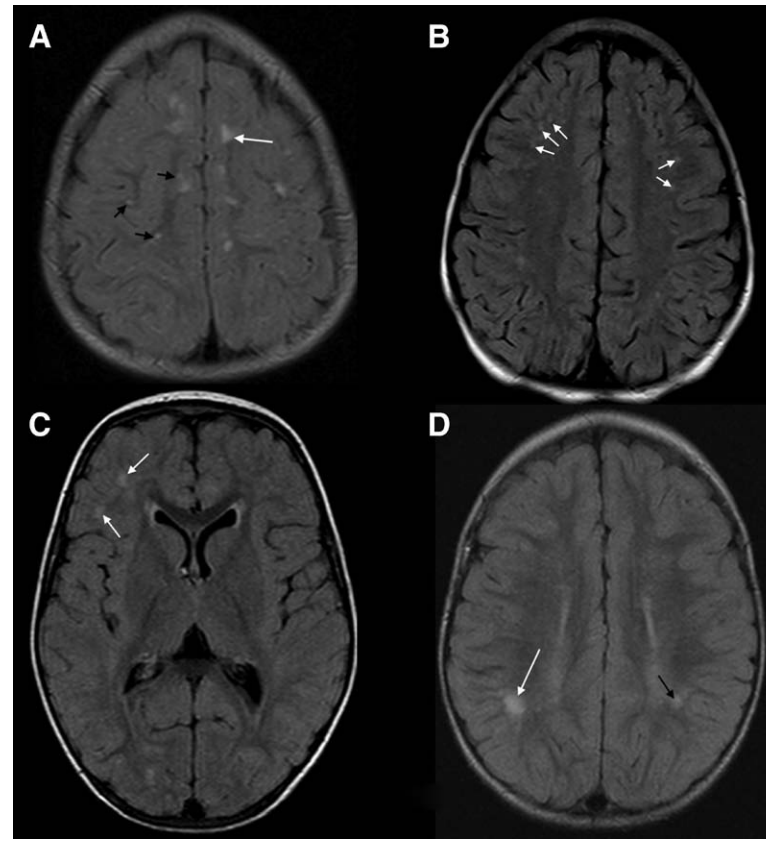

FIGURE 1. A) Axial FLAIR MRI: pinpoint white matter signal abnormality (WMSA) (black arrows) in addition to larger measurable lesions (white arrow) of various shapes and sizes all <1 cm in both of the superior frontal lobes. B) Axial FLAIR MRI: multiple bilateral pin point WMSA, involving predominantly subcortical (white arrows) and to a lesser degree deep white matter in the superior frontal lobes. C) Axial FLAIR MRI: 2 right frontal subcentimeter focal lesions. D) FLAIR MRI: bilateral parietal WMSA, on the right >1 cm (white arrow) and on the left >1 cm (black arrow) extending from the subcortical to the deep white matter.

after controlling for gender).There was no statistical difference when controlling for age and time on ART between the 2 groups. Of the 26 children randomized to early limited ART, 12 had WMSA and 14 did not.

DISCUSSION

Imaging findings in children with HIV in the pre- and post-ART eras include atrophy,[1,15] calcification[16] and more recently, WMSA.[17] We have described, for the first time, the distribution and characteristics of WMSA in children who received early ART in infancy. Fifty percent of those referred for MRI because of concern of HIV-related brain disease had WMSA on T2/FLAIR MRI. Lesions occurred most commonly in superficial and deep white matter and predominantly in the frontal and parietal lobes. Most importantly, WMSA was present in children with both early limited, early continuous and deferred ART. There was no correlation between the distribution of WMSA or the lesion load with immunologic or developmental scores.

There was a surprising association between WMSA and normal head growth ($P = 0.01$), rather than acquired microcephaly. However, there was no association with either developmental delay or increased tone and tendon reflexes. These observations require further investigation in a larger cohort. A possible explanation may be that early ART is neuroprotective and that imaging findings in these children represent arrested brain disease but with ongoing inflammation or low-level viral replication. Unfortunately, head circumference-for-age Z-scores, which may have increased our ability to interpret this finding, were not documented over time.

The lack of correlation of WMSA and GMDS scores is possibly because of early identification of suspected HIV-related brain disease by performing the GMDS regularly in all children. Some GMDS scores were in the normal range, as other criteria for neurologic compromise were met (poor head growth and acquired symmetric motor deficits). It may also be that the GMDS has insufficient sensitivity to assess the more subtle effects corresponding to WMSA based on T2/FLAIR, and the children were too young for more detailed neuropsychologic assessments to assess specific domains of functioning. Stability of the GMDS over time is also not clear in South African children, since it was standardized in the United Kingdom[12,13] with varying reports of performance on the

TABLE 2. Distribution of WMSA in Children With HIV-related Brain Disease by Number of Patients With at least 1 Lesion in the Listed Location (Note That Some Patients Had More Than 1 Site Involved)

Location	Cumulative Number of Patients	Right		Left	
		Superficial	Deep	Superficial	Deep
Frontal	20 (91%)	18 (82%)	5 (23%)	17 (77%)	7 (32%)
Parietal	17 (77%)	11 (50%)	9 (41%)	12 (55%)	8 (36%)
Temporal	1 (5%)	1 (5%)	0	1 (5%)	0
Occipital	3 (14 %)	3 (14 %)	0	1 (5%)	0

GMDS in South Africa.[18–22] We did not collect data on socioeconomic status, but these children are all from similar background low-socioeconomic communities.

There was a trend towards presence of WMSA and time on ART, with longer time on treatment associated with increased WMSA ($P = 0.13$). The association is of unclear significance (power = 34%) and requires further study in larger groups as WMSA could either represent more severe disease or cumulative ART toxicity, specifically as all guidelines recommend early continuous ART in all HIV-infected infants.[23] Also, a trend towards more WMSA in those who, although randomized to early limited ART remained on continuous ART, suggests more severe HIV disease. No children were on efavirenz, which may be neurotoxic in adults.[24] There was also no correlation between WMSA and different treatment arms on the CHER trial; however, this is a relatively small descriptive study of clinical referrals and conclusions cannot be drawn from these small numbers.

There was no correlation between WMSA and VLs, CD4 counts or CD4% closest to the time of scan. However, the time between the scans and these parameters ranged from 0 to 12 months, because it was not part of the research design to obtain these at the time of scan. There was a trend showing a negative association with nadir CD4%. In adults, nadir CD4 levels correspond to episodes of severely impaired immune function, which place the brain at greatest risk of HIV involvement.[25] The WMSA in our patients may represent damage from HIV during exposure to high VLs before ART, or other pathogens may have accessed the brain. Focal white matter lesions without enhancement or mass effect have increased in HIV-infected children between 1991 and 1998, etiologies including viral encephalitis, focal HIV-encephalopathy and progressive multifocal leukoencephalopathy.[15] The latter was a problem in the pre-ART era resulting in WMSA, possibly because of delayed initiation of ART and using medications with lower CNS penetration. Differential diagnoses to consider with WMSA include maternal recreational drug exposure, intrauterine CNS infections such as toxoplasmosis, CMV and cerebral malformations with cortical dysplasia.[5] Infants coinfected with CMV and HIV have a higher rate of progression to symptomatic stages of AIDS as well as higher incidence of encephalopathy.[5,6] Although we showed a possible link between CMV at 6 weeks of age, data were missing for 6 children with and 3 without WMSA. Also, we could not distinguish congenital from acquired CMV infection. The lack of control subjects is a limitation of our study; however, WMSA in children >1.5 years of age is abnormal.[26]

Changes occurring in the CNS in the earlier stages of HIV-1 infection remain poorly understood and the evidence is conflicting. Progressive encephalopathy can be associated with normal imaging studies,[1] and there may even be abnormalities on CT scan in asymptomatic children.[1]

HIV leukoencephalopathy, visualized as WMSA on MRI, is a triad of diffuse myelin loss, astroglial proliferation and infiltration by mono- and multinucleated macrophages.[8,27] The myelin pallor is diffuse, involves deep white matter and spares superficial (subcortical) white matter and corpus callosum,[27] in contrast to progressive multifocal leukoencephalopathy which tends to involve subcortical and periventricular white matter, corpus callosum, internal and external capsules and the myelinated fibres of the deep grey nuclei.[28,29] Our imaging findings suggest that superficial white matter is not spared as WMSA involving the subcortical white matter was noted in many children in our series. It may be difficult to distinguish from other causes of WMSA such as prenatal/perinatal injury,[5] especially in the peritrigonal area, which is susceptible to global hypoxic insults and is also a terminal zone of maturation.[30] However, only 7 (16%) of our patients showed pathologic asymmetric WMSA in the peritrigonal region, with birth asphyxia having been excluded in our study.

Documenting WMSA is important in the clinical management of HIV-infected adults as it provides supporting evidence for HIV-1–associated cognitive motor complex,[7] correlates with clinical improvement following ART[7] and suggests that disease regression in patients with AIDS dementia complex on ART can be characterized and monitored by MRI.[8] Currently, neurodevelopmental testing is performed routinely in HIV-infected children to assess cognitive function and effectiveness of ART in the CNS. By the time cognitive deficits are detected; however, significant brain injury may already have occurred[31] as shown in the Pediatric Randomized Early versus Deferred Initiation in Cambodia and Thailand trial. Here, children between 1 and 12 years of age were randomized to early or deferred ART, performed worse than HIV-uninfected control children on intelligence quotient, Beery Visual Motor Integration, Binet memory and Child Behavioral Checklist.[32]

The usage of detecting WMSA in children requires prospective study. Qualitative MRI analysis of early white matter changes in HIV-encephalopathy can be difficult.[7] Alternative quantitative imaging (eg, MRI spectroscopy and relaxometry) can detect encephalopathy, disease progression or improvement on treatment.[33] Diffusion tensor imaging provides quantitative information on the integrity of white matter tracts and correlates with cognitive impairment in adults.[34] In children, this offers new challenges relating to immaturity of myelination, which may affect measurable fractional anisotropy and because these studies are time consuming. Our limited MRI resources at the time curtailed our capacity to perform these advanced sequences, but are included in our continuing work.

CONCLUSION

Our results demonstrate that half of the children referred for suspected HIV-related neurologic problems have WMSA on T2/FLAIR, involving mainly the frontal and parietal lobes, superficially and in the deep white matter. The lesion load and distribution did not correlate with the developmental scores or viral load. We suspect that WMSA can occur early and that initiating ART by 7–8 weeks of life may already be too late to prevent HIV from entering the CNS.

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