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Perinatally HIV-Infected Youth Presenting with Acute Stroke: Progression/Evolution of Ischemic Disease on Neuroimaging

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Abstract

Background and Purpose—Although HIV infection is decreasing in infants and children, there is a steady cohort of perinatally HIV-infected (PHIV) children that are growing older. Increased risk of acute stroke has been reported in PHIV children. Our goal was to evaluate evolution/progression of neuroimaging findings in PHIV youth initially presenting with acute stroke.

Materials and Methods—The medical records of PHIV pediatric patients (n=179) from 1996 to 2010 were reviewed and patients with clinical documentation of acute stroke referred to the neuroradiology service were eligible for the study. Neuroimaging (brain CT, MRI, and MRA) and charts were evaluated; clinical and neuroimaging findings at the initial acute stroke and at the last presentation to the neuroradiology service were documented and analyzed.

Results—Eight PHIV patients with clinical findings of acute stroke referred to the neuroimaging were identified. CT and MRI findings of infarction were found in all (8/8) patients in their first and/or last neuroimaging study; including basal ganglia-thalami (BGT) infarction (7/8), focal cortical infarction (4/8), and internal capsule infarction (4/8). Imaging depicted cortical atrophy (5/8), BGT calcification (3/8), and posterior reversible encephalopathy syndrome, wallerian degeneration, and periventricular white matter hyperintense T2 signal each in one patient. No tumors or infectious masses, cysts or abscesses were identified. Subsequent available neuroimaging revealed progression of the cerebrovascular disease in 7 patients, 5/7 in the absence of new clinical signs or symptoms. Segmental occlusion, narrowing or narrowing/dilatation in the circle of Willis was found in 6/6 patients who underwent MR angiography and fusiform aneurysms were detected in three of them, a saccular aneurysm in one patient.

Conclusion—Asymptomatic progression of cerebrovascular disease was found in PHIV adolescents with prior stroke. These findings may have implications for long term risk and outcomes for this patient population. There should be a low threshold to evaluate for CNS pathology even with minor symptoms in this population. More studies are necessary to determine if there is a benefit from screening of asymptomatic patients.

Keywords

HIV; AIDS; Stroke; Cerebrovascular accident; Imaging; Perinatal

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Introduction

While human immunodeficiency virus (HIV) infection in infants and children is decreasing due to the advances in diagnosis of HIV infection in women of childbearing age and implementation of highly active antiretroviral therapy (HAART) for the prevention of maternal to child transmission [1], there is a steady cohort of HIV-infected children that are growing older [2].

Studies of diagnostic imaging, specifically CT and MRI, have demonstrated diffuse cerebral atrophy as the most prevalent finding affecting 90% of HIV-infected pediatric patients and basal ganglia-thalami (BGT) calcification affecting one-third of HIV-infected children [3]. However, HIV does have a direct effect on the vasculature, with studies demonstrating accelerated atherosclerosis and vasculopathy in infected patients [4,5]. Additionally, HAART, which is known to impact metabolic profiles, resulting in dyslipidemia, fat redistribution, and insulin resistance, may predispose to accelerated atherosclerosis and cerebrovascular attack (CVA) [6]. Autopsy findings have revealed CVAs in 25% of pediatric HIV-infected cases of whom the majority were asymptomatic through their lives with just 1.3–2.6% reported to have symptomatic CVAs [7–11].

With age, the interaction of longstanding infection, unchecked viral replication, antiretroviral therapy, and opportunistic infections, particularly in the setting of the developing brain, may lead to unique clinical presentations and radiographic findings in adolescents and young adults with perinatal HIV infection and may have implications for long term risks and outcomes. Studies that have previously examined neuroradiologic manifestations have focused on either pediatric or adult patients, mostly in the pre-HAART era [2, 3]. No studies have examined the perinatally-infected adolescent and young adult. Additionally, most studies have been cross-sectional, without longitudinal assessment of the evolution of clinical and neuroradiologic findings. In this case series our goals were to describe neuroimaging and clinical findings of perinatally HIV-infected (PHIV) patients who presented with acute stroke and to assess the evolution of neuroimaging findings in the available follow up interval.

Subjects and Methods

This was a retrospective, longitudinal study. The medical records of all PHIV patients (n=179) followed at the Johns Hopkins Hospital between 1996 and 2010 were reviewed. Patients with clinical documentation of acute stroke referred to the neuroradiology service were eligible for the study. Neuroimaging at initial acute stroke and at last follow-up visit (CT, MRI, and MRA) and charts of these patients, including demographic information, presenting symptoms, clinical diagnosis, medications, co-morbidities, laboratory findings, and outcome were evaluated. All patients were reviewed with respect to serial radiologic imaging, clinical data, treatment, and functional outcome. This study was approved by the Johns Hopkins Institutional Review Board.

Imaging

Images were obtained for clinical purposes and therefore various imaging modalities were utilized. CT scans of the head were obtained without contrast material and MR Imaging of the brain was performed by using standard brain sequences including DWI and ADC map, post-contrast axial and coronal T1 weighted images. Various CT and MR scanners (1–3 Tesla) in the department of radiology were utilized. T1-weighted MR images were obtained using TR range/TE range, 400–600/8–14, and T2-weighted MR images were obtained using 2000–4000/80–104 with spin-echo pulse sequences. MRA was performed in six patients utilizing time-of-flight technique. Two patients also underwent conventional cerebral

angiography. All CT and MR imaging studies were interpreted retrospectively by an experienced neuroradiologist (I.I.) on a picture archiving and communication system (PACS) workstation (Ultravisual, Emageon, AL, USA). On CT and MRI scans cortical atrophy, acute or chronic infarcts, BGT calcifications on CT, periventricular white matter T2 hyperintensity on MRI (a common finding in adults with HIV encephalitis) were documented for each patient. Other findings such as a mass, abscess, cyst or abnormal contrast enhancement on MRI were also documented when present. Cerebral lesions were classified as infarctions if they met the imaging criteria on CT or MR imaging: On CT, focal effacement of the sulci, loss of gray-white matter differentiation or hypoattenuation; on MRI restricted diffusion on DWI-ADC map, T1 hypointense, T2/FLAIR hyperintense signal of varying sizes were the imaging criteria of infarct. On MRA images vascular narrowing, dilatation, or occlusion, segmental narrowing/dilatation, aneurysms were documented. Cerebral aneurysms, when present, were characterized either as fusiform or saccular. The diagnosis of fusiform aneurysms was made if the lumen of an artery was found to be abnormally dilated at a focal segment in comparison with a comparable artery of the opposite hemisphere. Saccular aneurysms were diagnosed by the characteristic focal arterial dilatation connected to the wall of the parent vessel by a neck.

Results

Clinical and Demographic Findings

Eight (3 female, 5 male) PHIV patients with clinical and radiological findings of acute CVA (4.5% of the clinic cohort) were identified. Mean age, CD4 count, and viral load was 18.5±0.71 years, 96±136 mm^3, 19770±27959 copies/mL at the first neurologic event and 23±2.83 years, 373±528 mm^3, 16189±22895 copies/mL at the final follow-up, respectively (Table 1). Total follow-up duration was 4.5±3.5 years. While 75% of patients (6/8) had no recurrence of CVA symptoms, 2 of the 8 patients (25%) subsequently presented with CVA symptoms during the follow-up period. Five patients (62.5%) died during the course of follow-up, 3 from end-stage HIV disease, 1 from gunshot, and 1 from unknown causes, while he was doing well from an HIV standpoint.

Varicella zoster virus (VZV)

At the time of their acute events, 5 patients had specific cerebrospinal fluid testing for VZV (polymerase chain reaction) of which 2 were positive and 3 were negative. The two patients were treated appropriately with antivirals. The other 3 patients were not tested for VZV at the time of their presentation; notably 2/3 of them had had a history of +VZV (one from skin lesion, other from CSF) several years before their presentation; a common finding in end-stage HIV.

Imaging Findings

Acute, subacute or chronic infarctions were found in all (8/8) patients in the first and/or last neuroimaging; including BGT infarctions in 7/8 (87.5%, Fig. 1), focal cortical infarctions in 4/8 (50%, Fig. 2–4), and internal capsule infarction in 4/8 (50%) patients. Segmental narrowing or segmental narrowing and dilatation of the proximal circle of Willis arteries were found in all patients for whom MRA was performed (6/6 [100%]) (Fig. 3C and D, Fig. 5A and B) and fusiform aneurysms were detected in 3/6 (Fig. 2C, 2D, Fig. 4D), one saccular aneurysm (Fig. 4H) was detected in one patient. Cerebral angiograms in 2 patients showed the segmental narrowing or segmental narrowing/dilatation in the proximal circle of Willis arteries as well as distal branches (Fig. 6). Imaging depicted cortical atrophy in 5/8 patients, BGT calcifications in 3/8 (Fig. 4A and 4E), cerebellar atrophy in 2/8; posterior reversible encephalopathy syndrome (PRES), wallerian degeneration secondary to the initial cortical

infarcts (Fig. 3A and B), and periventricular white matter hyperintense T2 signal in one patient.

Neuroimaging revealed progression of the cerebrovascular ischemic lesions during the follow-up period in all patients with available follow-ups (7/7) (Table 2) (Fig. 4 and 5). There was no further radiographic follow-up in one patient due to sudden death after gunshot.

Discussion

In this case series of 8 PHIV patients presenting with acute stroke with corresponding neuroradiologic findings, the most common lesions were segmental narrowing and dilatation of major cerebral arteries (6/6 with MRA), BGT infarction (7/8), and cortical atrophy (5/8). While only 2 out of 7 patients developed subsequent CVA symptoms, all had progression of neuroradiographic findings on follow up imaging.

Since the introduction of HAART in 1996, HIV has become a chronic, manageable disease with marked reduction in morbidity and mortality [2]. Consequently, there is an aging cohort of infected children that are now adolescents and young adults who have been living with HIV infection and are now developing the sequelae of long-term infection. This cohort, who did not succumb to early manifestations of disease, including encephalopathy and opportunistic infections during the first years of life, has been exposed to years of treatment including serial mono- and dual antiretroviral therapy, followed by suboptimal and often unpalatable antiretroviral combinations that have resulted in nonadherence and multi-drug resistant virus that is challenging to treat. Longstanding HIV infection, particularly when not adequately treated, leads to unchecked viral replication, immunologic deterioration, and resultant inflammation in the body and specifically in the vasculature, places individuals at risk for sequelae including malignancy, atherosclerosis, and specifically for this report, central nervous system (CNS) pathology [12, 13].

It is well known that HIV traverses the blood-brain barrier as virus has been detected in the cerebrospinal fluid and brain parenchyma on brain biopsy [14]. Additionally, it has been postulated that the brain constitutes a compartment where antiretroviral therapy may penetrate at suboptimal levels resulting in discordant viral load levels in the CSF as compared to the plasma [15]. While elevated plasma viral load correlates with elevated CSF levels, even in the setting virologic suppression in the plasma due to HAART, the brain may continue to be impacted by suboptimal virologic control in the CSF. HIV infection has been associated with endothelial dysfunction potentially through increased expression of adhesion molecules (e.g., intercellular adhesion molecule (ICAM-1)) and inflammatory cytokines (e.g., tumor necrosis factor (TNF-alpha)), with resultant endothelial injury and vascular disease [16]. It has therefore been theorized that stroke after the initiation of HAART in HIV infected patients is related to the reactivation of immune system and attack against the infected endothelium [17, 18].

Various patterns of vasculopathy have been mentioned in infected infants as the early imaging findings using different imaging modalities [19]. Cranial US may show echogenic stripes in the area of the lenticulostriate vessels [20]. Matching with US, this is the area that has been reported to have calcifying microangiopathy on CT scan [21]. MRA is the most sensitive non-invasive imaging modality to demonstrate intracranial vasculopathy without requiring interventional catheterization and contrast injection. MRA clearly demonstrated narrowing or occlusion, segmental narrowing/dilatation and fusiform/saccular aneurysms in the large and medium sized arteries in all of our cases that MRA was performed. Cerebral angiography in 2 cases additionally showed segmental narrowing/dilatation in the distal

smaller branches of cerebral arteries. Concomitantly MRI of the brain produces superb contrast and temporal resolution to identifying other abnormalities associated with HIV vasculopathy such as acute or chronic infarctions as well as cerebral atrophy, periventricular white matter signal changes due to HIV encephalitis, opportunistic infections and tumors. Interestingly we have seen periventricular white matter hyperintensity on T2-weighted images only in one patient which is one of the most common MRI findings in HIV infected adults.

Both primary VZV infection and secondary reactivation of VZV are well associated with stroke in children and adults [22]. The interaction of the endothelial effects of HIV and VZV may be additive. Particularly with end-stage HIV, VZV reactivation may be more common. Gutierrez J. et al. [23] reported in their case review of 9 patients (7 adults, 2 adolescents); HIV infected patients with VZV tend to present with deep, subcortical ischemic stroke and vasculopathy affecting large and small arteries while HIV patients without VZV predominantly present with large size artery fusiform dilatation and large cortical stroke. In our case series, two patients had VZV detected from CSF during their acute presentation and 2 patients had prior history of VZV positivity, however, all of our patients had multiple small infarcts particularly in deep gray and/or white matter regardless of their VZV status. Larger studies are needed to test whether VZV positivity changes the pattern of strokes or vasculopathy in AIDS patients. We think that coexistent VZV vasculitis with HIV vasculopathy is a possibility in 2 of our patients [22, 23].

Given that the majority (7/8) of our patients presented during their adolescence, our results suggest that the first clinical presentation of CVA in perinatally-infected patients tend to happen during adolescence implying that it may take a period of time for the accumulation of inflammation and damage in the vessel wall. Also, the majority of strokes happen in the setting of advanced HIV infection in patients who are non-compliant on their drug therapy or have just recently started HAART regimen (i.e., immune reconstitution inflammatory syndrome (IRIS)). This may suggest that virologic control resulting in the control of inflammation may minimize the risk of cerebrovascular events. Therefore, even though there may be virologic escape in certain compartments (e.g., CNS), which was not measured in these patients, low plasma viral load is more likely to correlate with low CNS viral loads [24, 25].

It is of concern that even without clinical manifestations, 100% of those with subsequent imaging had progression of radiographic features of cerebrovascular disease which has the potential for long term implications on cognitive and physical functioning. It is important to understand factors that may promote (e.g., uncontrolled viral replication, smoking) and retard (e.g., anti-platelet agents) the development and progression of CNS lesions as there may be a role for the study and targeted use of agents [e.g., non-nucleoside reverse-transcriptase inhibitors (NNRTIs), anti-platelet agents] and behavioral modifications (e.g., smoking cessation) to impact progression of lesions in this population [26]. To our knowledge this is the first study in the literature documenting longitudinal neuroimaging changes in a small cohort of PHIV population and there is limited experience with this respect.

There are several study limitations that should be considered in interpreting our findings. This is a small retrospective case study with a convenience sample. Findings of our series may not be generalizable to all HIV-infected patients or HIV clinics. There may be an underestimation of the reported rates of radiographic CNS manifestations as not all of the patients in the PHIV clinic have undergone neuroimaging.

Conclusion

As PHIV children are experiencing increased survival due to advances in care, including opportunistic infection prophylaxis and HAART, an aging cohort of adolescents and young adults are at risk for the long term sequelae of prolonged HIV, opportunistic infections, and antiretroviral therapy. The CNS manifestations that we report and particularly the asymptomatic progression of the lesions are noteworthy as they may have implications for long term risk of deleterious outcomes such as cognitive and physical deficits and CNS catastrophes (i.e., strokes, seizures) for PHIV patients. While it is unclear if screening would be beneficial for asymptomatic children, there should be a low threshold to evaluate for CNS pathology even with minor symptoms in this population. Longitudinal cohort studies are essential to defining the prevalence and associated risk factors for development and progression of lesions as well as assessing the outcomes. Additionally, studies examining treatment modalities that may alter the progression of CNS lesions may be particularly relevant for this population.

Acknowledgments

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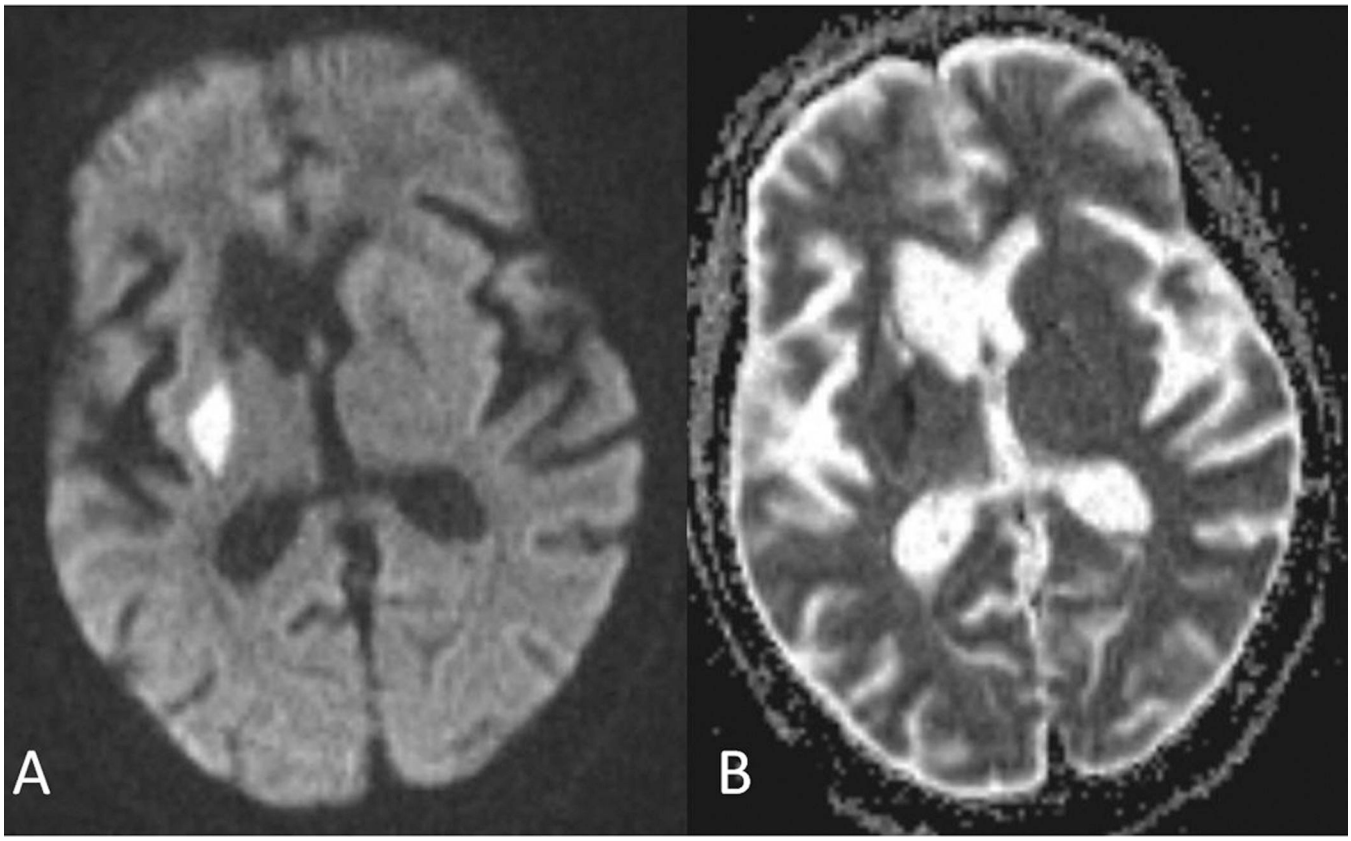

Fig. 1.
Patient #8. DWI (A) and ADC map (B) show an acute infarct in the right basal ganglia with restricted diffusion. There is also an old infarct in the right caudate head with volume loss, increased diffusion and ex-vacuo dilatation of the right frontal horn.

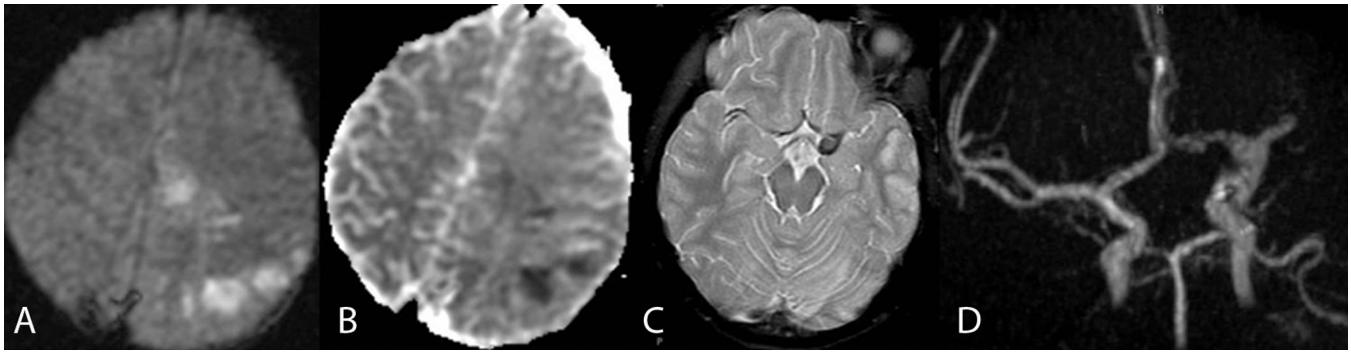

Fig. 2.

Patient #3. Small focal areas of restricted diffusion consistent with acute infarcts are noted in the left frontoparietal region on DWI and ADC map (A and B) due to left MCA occlusion. On T2-weighted axial image at a lower level (C) left temporal lobe cortical swelling and hyperintense signal are seen. The hypointense fusiform structure in the left slyvian fissure in (C) correlates to an aneurysm at left ICA terminus on MRA image (D).

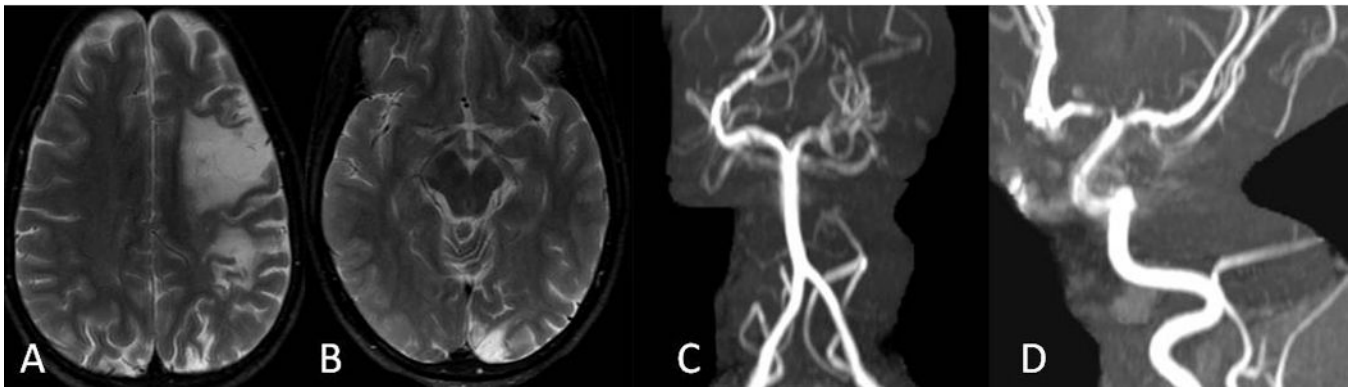

Fig. 3.

Patient #2. T2-weighted axial image shows left frontal and frontoparietal chronic infarcts (A) which resulted in wallerian degeneration in the left cerebral peduncle (B). An old infarct in the left occipital lobe is also shown on image B. MRA shows significant narrowing of the left PCA (C) and focal stenosis in the left A1 segment and inferior M2 segment (D).

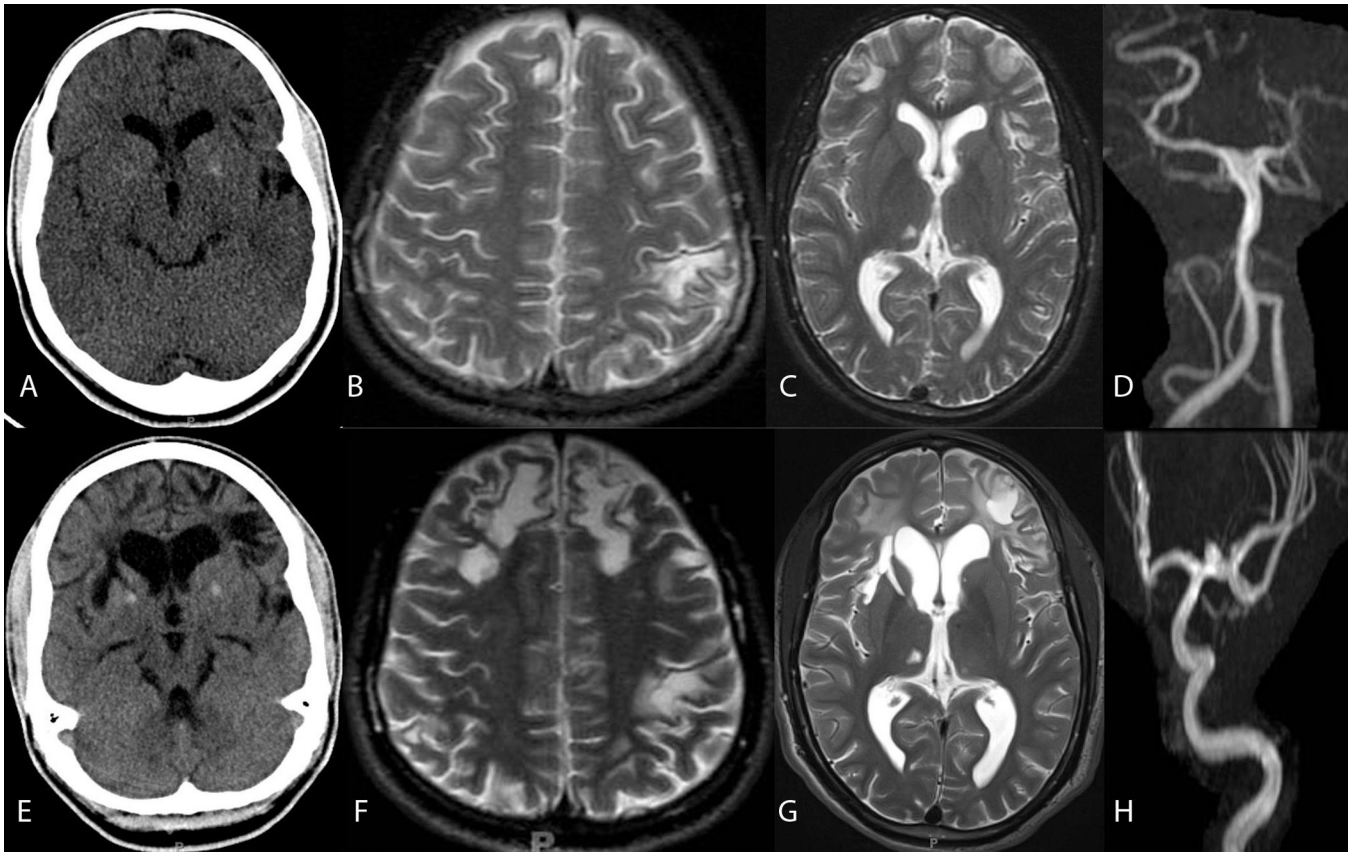

Fig. 4.

Patient #4.The first row shows representative CT and MRI findings at the first presentation. The second row shows same patient's CT and MR images at similar levels after 6 years. Note the increase in basal ganglia calcifications, increased number of focal infarcts and increase in cerebral volume loss.

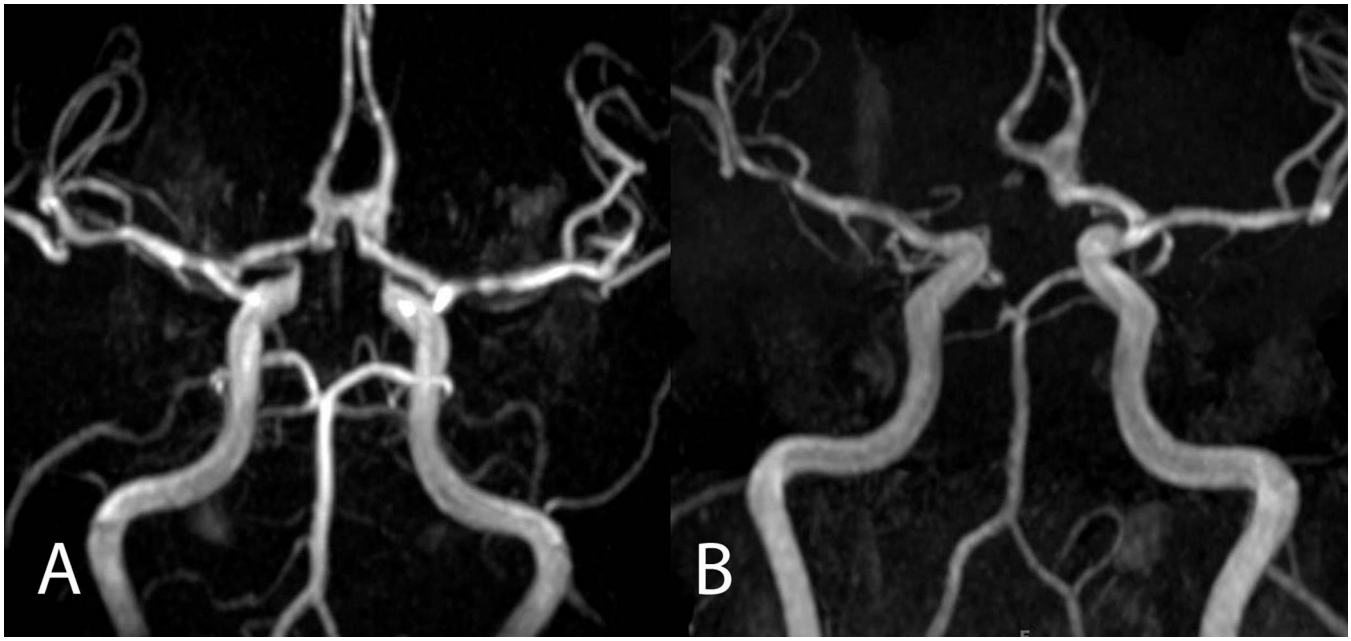

Fig. 5.
Patient #1. MRA MIP images show segmental narrowing and dilatation of bilateral MCA and ACA as well as multiple fusiform aneurysms at ACOM, and at bilateral A1 segments (A). Six years later right A1 is occluded or severely stenosed and fusiform aneurysm in the right A1 is not visualized. The remainder of the findings is stable (B).

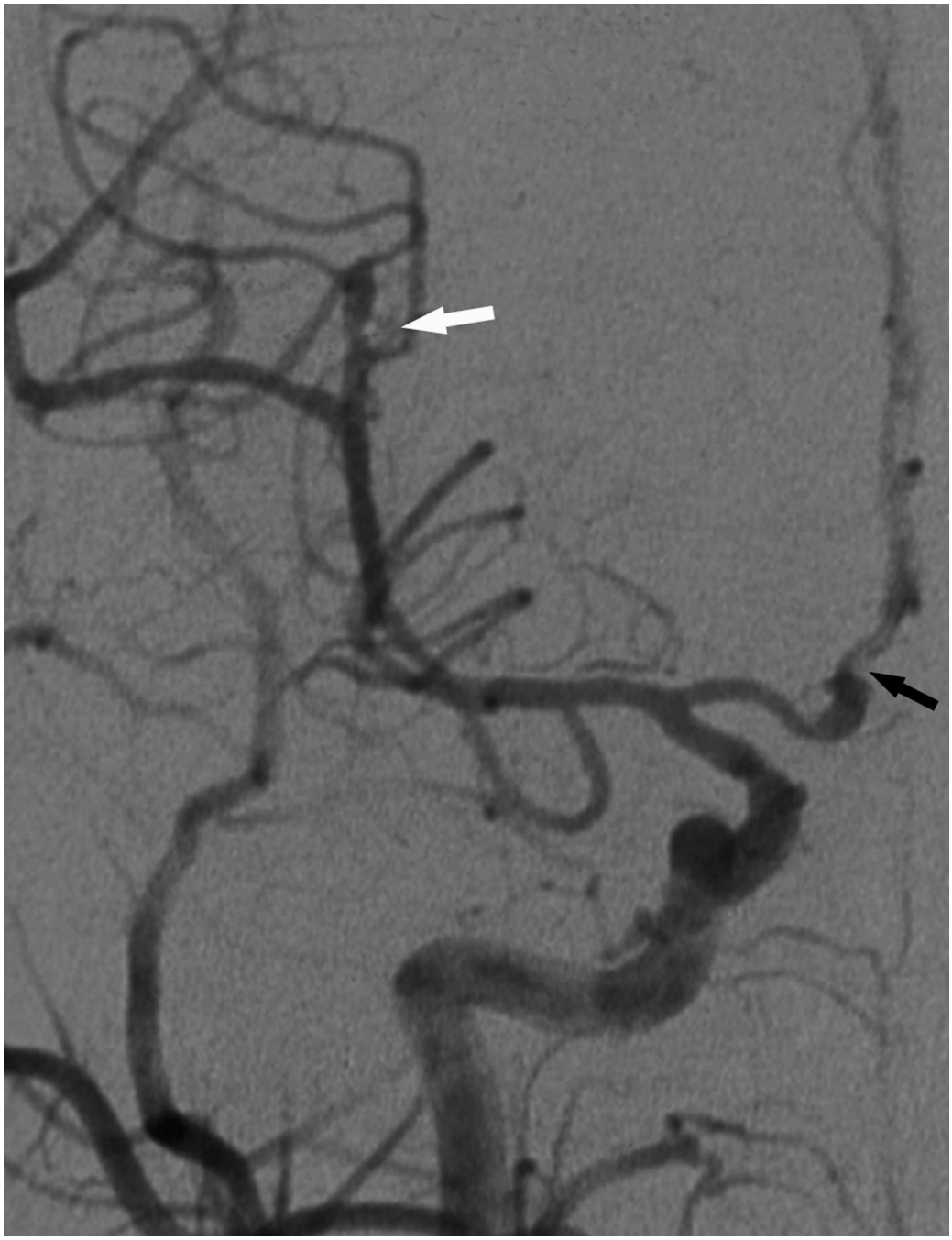

Fig. 6.
Patient #1. Cerebral angiogram (performed at the same time when first MRA was performed in Fig. 5 A). Right ICA injection shows fusiform aneurysm at right A1-A2 junction and focal narrowing in the immediate right A2 (black arrow). Additionally CA shows focal narrowing and fusiform dilatation in the right MCA superior M2 segment (white arrow).

Table 1

Clinical and demographic findings of patients with PHIV infection presented with acute stroke.

Variables	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Gender (M/F)	M	M	M	M	F	M	F	F
Age[1] (year)	18	17	17	15	15	9	16	19
Follow-up duration (year)	7	5	0	6	3	3	5	2
Neuroimaging performed	CT, MRI, MRA, CA	CT, MRI, MRA	CT, MRI, MRA	CT, MRI, MRA, CA	MRI	MRI	MRI, MRA	CT, MRI, MRA
HAART start age (year)	17	16	17	14	9	12	21	21
CD4 count[1]	204	18	13	7	15	1	184	12
CD4 count[2]	750	454	---	500	1	2	8	4
Viral load[1]	50	25239	31077	69209	503945	750000	19089	39590
Viral load[2]	50	50	---	50	5683	750000	50	32429
Neurologic exam at the first presentation	Mild Lt face, leg, and arm weakness, dysarthria, transient loss of vision	Rt facial, Lt upper and lower extremity weakness, dysarthria	Rt sided hemiparesis, facial droop	Rt arm and leg weakness Transient imbalance	History of acute transverse myelitis and present with seizures	Memory loss, confusion, dysarthria, stumbling gait; muscle weakness in hands, thighs, and hips	Headache, transient imbalance and dysarthria	Tonic-clonic seizure
Reason for last imaging	Jaw abscess	Lower extremity weakness	Stroke	Rt hand choreoathetosis	Follow-up	Decreased responsiveness	Headache, eye pain, confusion	Le sided weakness
Neurologic exam at the last presentation	Lt hemiparesis, dysarthria (residual)	Rt sided residual weakness	Rt sided hemiparesis	Rt hand choreoform movements	Stable paraplegia (no new symptoms)	Decreased mental status, dementia	Confusion, blurry vision, photophobia	Lt facial, upper and lower extremities weakness, brisk bilateral reflexes
Co-morbidities	Htn.	Htn, Hepatitis C, Low platelet	Mild hyperhomocysteinemia	Low platelet	VZV, Asthma, Disseminated MAC	ARF, TTP	VZV, Disseminated MAC	Disseminated MAC
Outcome	Alive	Alive	Died at age 20 due to gunshot	Died at age 23 due to unknown cause	Died at age 18 due to end-stage HIV disease	Died at age 12 due to end-stage HIV disease	Alive	Died at age 21 due to End-stage HIV disease

[1] at the first presentation,

[2] at the last presentation.

M = Male, F = Female, Rt = Right, Lt = Left, Htn = Hypertension, TTP = Thrombotic Thrombocytopenic Purpura, MAC = Mycobacterium Avium Complex, ARF = Acute Renal Failure.

Table 2

Radiographic findings at the first presentation and at the follow-up.

Pt	First Imaging		Follow-up Imaging	
	Age (year)	Modality: Findings	Age (year)	Modality: Interval New Findings
1	18	**CT:** Rt. BGT acute infarction. **MRI:** Rt. BGT acute infarction. **MRA:** Bilateral mild proximal MCA narrowing, bilateral A1-A2-ACA junction fusiform aneurysms, left larger than right side. **CA:** Same findings as MRA; additionally segmental narrowing/dilatation in distal segments	25	**MRI:** Left BGT chronic infarction. **MRA:** Occlusion of right A1, occlusion of right P1 but widely patent PCOM feeding right PCA. **CA:** Occlusion of right A1 and right P1 and large PCOM feeding right PCA.
2	17	**CT:** Lt. frontal & BGT chronic infarction. **MRI:** Lt. frontal & BGT chronic infarction. **MRA:** Lt. ICA terminus, Lt. A1, Lt. M1 and M2 segmental narrowing and dilatation, Lt. ICA terminus fusiform aneurysm.	23	**CT:** Lt. occipital chronic infarction. **MRI:** Lt occipital chronic infarction, Lt. wallerian degeneration. **MRA:** Increased narrowing at Lt. A1, Lt. M2 proximal segments, lt. PCA proximal narrowing with distal segmental narrowing and dilatation.
3	17	**CT:** Lt. MCA territory acute infarction **MRA:** Lt. MCA occlusion, Lt. ICA terminus fusiform aneurysm, Rt. PCA narrowing.	17	No follow-up available.
4	15	**CT:** Small bilateral BGT calcifications, Mild diffuse cortical atrophy. **MRI:** Lt. pontine & occipital acute infarction, old bilateral frontal, Rt. thalamic, Lt parietal focal hemorrhagic infarcts. **MRA:** Lt. M1 saccular aneurysm, Lt. trifurcation fusiform aneurysm, distal basilar artery fusiform aneurysm, Lt. PCA narrowing. **CA:** Similar findings as MRA; additionally segmental/narrowing dilatation in distal segments	21	**CT:** Increased number of focal chronic infarcts, slightly increased bilateral basal ganglia calcifications, increased diffuse cortical atrophy. **MRI:** Interval bilateral frontal, Rt. caudate head, deep frontal/ anterior limb of the internal capsule chronic focal hemorrhagic infarcts. **MRA:** New Lt. A1 segmental narrowing and dilatation, basilar artery new segmental narrowing and dilatation.
5	15*	**CT:** Mild cortical atrophy. **MRI:** Mild cortical atrophy.	18	**MRI:** Advanced cortical atrophy, bilateral focal cortical, Lt. PLIC, Rt. thalamus, Lt. parieto-occipital infarctions, meningeal contrast enhancement suggestive of infectious meningitis.
6	9*	**MRI:** Mild cortical atrophy.	12	**CT:** Basal ganglia calcifications **MRI:** Progression of cortical atrophy, bilateral caudate and putamen infarctions and basal ganglia T1 hyperintensity possibly related to calcifications.
7	16	**MRI:** Mild cortical atrophy, mild PVWM hyperintense T2 signal.	21	**MRI:** Advanced cortical atrophy, interval mild cerebellar atrophy. Rt. internal capsule punctate acute infarction, Lt. thalamic chronic infarction. **MRA:** Subtle bilateral A2 segmental narrowing and dilatation.
8	19	**CT:** Mild cortical atrophy, minimal bilateral BGT calcifications. **MRI:** Mild cortical atrophy, PRES.	21	**CT:** Rt. caudate nucleus chronic infarction, advanced cortical atrophy. **MRI:** Rt. caudate nucleus chronic infarction, Rt. corona radiata acute infarction, advanced cortical atrophy and interval mild cerebellar atrophy. **MRA:** Mild segmental narrowing and dilatation of bilateral MCA, ACA, PCA and major branches, Lt. ICA petrous segment mild fusiform dilatation.

*Findings from reports, images were not available.

M = Male, F = Female, Rt = Right, Lt = Left, Pt = Patient number, PCA = Posterior Cerebral Artery, ACA = Anterior Cerebral Artery, MCA = Middle Cerebral Artery, ICA = Internal Carotid Artery, PVWM = Periventricular White Matter, PLIC = Posterior Limb of the Internal Capsule PRES; posterior reversible encephalopathy syndrome, CA = Cerebral Angiogram