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Research Article

DIAGNOSTIC ACCURACY OF DIGITAL SUBTRACTION ANGIOGRAPHY (DSA) IN CORRELATION WITH COMPUTED TOMOGRAPHY (CT) AND MAGNETIC RESONANCE ANGIOGRAPHY (MRA) IN EVALUATION OF MOYAMOYA DISEASE: A COMPARATIVE STUDY IN A TERTIARY CARE HOSPITAL

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Moyamoya Disease, Digital Subtraction Angiography, Magnetic Resonance Angiography, Non-contrast Computed Tomography, Ischaemic Stroke.

A B S T R A C T

Introduction: Moyamoya disease (MMD) is an idiopathic, non-inflammatory, non-atherosclerotic progressive vasculo-occlusive disease involving the circle of Willis, typically the supraclinoid internal carotid arteries. MMD is most prevalent in Japan and Korea where its estimated incidence is 0.35-0.54 per 100,000 people. It has bimodal peak of presentation – two-third in early childhood and one-third in 3rd-4th decade.

Purpose: We assessed the performance of NCCT and MRA in **diagnosis**, **evaluation** and **staging** (Suzuki and Takaku) of Moyamoya disease as the cause of recurrent cerebral strokes compared to DSA and effects of above parameters on the sensitivity of these imaging modalities, taking DSA as gold standard.

Materials and Methods: We investigated 60 patients (120 hemispheres) of recurrent strokes referred to our department between May 2018 and July 2019 after they met the inclusion criteria. Each patient underwent NCCT, MRA and DSA. The findings were recorded in predesigned and pretested case record sheet and were analysed later.

Results: A total of 9 cases of Moyamoya disease (Male- 3, Female- 6) were diagnosed on DSA. Among 18 examined hemispheres of 9 confirmed cases of MMD on DSA, MRA missed 2 and incorrectly diagnosed 4 hemispheres. Out of the 9 cases, 8 showed recurrent ischaemic strokes while only one showed haemorrhagic stroke which both NCCT and MRI could localise and diagnose with 100% efficacy. Out of 7 ICA occlusions, 10 ICA narrowing, 17 cases of anterior circulation involvement and 8 cases of posterior circulation involvement, MRA correctly diagnosed all cases of ICA occlusion and narrowing, 11 cases of anterior circulation involvement and only 1 case of posterior circulation involvement. **The overall sensitivity of MRA for diagnosis and correct staging of Moyamoya disease were 77.8 % and 44.4 % respectively**.

Conclusion: Digital Subtraction Angiography (DSA) is more sensitive and accurate than Magnetic Resonance Angiography (MRA) in evaluation of Moyamoya disease. Staging of Moyamoya disease is best done by DSA study.

INTRODUCTION

Moyamoya disease (**MMD**) is an idiopathic, non-inflammatory, non-atherosclerotic progressive vasculo-occlusive disease involving the circle of Willis, typically the supra-clinoid internal carotid arteries with prominent arterial collateral circulation. **[1]**

Described first in Japan in 1957, the name 'moyamoya' is derived from Japanese term meaning "puff of smoke" which simulates the characteristic 'moyamoya collaterals'. **[2]** MMD is most prevalent in Japan and Korea where its estimated incidence is 0.35-0.54 per 100,000 people, with a female preponderance. While the incidence is relatively lower in other Asian countries, in Europe it appears to be about 1/10th of that observed in Japan. **[2, 3, 4]**

MMD is relentlessly progressive and long-term outcome is generally poor. Even relatively "asymptomatic" patients commonly have cognitive disturbances and silent ischemic infarcts. **[2]** The only approach that could prevent this outcome is early diagnosis and cerebral revascularization surgery.

Though Non- contrast CT Brain is the imaging modality of choice for initial screening of stroke, Digital Subtraction Angiography (DSA) is considered gold standard for diagnosis and staging of Moyamoya disease. Among other alternative

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diagnostic tests, **MR Angiography (MRA)** has attracted much attention as a substitute due to its high accuracy, non invasive nature, availability and favourable technical aspects as diffusion and perfusion weighted imaging, shorter acquisition time. MR-Angio imaging has a great advantage of demonstrating blood vessels without requiring use of contrast medium.

AIM

To assess the performance of NCCT and MRA in diagnosis, evaluation and staging of Moyamoya disease as the cause of recurrent cerebral strokes, compared to DSA and effects of above parameters on the sensitivity of these imaging modalities, taking DSA as gold standard.

MATERIALS AND METHODS

Study Design: Retrospective observational study.

Sample Selection: 60 patients (120 hemispheres) of recurrent strokes referred to the department of Radio-diagnosis between May 2018 and July 2019, were included in the study, after they met the inclusion criteria.

Inclusion Criteria

a. Patients diagnosed with recurrent episodes of stroke (non-traumatic) of unexplained etiology.
b. Patients who gave consent to take part in the study.

Exclusion Criteria

Atherosclerosis, Autoimmune disease, History of cranial irradiation, Brain neoplasms, Neurofibromatosis, Meningitis.

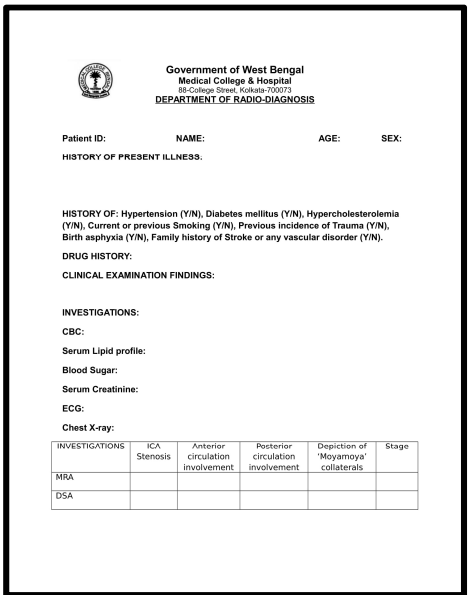
Procedure: The following informations were collected from each patient.

Age, Sex, H/O headache, hemiparesis, aphasia, seizures, cognitive dysfunction, involuntary movements and visual problems; H/O hypertension, diabetes mellitus, hypercholesterolemia, current or previous smoking, previous incidence of any trauma, history of birth asphyxia; Family history of stroke or any vascular disorder. Detailed drug history was taken. Clinical features and examination findings were noted. Investigations like CBC, serum lipid profile, blood sugar, serum creatinine, ECG, Chest X-ray were also done.

Each patient underwent Digital Substraction Angiography by our Philips Allura Xper FD20 machine via a femoral arterial approach, as well as MRA, which was done by GE Signa Voyager 1.5T at EKO MRI section of Medical College Kolkata. All investigations were done free of cost. Identification of the diagnostic radiologic findings of the disease, evaluation of the site and extent of involvement of ICA, anterior and/or posterior circulation was done. Characterisation and staging of the disease was done based on the 'Suzuki & Takaku' Classification system [Chart 1]. Biplanar DSA was used as the gold standard. The findings of DSA and MRA were compared to obtain the effects of above parameters on the sensitivity of these two imaging modalities.

Chart 1 Suzuki Staging of Moyamoya Disease [16]

Stages	Features
Stage I	**"Narrowing of the Carotid fork"**
	• Narrow ICA bifurcation
Stage II	**"Initiation of the Moyamoya"**
	• Dilated ACA, MCA and narrowed ICA bifurcation with moyamoya changes
Stage III	**"Intensification of the Moyamoya"**
	• Further increase of the moyamoya change of the ICA bifurcation
	• Narrowed ACA, MCA
Stage IV	**"Minimization of the Moyamoya"**
	• Moyamoya changes reducing with occlusive change in the ICA
	• Tenuous ACA and MCA
Stage V	**"Reduction of the Moyamoya"**
	• Further decrease in moyamoya changes with occlusion of ICA, ACA & MCA
Stage VI	**"Disappearance of the Moyamoya"**
	• ICA essentially disappeared with supply of brain from ECA



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DEPARTMENT OF RADIO-DIAGNOSIS

Patient ID: NAME: AGE: SEX:

HISTORY OF PRESENT ILLNESS.

HISTORY OF: Hypertension (Y/N), Diabetes mellitus (Y/N), Hypercholesterolemia (Y/N), Current or previous Smoking (Y/N), Previous incidence of Trauma (Y/N), Birth asphyxia (Y/N), Family history of Stroke or any vascular disorder (Y/N).

DRUG HISTORY:

CLINICAL EXAMINATION FINDINGS:

INVESTIGATIONS:

CBC:

Serum Lipid profile:

Blood Sugar:

Serum Creatinine:

ECG:

Chest X-ray:

INVESTIGATIONS	ICA Stenosis	Anterior circulation involvement	Posterior circulation involvement	Depiction of 'Moyamoya' collaterals	Stage
MRA					
DSA					

Figure 1 Proforma used for the study

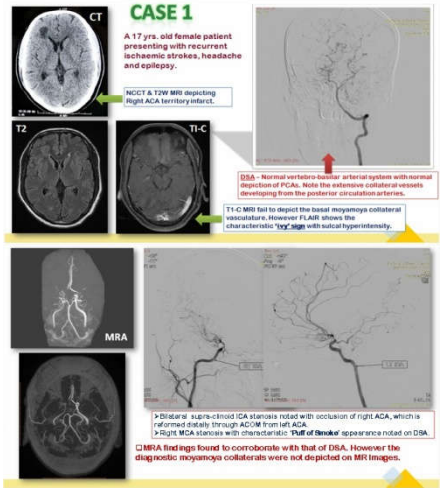

Figure 2 Case study showing NCCT, MRI, MRA and DSA findings in a 17 years old female diagnosed with Moyamoya disease

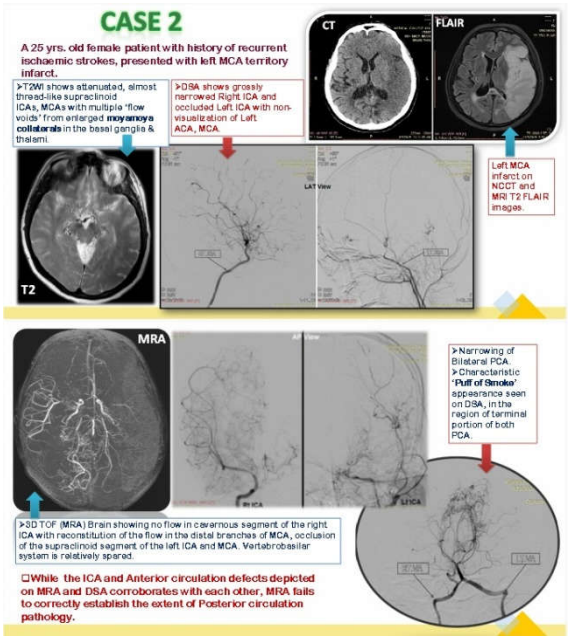

Figure 3 Case study showing NCCT, MRI, MRA and DSA findings in a 26 years old female diagnosed with Moyamoya disease.

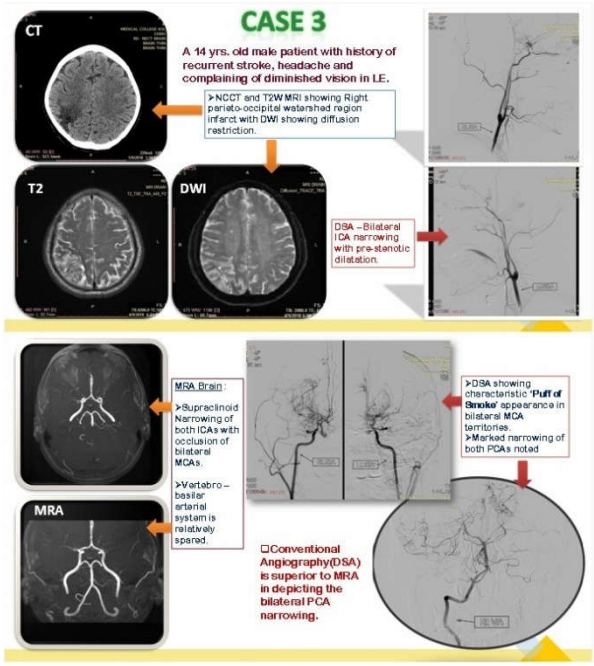

Figure 4 Case study showing NCCT, MRI, MRA and DSA findings in a 14 years old male diagnosed with Moyamoya disease.

RESULTS

1. Out of 60 cases(120 hemispheres) selectively included in the study, 9 cases(17 hemispheres) were diagnosed as Moyamoya disease by DSA.
2. 4 patients were children below 15 years, 3 patients were in the age-group of 15-20 while only 2 patients were above 20 years of age.
3. Male female ratio was 1:2 (Male-3 & Female-6).
4. Of all the 9 cases only 1 presented with unilateral disease.
5. All the study patients(100%) had presented with hemiparesis and aphasia, while 1 patient had an episode of seizure.
6. While headache and cognitive dysfunction were present in all patients(100%), 5 patients(55.5%) had complaints of diminished vision and only 2 patients(22.2%) had involuntary movements as symptoms.
7. Only 1 patient gave history of similar disease in the family.
8. Regarding the presence of risk factors, 11.1% were diabetic and 33.3% had H/O birth asphyxia.
9. Most of the cases (8) showed recurrent ischaemic infarcts while only one patient of 28 yrs. age presented with haemorrhagic stroke, which both NCCT and MRI could localise and diagnose with 100% efficacy.
10. Among 17 examined hemispheres of confirmed cases of MMD on DSA, MRA incorrectly diagnosed 4 hemispheres(i.e. 2 cases) as isolated atherosclerotic ICA stenosis.
11. Out of 7 ICA occlusions, 10 ICA narrowing, 17 cases of anterior circulation involvement and 8 cases of posterior circulation involvement, MRA correctly diagnosed all cases of ICA occlusion and narrowing, 11 cases of anterior circulation involvement and only 1 case of posterior circulation involvement [Chart 2].
12. Correct staging of the disease was done by MRA in 4 out of 9 cases [Table 1]. DSA was considered gold standard for the purpose of disease staging.
13. The overall sensitivity of MRA for diagnosis and correct staging of Moyamoya disease were 77.8 % [Table 3] and 44.4 % respectively.
14. MR Angiography accurately depicted stenosis of all the major arteries (ICA, MCA, ACA). However the degree of stenosis was overestimated in 42.8% of the affected arteries [Table 2].
15. Basal cerebral moyamoya vessels were depicted in all 17 hemispheres with conventional angiography and in 13(76.4%) hemispheres with MR Angiography and MR Imaging.

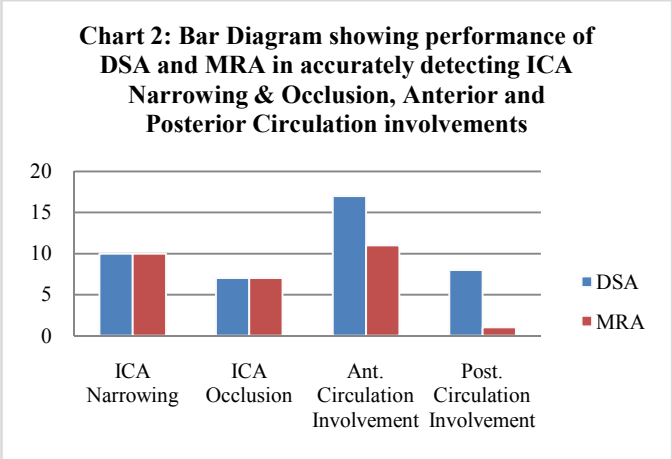

Chart 2 Bar Diagram showing performance of DSA and MRA in accurately detecting ICA Narrowing & Occlusion, Anterior and Posterior Circulation involvements

Table 1 Comparison of Staging of Moyamoya disease cases done by DSA and MRA

Modality	Diagnosed and Staged Cases						Missed Cases
	Stage I	Stage II	Stage III	Stage IV	Stage V	Stage VI	
DSA	1	1	2	3	2	0	0
MRA	0	0	1	3	3	0	**2**

Table 2 Comparison of Accuracy of MRA with respect to DSA in Staging of Moyamoya disease

Modality	Correctly staged cases	Under-estimated/Missed cases	Over-estimated cases	Incorrectly staged cases
DSA	9	0	0	0
MRA	4	2	3	5

Table 3 MRA % MRI as Diagnostic Tool for Moyamoya Disease

Parameters	Percentage
Sensitivity	**77.8 %**
Specificity	**100 %**
Positive Predictive Value (PPV)	**100 %**
Negative Predictive Value (NPV)	**96.2 %**

DISCUSSION

MMD has bimodal peak of presentation – two-third in early childhood (peak in 10-14 yrs.) and one-third in 3rd-4th decade. **[1, 5]** Our study found highest number of cases (4 out of 9) in the age-group of below 15 years, while 3 cases were between 15-20 years age.

Only 1 patient gave a history of similar disease in the immediate family. According to Osborne AG **[2]**, approximately 5-10% of Asian MMD cases are familial. Mineharu Y *et al* (2008) [6] mentions that a variant of the RNF213 gene (encodes a protein that is involved in proper vascular development) on chromosome 17q25.3 is an important susceptibility factor for moyamoya disease in East Asian populations. MMD is also associated with several genetically transmitted disorders, including NF-1, Trisomy 21 (Down syndrome), Grave's disease, Alagille syndrome a spectrum of hemoglobinopathies such as Sickle Cell Anemia, Collagen vascular diseases like Marfan and Ehlers-Danlos syndromes. **[2, 7-10]**

The terminal ICAs show severe stenosis with concentric and eccentric fibrocellular intimal thickening without significant inflammatory cell infiltration. Subintimal lipid deposition, hemorrhage, and necrosis are absent. The internal elastic lamina is typically tortuous and stratified. Stenosis may also affect the extra-cranial and systemic arteries, most frequently Renal arteries. **[2]** Multiple enlarged "telengiectatic" lenticulostriate, thalamo-perforating, leptomeningeal, dural and pial arteries develop as compensatory circulation, called 'moyamoya vessels'.

Osborne AG [2] describes the clinical features of MMD presenting in childhood as usually ischaemic (TIA & Infarcts). Among adults, approximately 50% patients develop intracranial hemorrhage from rupture of the fragile moyamoya collateral vessels. The other 50 % present with ischaemic strokes and epilepsy. The present study showed 8 out of 9 cases (88.9 %) presenting with recurrent ischaemic episodes while only one patient came with hemorrhagic stroke. Headache and cognitive dysfunction were noted in all the 9 patients and 5 patients had accompanied diminished vision. In the study by **Song P *et al* (2019) [11]** limb paresis, headache and impressive aphasia were the most common clinical syndromes, which accounted for 86.2%, 39.5% and 36.2% of the total patients. According to **Pineda Sánchez J *et al* (1999) [12]** the most common clinical symptoms of the disease include: sudden onset of hemiplegia, with sensation disturbances and aphasia. There may also appear headaches, vertigo, seizures and involuntary movements **[13]**.

Multiple enhancing punctate "dots" (CECT) or "flow voids" (MR) in the basal ganglia are the most striking findings in MMD, along with T1 and T2 scans showing markedly narrowed supraclinoid ICAs. The characteristic 'ivy sign' due to slow flow in leptomeningeal collaterals is seen on FLAIR. Angiographic findings include occlusion/stenosis of bilateral ICAs (Bottle neck sign), with the characteristic 'Puff of smoke' appearance of the moyamoya collaterals. Although DSA show predominantly anterior circulation disease, over 50% patients also have posterior circulation involvement. **[2, 14]**

In our study, MRA correctly detected occlusion or stenosis of all the major arteries such as ICA, MCA and ACA. However the degree of stenosis was overestimated in 42.8 % of the cases [Table 2]. As such the correct staging of MMD was done in 4 out of 9 cases by MRA. The study by **Yoon HK *et al* (2000) [15]** revealed that in 37 (73%) of 51 internal carotid arteries, the degree of stenoocclusive lesions was correctly depicted on MR angiography. In 14 hemispheres (27%), steno-occlusive lesions were overestimated compared with those on conventional angiography.

The staging system for moyamoya disease first described by **Suzuki and Takaku** in their seminal 1969 article1 is still in use today. Formally, the staging refers to findings on conventional angiography, although there are efforts to apply similar systems to MR angiography. **[16]**

The present study results showed the overall sensitivity of MRA for diagnosis and correct staging of Moyamoya disease were 77.8 % and 44.4 % respectively [Table 1 & 3]. **Yamada I *et al*. (1995) [17]** reported that MR angiography accurately depicted 217 (82%) of 264 arteries, but the degree of stenosis was overestimated in the other arteries. Basal cerebral moyamoya vessels were depicted in all 52 hemispheres with conventional angiography and in 42 (81%) hemispheres with MR angiography. The respective sensitivity and specificity for diagnosis of moyamoya disease were 73% and 100% for MR angiography. A previous study by **Cosottini M *et al* (2003) [18]** also found similar MRA sensitivity of 82 % for cerebral vessels.

MR Angiography and MRA Imaging were able to depict the basal cerebral moyamoya vessels in 13 (76.4 %) out of 17 hemispheres. **Yoon HK *et al* (2000) [15]** found that, in 33

hemispheres (65%), the degree of moyamoya vessels was correctly depicted on MR angiography.

Cerebral revascularization surgery is the treatment of choice. In adults ECA-MCA anastomosis [superficial temporal artery to middle cerebral artery (STA-MCA) bypass] and in children encephalo-duro-arterio-synangiosis has been performed with some success. **[2]**

Before modern angiographic examinations (such as CTA or MRA) were introduced to a wide clinical practice, the final diagnosis of the vascular changes was based on conventional angiography or digital subtraction angiography (DSA) **[19]** MR angiography is safer and easier to perform than conventional angiography. Conventional cerebral angiography is still considered necessary for a definite diagnosis although it has a risk of complication. Although MR angiography has a limitation in accurate preoperative staging, it may have a promising role for evaluating postoperative outcome. **[15]** Therefore, although now used less frequently than MRA and CTA, conventional cerebral angiography is the gold standard for the diagnosis of moyamoya disease.

CONCLUSION

DSA perfectly correlates with MRA in detecting occlusion or stenosis of ICA or other major arteries. However DSA is more sensitive in depicting the basal cerebral 'moyamoya vessels' than MRA. The performance of DSA in identification of stage of Moyamoya disease is also better compared to MRA. Hence DSA is more sensitive and accurate than MRA in evaluation and staging of Moyamoya disease.

Limitations

- ✓ Increased duration of the study would have rendered increase in sample size, thereby increasing the significance of the study.
- ✓ Only the patients who were referred to our department were included in the study, therefore high possibility of evaluating relatively complicated cases.
- ✓ Use of 3 Tesla MRI or more modern MR scanners with shorter scanning times, thinner sections, and volume-rendered image display would improve the image quality of MRA.
- ✓ The reason why overestimation of MMD Stage was done by MRA were not analyzed.
- ✓ The relationships between MMD stage, MRA score, MRA grades and moyamoya vessel scores were not analyzed.

Recommendations

- ✓ Use of 3 Tesla or more modern MR Scanners.
- ✓ Prospective studies with larger sample sizes should be performed.
- ✓ Application of improved settings like SPECT and Perfusion MR Imaging may help quantitative evaluation of haemodynamic disturbances of the cerebral circulation in the course of the moyamoya disease.

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