Original Article

Clinical and Imaging Clues of Arteriopathy-Related Pediatric Arterial Ischemic Stroke: A Single Center Experience

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Abstract

Background and Purpose: Arteriopathy is a common etiology for childhood arterial ischemic stroke (AIS). In this study, we aimed to address clinical, demographic, and neuroimaging characteristics and the reversibility of vasculopathy in patients with childhood stroke due to arteriopathy by classifying them according to Childhood AIS Standardized Classification and Diagnostic Evaluation (CASCADE) criteria. **Methods:** We included 15 patients with AIS due to arteriopathy presented between 2013 and 2018. All patients were diagnosed and followed up using magnetic resonance imaging (MRI) studies. All acute AIS patients were classified by acute CASCADE criteria (1–4). Moreover, each group was categorized according to the chronic CASCADE criteria, including progressive, stable, reversible, and indeterminate courses. **Results:** In the study population, CASCADE 2 patients were the most common group, and basal ganglia involvement was the most common involvement in CASCADE 2 patients. Of CASCADE 2 patients, 71.4% received steroids, which was compatible with a favorable outcome. In the study, trauma was present in 33.3% of patients, 60% of which was related to CASCADE 4. In the control visit on month 24, there were neuromotor sequelae of 60%, including hemiparesis, facial paralysis, and decreased fine motor skills; furthermore, the recurrence rate was 20%. **Conclusion:** We strongly emphasize that arteriopathy should be kept in mind in school-age children presenting with hemiparesis and headache. Moyamoya disease must be considered in the differential diagnosis with anterior circulation involvement, while focal cerebral arteriopathy (FCA) in patients with basal ganglia involvement was detected on MRI and dissection in the patients with a history of head-neck injury. We think that steroids have positive influences on neurologic prognosis in patients with FCA.

Keywords: Arterial ischemic stroke, CASCADE, focal cerebral arteriopathy, MRI, pediatric

Introduction

Arterial Ischemic Stroke (AIS) is a major cause of morbidity and mortality in the pediatric population worldwide. In the literature, the annual incidence of pediatric stroke (age 1 month-17 years) has been reported as 1.2–7.9 per 100,000 in developed countries.[1,2] In pediatric stroke, the mortality rate ranges from 7% to 28%.[3,4]

Childhood AIS has a multifactorial pathophysiology that hasn't been fully understood.[5,6] Beside cardio-embolic stroke and prothrombotic conditions,[5-9] non-atherosclerotic intra- and extra-cranial arteriopathy is the most common etiology in childhood AIS.[6,10]

There was no consensus-based uniform classification and nomenclature for arteriopathy until the early 21st century. The first consensus-based definitions for childhood arteriopathy subtypes were proposed by Sebire *et al*. in 2004[11]. The definitions were revised by the Vascular Effects of Infection in Pediatric Stroke study group[12] and simplified according to The Childhood AIS Standardized Classification and Diagnostic Evaluation System (CASCADE) by the International Pediatric Stroke Study (IPSS) work group,[13] establishing the currently used version. The primary CASCADE criteria are based on the anatomic site of disease. According to CASCADE classification, primary acute childhood AIS classification involves seven categories (1: Small vessel arteriopathy; 2: Unilateral focal cerebral arteriopathy (FCA); 3: Bilateral FCA; 4: Aortic/Cervical arteriopathy; 5: Cardio-embolic; 6: Other; 7: Multi-factorial). While the unilateral FCA group was divided into two subgroups as anterior and posterior, the bilateral cerebral arteriopathy group was sub-classified into two groups: 'with collaterals (Moyamoya disease, fibromuscular dysplasia, etc.)' and 'without collaterals.' The group of aortic/cervical arteriopathy was divided into three subgroups: dissection, Takayasu arteritis, and others. Furthermore, each group was classified as progressive, stable, reversible, and indeterminate at the chronic stage.[13] Thus, CASCADE has provided a

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standardized anatomic classification with common language for clinicians dealing with stroke.

In this study, we aimed to address clinical, demographic, and neuroimaging characteristics and the reversibility of vasculopathy in patients with childhood stroke due to arteriopathy by classifying them according to CASCADE criteria.

Materials and Methods

We retrospectively reviewed the files of 47 patients (aged 29 days–18 years at presentation) who were followed with a diagnosis of AIS at the pediatric neurology department of Ankara University, Medicine School, between January 2013 and December 2018.

The AIS was defined as the presence of restricted diffusion compatible with a certain vascular territory and an apparent diffusion coefficient (ADC) lesion at the corresponding area on diffusion-weighted images (DWI) in a patient with an acute neurological deficit.[14] Arteriopathy was defined as the presence of any abnormality other than isolated vascular occlusions such as stenosis, irregularity, banding, pseudo-aneurysm, or dissection flap on vascular imaging.[15]

In our sample, there was cardio-embolic stroke in 9 patients and prothrombotic stroke in 12 patients (Protein C, S deficiency, MTHFR homozygous mutation, etc.). The etiology could not be determined in seven patients. Thus, these patients were excluded. The remaining 19 patients were classified into groups based on anatomic characteristics as vasculopathy-related strokes using the CASCADE classification. Of 19 patients, 4 were lost during follow-up; thus, the final study population included 15 patients (CASCADE 1-4) [Figure 1]. Table 1 summarizes the demographic, clinical, and radiological findings, treatment, and outcome of the patients included.

All patients underwent MRI, including DWI, ADC, fluid-attenuated inversion recovery (FLAIR), T2-weighted images, and 3-dimensional time-of-flight magnetic resonance angiography (MRA) at the time of presentation. Despite the ease of use of MRA, it tends to exaggerate vascular involvement (stenosis/occlusion). The MRI and MRA studies were repeated in patients showing neurological deterioration

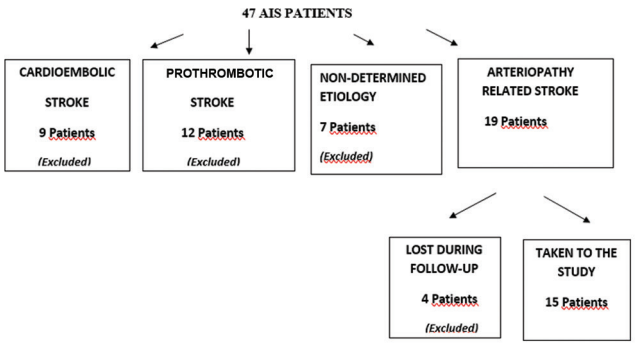

Figure 1: Breakdown and inclusion criteria of our patients

during clinical follow-up. Patients with at least 2 years of follow-up who met the following criteria were included in the study: a) absence of thrombotic disease or cardiac disorders, including patent foramen ovale, after standard blood testing and cardiac examination with transthoracic ECHO; and b) presence of repeated vascular neuroimaging studies on months 3, 6, and 12. During 2 years of follow-up, the patients were classified into subgroups as progressive arteriopathy, stable arteriopathy, and reversible arteriopathy according to CASCADE criteria. There were no patients in the intermediate group.[13] Based on these criteria, the term "progressive" was used if stenosis was increased on the control MRA, the term "reversible" was used if decreased, and the term "stable" was used if not changed.[13] Moreover, recurrent stroke was defined as de novo MRI lesions accompanying a newly developed neurological deficit.

In addition, ischemic lesions were classified according to involvement of the basal ganglia. Again, they were classified according to the arteries involved. Patients with internal carotid artery (ICA), middle cerebral artery (MCA), or anterior cerebral artery (ACA) involvement were recorded as "anterior" while those with posterior cerebral artery (PCA), vertebral artery (VA), and basilar artery (BA) involvement were recorded as "posterior."

The presenting symptoms were classified as hemiparesis, headache, aphasia, facial paralysis, seizure, loss of vision, and paresthesia of the extremities. Only one patient (Patient 14) had history of chronic disease; namely, thalassemia major diagnosed before admission.

Acute anti-thrombotic treatments were recorded as aspirin, low molecular weighted heparin (LMWH), aspirin plus LMWH (We initiated LMWH first, then stopped LMWH and started aspirin as maintenance therapy.), and recanalization therapies such as tissue plasminogen activator (tPA). Steroid therapy was given to patients with unilateral FCA who showed clinical and also radiological progression on MRA within the first 5–7 days. The steroid regime was used according to dosage and formulation described in pediatric demyelinating and inflammatory disorders by Steinlin *et al*.[16,17] Accordingly, pulse methylprednisolone (20 mg/kg/day over 5 days) was given, followed by tapering with oral prednisolone over 6–12 weeks. The patients were assessed using physical examination findings and a modified Rankin score at months 6, 12, and 24 after discharge. The changes in sequelae were recorded if present.

Informed consent was obtained from the legal guardians of all participants. The study was approved by the Ethics Committee of Ankara University's Medicine School. The study was conducted in accordance with the tenets of the Helsinki Declaration. The results are given as median and minimum-maximum.

Results

In the study population, there were seven girls and eight boys. The male:female ratio was 1.14. The median age at presentation

Table 1: Demographic, Clinical, Radiological Findings, Treatment and Outcome of 15 Patients with AIS-Related Arteriopathy

Case	Gender	Age (Year)	CASCADE Classification	Cranial-Cervical MRA involvement	Acute treatement	Steroid	Side L/R/B	History of Trauma	Initial Neurological Symptoms	Neurological sequelae on Month 24	Reversible (R)/ Irreversible (I) on MRA	Diagnosis	Recurrence
1	F	11+5/12	2	MCA, ICA	Aspirin + LMWH	+	L	-	Headache, Hemiparesis, Facial paralysis, Aphasia	-	R	FCA	-
2	F	8+8/12	2	PCA	Aspirin	+	R	-	Headache, Hemiparesis	-	R	FCA	-
3	F	7+10/12	2	ICA	Aspirin + LMWH	-	R	-	Hemiparesis	Facial paralysis	R	FCA	-
4	F	15+4/12	3	ICA	Aspirin	-	B	-	Headache, Hemiparesis	-		Moyamoya	-
5	M	6+8/12	2	MCA, ICA	LMWH	-	L	-	Hemiparesis, Facial paralysis, Aphasia	Decrased fine motor skills	R	FCA	-
6	M	15	2	VA, BA	Aspirin + LMWH	+	R	+	Headache, Hemiparesis, Facial paralysis	-	R	FCA	-
7	F	7+4/12	2	ACA, MCA	Aspirin	+	L	+	Hemiparesis, Aphasia	-	R	FCA	-
8	M	3+6/12	4	VA	Aspirin + LMWH	-	R	+	Hemiparesis, Aphasia	-	R	Dissection	-
9	M	14	3	ICA	Aspirin	-	B	-	Headache	-	I	Moyamoya	-
10	F	2+1/12	3	ICA	Aspirin	-	B	-	Hemiparesis, Facial paralysis, Seizure	Hemiparesis, Facial paralysis	I	Moyamoya	+
11	F	3+5/12	3	ICA, MCA	Aspirin + LMWH	+	B	-	Hemiparesis	Hemiparesis	I	Bilateral Cerebral Arteriopathy	+
12	M	6+5/12	4	ICA, MCA	Aspirin + LMWH	-	L	-	Headache, Hemiparesis,	Hemiparesis	I	Dissection	-
13	M	12+9/12	4	ICA (extracranial segment)	LMWH	-	L	+	Hemiparesis	-	R	Dissection (Eagle Syndrome)	-
14	M	6+11/12	2	ICA, MCA	tPA + LMWH + Aspirin	+	L	-	Hemiparesis	Hemiparesis	I	FCA	+
15	M	4+2/12	4	ICA, MCA	LMWH	-	R	+	Hemiparesis, Facial paralysis	Hemiparesis	I	Dissection	-

MRA: MR Angiography, F: Female, M: Male, ICA: Internal Carotid Artery, MCA: Middle Cerebral Artery, ACA: Anterior Cerebral Artery, PCA: Posterior Cerebral Artery, VA: Vertebral Artery, BA: Basilar Artery, LMWH: Low Molecular Weight Heparin, PA: tissue plasminogen activator, L: Left, R: Right, B: Bilateral

was 7.3 years (range: 2–15.3 years). The most common presenting symptom was hemiparesis in 14 patients (93.3%), followed by headache in six patients (40%), facial paralysis in five patients (33.3%), aphasia in five patients (33.3%), seizures in two patients (13.3%), and loss of vision in one patient (6.6%) [Table 2].

According to CASCADE classification, seven patients (46.6%) were classified as unilateral FCA (CASCADE 2) while four patients (26.6%) as bilateral cerebral arteriopathy with collaterals (CASCADE 3) and four patients (26.6%) as dissection from the aortic/cervical arteriopathy group (CASCADE 4). Of the patients with unilateral FCA, 71.5% were in the anterior group (CASCADE 2b), whereas 28.5% were in the posterior group (CASCADE 2c) [Table 2].

Of 15 patients, 2 had no lesion on T2-weighted or FLAIR MRI. Of the remaining 13 patients, there was basal ganglia involvement in 9 patients including 2 patients with isolated basal ganglia involvement. In addition to basal ganglia involvement, there was thalamic involvement in two patients, cerebral hemisphere involvement in four patients, and both thalamic and cerebral hemisphere involvement in one patient. Of the four patients without basal ganglia involvement, there was thalamic involvement in one patient, cerebral hemisphere involvement in one patient, and brainstem and cerebellar involvement in two patients. In addition, basal ganglia involvement was present in 71.4% of the FCA group.

There was a history of trauma in five patients (two patients from the unilateral FCA group and three patients from the dissection group). No patient had a previous history of infection. The patient 13 presented with numbness in the right arm. There was a history of trauma in the patient, and physical examination was normal at presentation. Cranial vasculature was found to be normal in the neuroimaging study performed due to suspected dissection; however, the patient was diagnosed with "Eagle syndrome" associated with the presence of peripheral thrombus and stenosis of the left ICA cervical segment due to dissection due to compression by styloid process [Figure 2]. The patient was given LMWH, and MRI and MRA studies were found to be normal at month 3. The LMWH treatment was discontinued at the end of month 5, and no recurrence was observed during the 2-year follow-up.

Table 2: Baseline Characteristics

Clinical and demographic findings	All (*n*=15)
Median age (year)	7.3 (min:2 max:15.3)
Gender (Male:Female)	1.14
CASCADE Subtype- Arteriopathy, *n* (%)	
Unilateral Focal Cerebral Arteriopathy	7 (46.6) (anterior: 71.5, posterior: 28.5)
Bilateral Cerebral Arteriopathy	4 (26.6)
Aortic/Cervical Arteriopathy	4 (26.6)
Median follow-up duration (month)	65 (min: 24 max: 95)
Clinical presentation, *n* (%)	
Hemiparesis	14 (93.3)
Headache	6 (40)
Facial paralysis	5 (33.3)
Aphasia	5 (33.3)
Seizure	2 (13.3)
Vision loss	1 (6.6)
Acute treatment, *n* (%)	
Aspirin	5 (33.3)
LMWH	3 (20)
Aspirin + LMWH	7 (46.6)
tPA	1 (6.6)

When MRI and MRA findings at presentation were assessed, left-sided involvement was 40% (n = 6), right-sided involvement was 33.3% (n = 5), and bilateral involvement was 26.6% (n = 4). On the other hand, it was found that there was anterior involvement in 80% and posterior involvement in 20% of the patients. The ICA was the most commonly involved artery (11 patients, 73.3%), 45.4% of which were isolated. The MCA was the second most commonly involved artery (seven patients, 46.6%). There was accompanying ICA involvement in 85.7% and ACA involvement in 14.2% of patients with MCA involvement. Posterior circulation was affected in the remaining three patients (PCA, VA, and BA) (20%).

We evaluated patients by neurological examination at presentation. Then we assessed all patients by neurological examination and modified Rankin scale (mRS) at discharge and during follow-up. The neurological examination was normal in three, patients and the mRS score was found to be "0" at discharge (20%). Two-thirds patients were diagnosed with Moyamoya disease, while the remaining patient was diagnosed with the extracranial-dissection-Eagle syndrome. In our study, the neurological deficit rate was 80% at discharge and 53.3% at the end of year 1 among all patients with AIS secondary to arteriopathy. By the way, in all patients with unilateral FCA, there were neurological sequelae at discharge (46.6%). Hemiparesis was the most common finding detected at discharge (73.3%), followed by facial paralysis (20%), aphasia, dysarthria (13.3%), and reduction in fine motor skills (6.6%). The mRS was assessed at discharge and at months 3, 6, 12, and 24. In the control visit in month 24, neurological examination was normal in six patients (40%) (mRS: 0), while hemiparesis (33.3%, n = 5), facial paralysis (13.3%, n = 2), and decreased fine motor skills (6.6%, n = 1) were detected in the remaining patients.

All but one patient (patient 14) received tPA, a thrombolytic therapy, due to delayed presentation (6.6%). Anti-thrombotic therapies were given to all patients, including aspirin in 5 patients (33.3%) and LMWH in 3 patients (20%), aspirin plus LMWH in 7 patients (46.6%) [Table 2]. Steroid therapy was given to 5 (71.4%) of 7 patients with unilateral FCA.

The median follow-up time was 65 months (range: 24–95 months). Recurrence was observed in three patients (2 from the bilateral cerebral arteriopathy group and 1 from the unilateral FCA group). The recurrence developed 12 months after the first attack in case 10 and 3 months after the first attack in case 14 [Figure 3], while case 11 experienced five

attacks before admission to our hospital. Immunosuppressive treatment was initiated for patient 11 with an additional diagnosis of primary cranial nervous system vasculitis who was classified as CASCADE 3; no recurrence was observed after immunosuppressive treatment. No recurrence was observed during the 2-year follow-up in the remaining arteriopathy groups. The recurrence rate was calculated as 20% in the whole study population and 14.2% in the unilateral FCA group.

Steroid therapy was given to 71.4% of patients in the unilateral FCA group. The patients with recurrence included those who had a poorer clinical presentation with acute progression or multi-vessel involvement. MRA studies showed that arteriopathy was reversible in 60% of patients given steroid therapy on month 3, whereas it was reversible in 80% on month 12. But reversibility was also observed on MRA in patients not given steroids. However, in clinical assessment, normal neurological examination (mRS = 0) was noted in 40% of the patients on month 6 and in 60% of the patients on month 12 in the group given steroid, and the lowest mRS was 1. All patients in the group who did not receive steroid therapy had sequelae, and mRS was found to be 3 and 2 at months 6 and 12, respectively, in two patients.

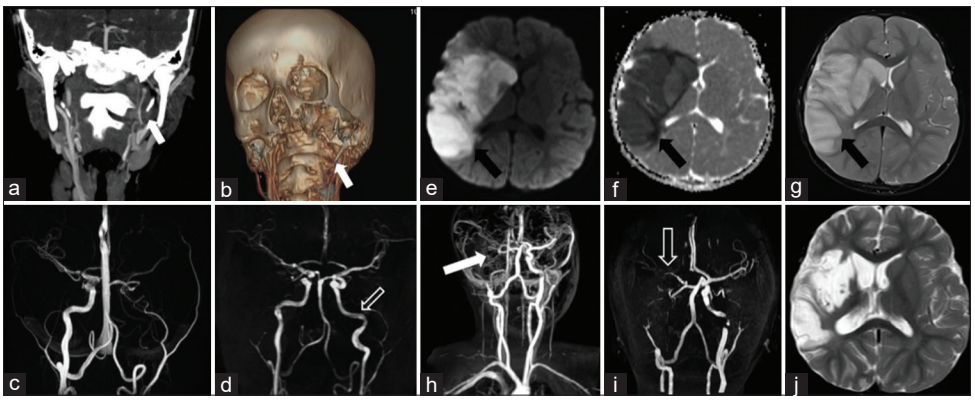

Figure 2: Patient 13: CTA (a) shows the presence of peripheral thrombus and stenosis of the left ICA cervical segment due to dissection. Volume-rendered 3D images (b) demonstrate the presence of the elongated styloid process (Eagle syndrome). While the initial MRA (c) revealed the occlusion of the left ICA, the follow-up MRI (d) showed the resolution of the left ICA occlusion. **Patient 15**: DWI image (e), ADC map (f), and T2WI (g) demonstrate diffusion restriction corresponding to the acute infarction in the right MCA territory (black arrows). MRA (h) shows occlusion of the right ICA and MCA due to dissection (White arrow). Follow-up MRA 1 year later (i) shows persistent right ICA occlusion that has not developed recanalization and the retrograde opacification of the MCA M1 segment via the right PCA (open arrow). Also, follow-up MRIs (j) demonstrate chronic encephalomalacia

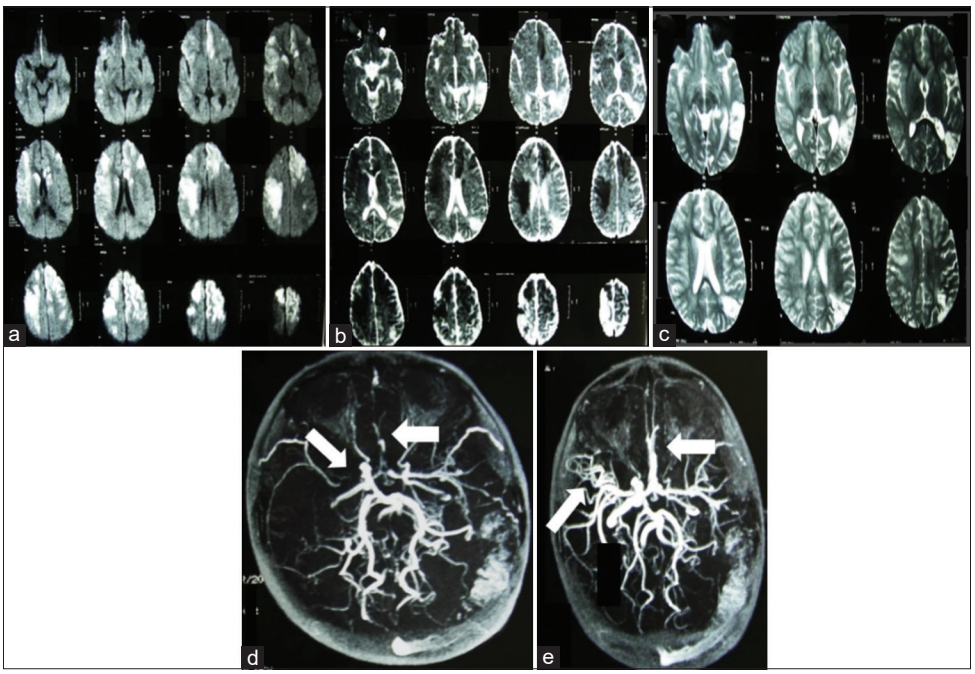

Figure 3: Patient 14: DWI (a) and ADC maps (b) of a patient with the diagnosis of FCA and recurrent ischemic attacks demonstrate the diffusion restriction in the bilateral frontoparietal lobes, right temporal lobe, and bilateral caudate nucleus due to acute ischemia. T2WI (c) shows the chronic encephalomalacia in the left parietal lobe associated with another ischemic attack. MRA (d) shows the occlusion of the right MCA and also the irregularity and stenosis of the bilateral ACA (white arrows). Follow-up MRA (e) after the tPA therapy, patent right MCA and ACA are seen

In the unilateral FCA group, it was seen that MRA findings were reversible in four (57.1%) of seven patients at month 3 and in six (85.7%) patients at month 12. There was thalamic involvement in the single non-reversible patient (patient 2) with PCA occlusion in the FCA group (16.6%). In patient 1 from the unilateral FCA group, left MCA occlusion was detected on MRA at presentation. It was seen that there was an enlargement in the lesion at the left basal ganglia on diffusion MRI, which was repeated due to a worsening clinical picture 2 days after presentation. LMWH was initiated first, and then pulse steroid therapy was started. During follow-up, it was observed that clinical findings were resolved without an increase in lesion size. It was seen that occlusion was stable on the MRA obtained on month 1, while re-canalization started on month 3, and complete re-canalization occurred on month 12 [Figure 4]. In all six patients with reversibility, there was basal ganglia involvement in two (33.3%), basal ganglia plus thalamus involvement in three (50%), and brainstem involvement in one (16.6%). It was seen that occlusion was completely resolved in patients 3 and 5 [Figures 5 and 6] with anterior circulation involvement and patient 6 with posterior circulation involvement on MRA obtained on month 12 [Figure 6].

Of four patients with dissection-related strokes, there was trauma-related dissection in three and spontaneous dissection in one patient. Of the patients with trauma, there was a head-neck injury (such as hyperextension injury) in two patients (patients 8 and 13) and a penetrating soft palate injury in one patient (patient 15). On imaging studies in patient 15, who presented with hemiparesis and facial paralysis, an acute infarct was observed in the MCA supply area, with dissection extending from the right ICA bulb to the distal portion of the right MCA M1 segment. No progression was observed in clinical findings in the patient given LMWH. On repeated MRA at year 1, no re-canalization was observed, and the patient was considered to be irreversible arteriopathy [Figure 2]. Reversibility was observed in 2–4 patients with dissection on the MRA obtained on month 12. Right vertebral artery involvement was detected in one patient, while involvement at the extra-cranial segment of the left distal ICA was detected in the other patient. All two patients remained stable during their 2-year follow-up. Table 1 presents demographic characteristics, imaging findings, and treatment details.

Seizures and/or subsequent post-stroke epilepsy were detected in five patients (33.3%) from the whole arteriopathy-related stroke group, while post-stroke epilepsy was detected in three patients (42.8%) from the unilateral FCA group. All three patients experienced focal epilepsy, which was controlled with anti-seizure medications. The remaining two patients were in the bilateral cerebral arteriopathy with collaterals group.

Discussion

In the literature, arteriopathy incidence was reported as 30–50% in children with stroke.[10,18] In agreement with the literature, this rate was found to be 31.9% (15/47) in our study. Although this is a single-center study with a relatively small sample size, it was concluded that AIS was found to be related to arteriopathy in almost one-third of children who had AIS and vascular imaging studies. It was seen that FCA was the common arteriopathy subtype.

Based on IPSS Group data, Rafay *et al*.[19] reported the median age as 7.45 years in childhood stroke secondary to arteriopathy; it was found to be 7.3 years in our study. Again, consistent with the above mentioned study, the most common presenting symptom was hemiparesis (93.3% vs. 81%), followed by headache (40% vs. 45%). In a study by Guilliams *et al*.,[20] it was emphasized that patients with arteriopathy-related stroke often presented with hemiparesis and headache. There was a male preponderance in our study, in agreement with findings reported in the literature.[3,19]

In a study by Böhmer *et al*.,[21] it was suggested that CASCADE classification at presentation was markedly correlated with

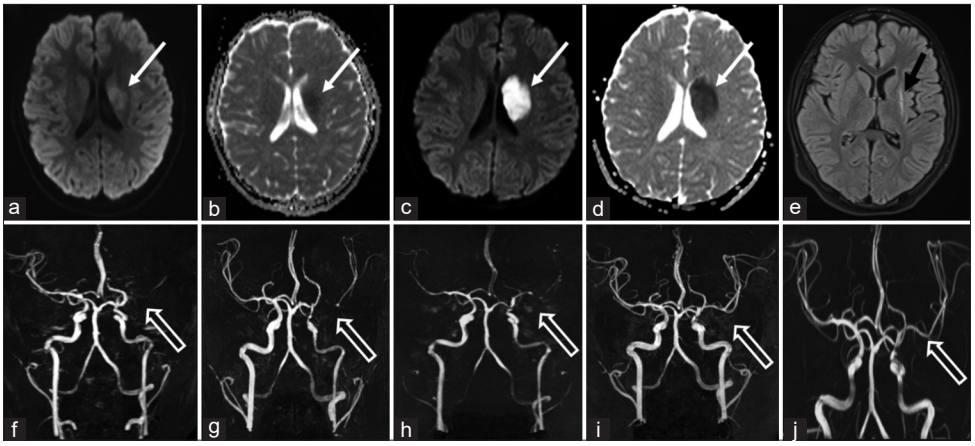

Figure 4: Patient 1: Initial DWI and ADC map (a and b) show the acute infarction within the left lentiform nucleus and follow-up MRI 1 day later (c and d) demonstrate the progression of the infarction area (white arrows). Follow-up MRI 1 year later (e), FLAIR image shows the encephalomalacia and gliosis within the left lentiform nucleus (black arrow). Initial MRA (f) reveals severe stenosis and beaded appearance of the left MCA M1-M2 segments. Follow-up MRIs at 1. month (g), 3. months (h), 6. months (i) and 12. months (j) show the resolution of the stenosis and irregularity over the time (open arrows)

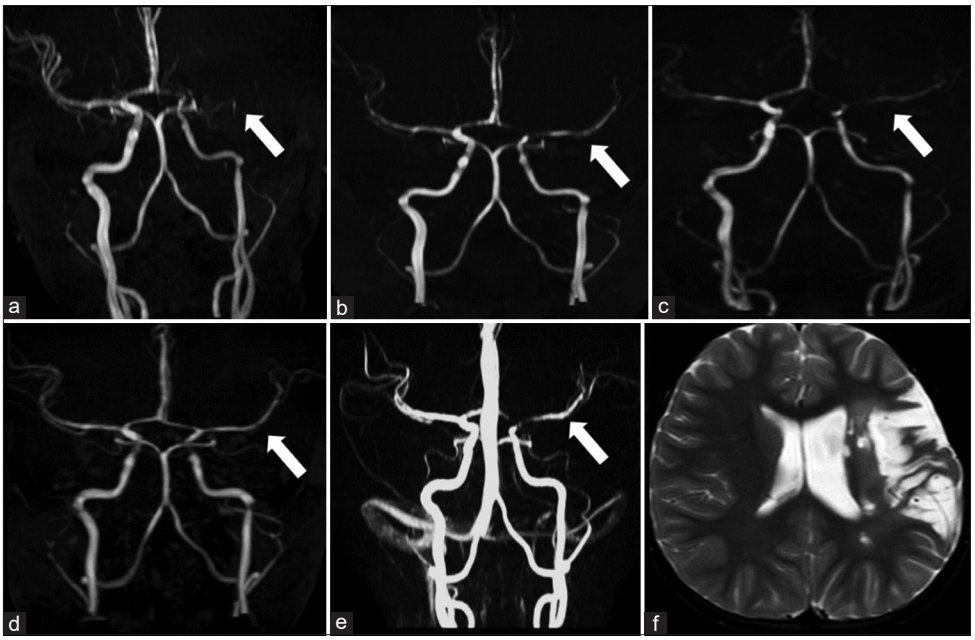

Figure 5: Patient 5: Initial MRA (a) shows the occlusion of the left MCA. Follow-up MRIs at 1 month (b), 6 months (c), 12 months (d), and 24 months (e) demonstrate the patency of the left MCA with minimal irregularity, and these indicate reversibility. On follow-up MRI after 2 years (f), T2WI shows the chronic infarction in the left temporoparietal lobe and also in the basal ganglia and external capsule

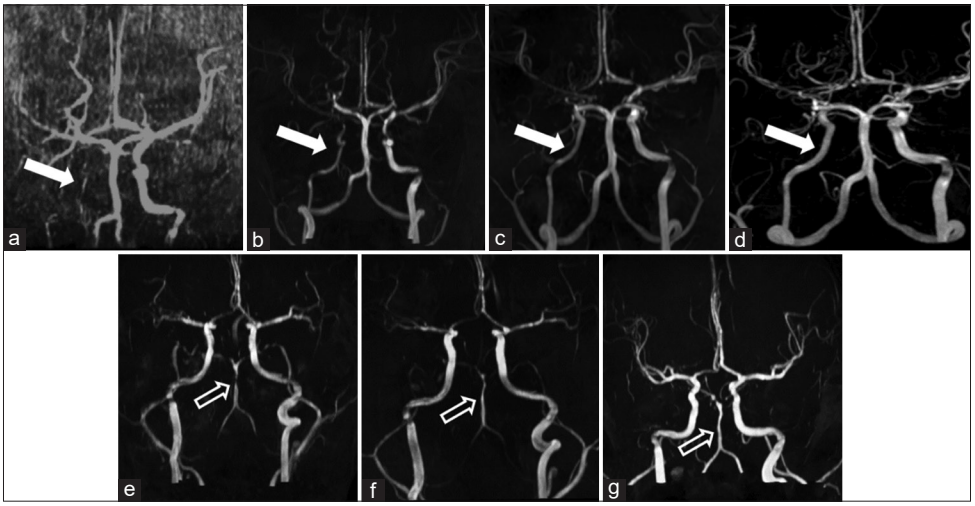

Figure 6: Patient 3: MRA (a) reveals severe stenosis and irregularity of the right ICA. Follow-up MRIs with a 1-year interval (b-d) show the resolution of the stenosis and irregularity over time (white arrows). **Patient 6:** MRA (e) shows severe stenosis and irregularity of the basilar artery (open arrow) and also the poor opacification of the vertebral arteries. Follow-up MR after 3 months (f) and after 12 months (g) demonstrate the resolution of the pathological findings. CTA: CT Angiography, MRA: MR Angiography, DWI: diffusion-weighted images, ADC: apparent diffusion coefficient, T2WI: T2-weighted images, FLAIR: fluid-attenuated inversion recovery, FCA: focal cerebral arteriopathy, ICA: internal carotid artery, MCA: middle cerebral artery, ACA: anterior cerebral artery, PCA: posterior cerebral artery, tPA: tissue plasminogen activator

stroke recurrence and arteriopathy courses. In addition, it was proposed that stroke recurrence was unlikely in CASCADE group 4, while there was a markedly high risk for recurrent stroke in CASCADE 2 and 3. Similarly, no recurrent stroke was observed in the CASCADE 4 group, while two patients had recurrent strokes in the CASCADE 3 group in our study. However, all but one patient experienced stroke recurrence in the CASCADE 2 group during the 2-year follow-up in our study. On the other hand, in agreement with the literature, FCA-related recurrent stroke frequency was reported to range from 3% to 25% in the literature (14.2%), although FCA is considered a monophasic disease.[15,22-25] In another study, it was found that the recurrence rate was significantly higher in arteriopathy-related strokes (21%) when compared to the non-arteriopathy group,[19] which was similar to the recurrence rate in our study (20%). In a study by Per *et al*.[26] from Turkey, the stroke recurrence rate was found to be 7% among 130 children with stroke during follow-up (5 months to

11 years). The higher recurrence rate in our study is attributed to the fact that the recurrence rate in our study was calculated solely in patients with arteriopathy, while Per *et al*. assessed all patients with stroke. Although the small sample size of the group may suggest that the risk for recurrence is higher in patients with arteriopathy-related stroke when compared to the non-arteriopathy group.

In a comprehensive study based on 2003–2014 IPSS data, it was found that anterior circulation was involved by 67%, posterior circulation by 22%, and both anterior and posterior circulation by 11%. In the same study, it was found that there was right-sided involvement in 39%, left-sided involvement in 36%, and bilateral involvement in 25% of patients.[19] In our study, there was anterior involvement in 80% and posterior involvement in 20% of the patients, while there was no case of anterior plus posterior involvement. Again, 40% were left-sided, 26.6% were right-sided, and there was bilateral involvement in 33.3% of our study. Consistent with IPSS data, anterior circulation was involved more commonly in our study; on the other hand, the left-sided involvement rate was higher.

The region involved in vasculopathy may inform classification. In previous studies, it was proposed that Moyamoya disease was more frequently associated with involvement in the anterior circulation.[27,28] On the other hand, it was emphasized that cervical ICA involvement should suggest dissection in childhood AIS.[15] In our study, the anterior circulation was involved in all patients with Moyamoya disease. In addition, in a patient with normal cranial MRA, extra-cranial dissection was diagnosed by extra-cranial involvement of cervical ICA. It was found that there was anterior circulation involvement of three and vertebral artery involvement in one of four patients with dissection. Again, there was a history of trauma in three of four patients in the dissection group. Carotid artery dissection and vertebral artery dissection are rare traumatic dissections, which are more frequently seen than non-traumatic dissections.[29,30] The primary traumatic mechanisms have been reported as direct head-neck injury or hyperextension,[29] sports activities, fights, falls, and motor vehicle accidents.[30,31] In our study, among four patients with dissection, there was a direct head-neck injury such as a crash or sport injury, whereas there was a penetrating soft palate injury by a pencil in one patient, which was reported as an example of a rare case report in the literature.[32] It was found that FCA is associated with basal ganglia infarction at rates as high as 62–78%.[23,33] In our study, basal ganglia involvement was seen in 71.4% of patients with FCA. Thus, we also think that Moyamoya disease should be considered in the differential diagnosis of AIS in the presence of anterior circulation involvement and FCA in the presence of basal ganglia involvement. In addition, we also support the idea that cervical MRA should be obtained for dissection in all patients with a history of trauma.

In the literature, it has been reported that vertebrobasilar circulation may also be affected, although the proximal MCA is the most commonly involved artery in FCA-related AIS.[23,33,34] On the other hand, primary involvement sites are the distal ICA and proximal segments of the ACA and MCA in childhood arteriopathies.[35] In our study, the most frequent involvement sites were proximal MCA and distal ICA in the unilateral FCA group; in addition, vertebrobasilar circulation was also affected in 20% of patients. The most common involvement site was the distal ICA among all arteriopathies in our study.

Although aspirin is a preferential treatment in arteriopathy, we added LMWH in patients with rapid progression of vasculopathy on aspirin. In patients with Moyamoya disease, surgical revascularization is recommended as the primary treatment.[36,37] However, the surgical therapy is challenging due to the need to fulfill several parameters, including indication, timing, selection of an appropriate technique, and expectations following revascularization. We also offered surgical treatment to patients with Moyamoya disease; however, their parents declined surgery.

In the study by Rafay *et al*.,[19] the neurological deficit rate was reported to be 82% at discharge and 52% at the end of year 1 in patients with AIS secondary to arteriopathy. In agreement with Rafay *et al*.,[19] the respective rates were 80% and 53.3% in our study. In children with AIS, arteriopathy has been defined as a common risk factor.[6] In addition, an association was reported between FCA and post-stroke epilepsy.[38] Amlie-Lefond *et al*.[10] reported seizure frequency as 23% in a study on patients with arteriopathy-related stroke, while Kopyta *et al*.[38] reported seizure and subsequent post-stroke epilepsy rates as 21% in children with AIS secondary to FCA. In our study, seizure frequency was found to be 33.3% in the whole group of arteriopathy-related strokes. On the other hand, the seizure frequency rate was 42.8% in the FCA-related group, which was higher than those reported by Kopyta *et al*.[38] Both rates were higher than those reported in the literature.[10]

In the literature, it was reported that arteriopathy recurrence and worsening occur around month 3.[23,39] And control vascular imaging was recommended for months 3–6 and 6–12.[11,16,40] In our study, we repeated MRI and MRA studies at months 3, 6, and 12, which allowed us to monitor recurrence and reversibility in the patients. By this approach, recurrence was detected in one patient at the control visit on month 3 and in another patient on month 12. Of the patients in the CASCADE 2 group, it was found that 57.1% were reversible on month 3, whereas 85.7% were reversible at month 12 in MRA. No recurrence was detected in our patients at the end of year 2 during a follow-up of 2–8 years. On the other hand, the radiological and clinical status at month 12 was comparable to those observed in subsequent years, implying that there is no ongoing improvement, recurrence, or worsening beyond year 1. Thus, we also support the concept that neuroimaging studies should be repeated at months 3, 6, and 12 to determine reversibility and recurrence in patients with AIS secondary to arteriopathy.

In a study on 73 pediatric cases in which the effects of steroids on FCA were assessed by the pediatric stroke outcome measure,

it was suggested that clinical outcomes were better in children who received steroid therapy in addition to anti-thrombotic therapies when compared to those who did not receive steroid, that the improvement was most marked in cognitive/behavioral domains, and that recurrence was low in both groups.[25] Although no cognitive assessment was performed in our study, a rapid and marked improvement on mRS was observed in the group receiving steroids, while favorable outcomes were also obtained in the group not receiving steroids; however, the recovery was slow and final outcomes were poorer in this group. Thus, we think that steroids may positively affect neurological outcomes in children with stroke secondary to FCA.

This study has some limitations, including a retrospective design and a small sample size. However, we think that the study population was homogenous, given that the majority of our findings are in agreement with the literature.

In conclusion, it was observed that arteriopathy-related stroke incidence was 31.9%, that neuromotor sequelae developed in almost one of every two children, and that the recurrence rate was 20%. We strongly emphasize that arteriopathy should be kept in mind for school-age children presenting with hemiparesis and headache. Moyamoya disease must be considered in the differential diagnosis with anterior circulation involvement on MRI, while FCA in patients with basal ganglia involvement was detected on MRI, as was dissection in patients with a history of head-neck injury. We think that steroids have positive influences on neurologic prognosis in patients with FCA.

Author contributions

All authors have made substantial contributions to all of the following:

1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work
2) Drafting the work or revising it critically for important intellectual content
3) Final approval of the version to be published
4) Agreement to be accountable for all aspects of the work ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflicts of interest

There are no conflicts of interest.

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