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Case Series

Aetiopathogenesis of ischemic stroke in rheumatoid arthritis: a case series study from tertiary care centre of South India

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ABSTRACT

Stroke is a major health concern worldwide. Published meta-analyses showed significant higher risk of ischemic and hemorrhagic stroke in patients with rheumatoid arthritis (RA) compared to the general population. Major etiopathogenesis of ischemic stroke in RA is non-atherosclerotic vasculopathy. Here the authors described varied aetiopathogensis of ischemic stroke in patients with RA which had been seldom reported in the literature. It was one of the first case series which threw light in this genre. Observational, prospective case series study was conducted over a period of one year. Amongst four cases presenting as an ischemic stroke with co-existing RA; each patient had a medium or small vessel vasculopathy, which had never been described earlier. Case 1 had cardio embolic source plus large vessel vasculopathy, case 2 had intracranial non-atherosclerosis vasculopathy; case 3 had secondary Moya-Moya disease; case 4 had both intracranial and extra cranial vasculopathy. Underlying aetiopathogensis of stroke in patients with RA can be attributed to insufficient cardiovascular treatment (well described in the literature) and vasculopathy of extracranial and intracranial vessels and secondary Moyamoya disease due to RA. Thorough evaluation is needed to prevent recurrence of stroke. The treatment strategy in these patients are immunotherapy apart from the conventional therapy with antiplatelet and statins.

Keywords: Stroke, Rheumatoid, Cerebral, Vasculitis, Aetiopathogensis, Immunotherapy

INTRODUCTION

Stroke is the second most common cause of mortality and major cause for disability across the world. The risk of stroke is increased among patients with RA.[1] The association between stroke and RA is not explored in various age groups.[1] This risk is higher in those with age ≤50 years, thus accounting for a fair percentage of stroke in young.[1] Literature shows that RA increases risk of ischemic and hemorrhagic stroke by 60 to 100% when compared to general population.[1] Systemic review showed that odds ratio for ischemic stroke in RA is 1.64 and for hemorrhagic stroke is 1.68 compared to general population.[1] Mechanism of ischemic stroke in RA is not well studied. Affection of medium and small cerebral vessels with an underlying vasculitis is considered cause of stroke in RA.[2] Rheumatoid vasculitis involving cerebral vasculature is very rare and depends on duration of RA and the higher titers of RA factor.[2] Cardiovascular complications like coronary artery disease has a higher incidence in patients with RA.[2] These patients thus form an important subset with a cardio embolic source of stroke.[2] Here we described a case series of patients diagnosed to have ischemic stroke and RA. TOAST classification was used for etiopathogenesis of ischemic stroke.[3]

CASE SERIES

We identified four patients who had RA with ischemic stroke. Age range of these cases was 36-55 years. Mean age was 46±7.87 years. Male to female ratio was 1:3. Table 1 shows the demography profile, clinical characteristics of the cases.

Case 1

55 year old lady, diagnosed as RA 5 years back and on disease modifying therapy, presented with acute onset right hemiplegia with global aphasia within a window period of 2.5 hours. At presentation patient had a cardiogenic shock. ECG showed atrial fibrillation. Other comorbidities were obesity, obstructive sleep apnea, hypertension and interstitial lung disease. NIHSS was 19. CT scan brain showed features of left MCA territory infarction. After improvement of blood pressure patient was thrombolysed with tenecteplase at dose of 0.25 mg/kg body weight. MRI brain showed large left MCA territory infarct and MRA showed non-visualization of left ICA and paucity of anterior circulation (Figure 1).

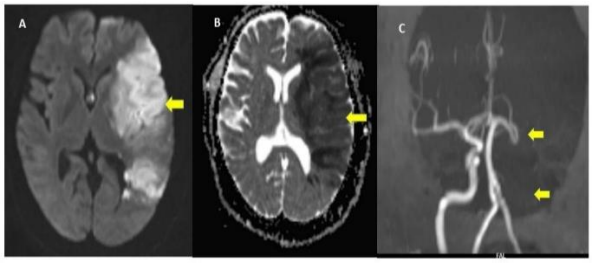

Figure 1: (Case 1) (A) showing diffuse restriction in left MCA territory as shown by yellow arrow, hyper intense in DW sequence; (B) hypointense on ADC; (C) images with left ICA not visualized as seen in MRA angiogram brain; features consistent with left MCA territorial infarct with extracranial ICA vasculopathy.

There was clinical improvement initially, eventually patient deteriorated secondary to aspiration pneumonia and sepsis. She succumbed on day 13 of hospital stay. Her labs showed dyslipidemia, 2D echo was suggestive of regional wall motion abnormality with left ventricular ejection fraction of 40%. This patient surprisingly had multiple risk factors (cardio-embolic, HTN, obesity and dyslipidemia) for stroke however, presence of vasculitis involving the large and medium vessels dictated a poor outcome. She qualified for an etiology corresponding to TOAST 5

Case 2

A 48 year old female with history of RA stopped disease modifying therapy for past 6 months presented with acute onset of dysarthria and weakness of left upper limbs of 2 days duration. She did not have any other comorbidities. NIHSS was 10 at baseline. MRI brain showed acute infarct in right MCA territory cortical branches (Figure 2 A and B). There was narrowing of right M3 and M4 branches of right MCA. Rest of the stroke work was negative. She was initiated on parenteral steroids, antiplatelet and disease modifying therapy. At 1 month follow up she recovered completely with MRS of 0. Attributing RA associated vasculitis as the etiology of stroke qualifying to being labeled as TOAST 4 in this patient. The other stroke work up was inconclusive as shown in Table 1.

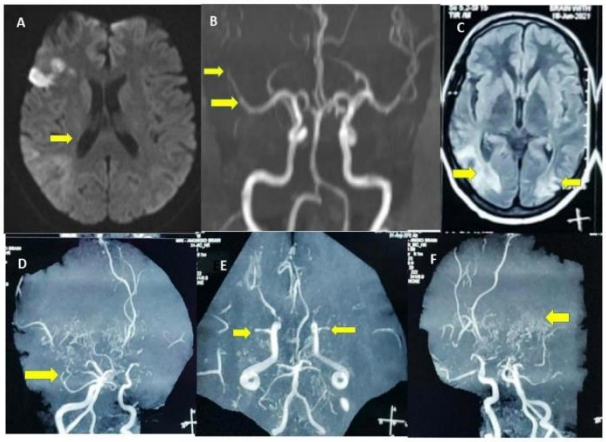

Figure 2: (Case 2) (A) showing diffusion restriction in right frontal region suggestive acute infarct with Right MCA M3 and M4 branches narrowed (B) marked by yellow arrow consistent with right MCA infarct and intracranial vasculopathy; (Case 3) (C) showing subacute to chronic bilateral parieto-occipital infarcts as seen in T2 flair sequence with absence of bilateral MCA, bilateral ACA and distal occlusion of bilateral ICA (E) with puff of smoke or collaterals distally noted as marked in (D) and (E) consistent with moyamoya features.

Case 3

36 year old man diagnosed as RA (RF strong positive with 4 years back not on immunomodulation therapy presented with visual symptoms of 2 weeks duration. He was extensively evaluated by the ophthalmologists, with no evidence of ophthalmological illness patient was advised MRI brain, which showed bilateral occipital infarcts. He was referred to our center after a significant delay of 3 months from the onset of the illness. He had high blood pressure and PRES (posterior reversible encephalopathy syndrome) secondary to hypertension was considered as a strong possibility. He had tobacco addiction as well. Rest of the blood work up for stroke was negative. He had prior history of polyarthralgias (involving small and large joints) not significant enough to impair his activities of daily living (ADL). Repeat MRI brain with angiogram done at our center showed chronic infarcts in the bilateral occipital region with puff of smoke appearance. Angiogram features were consistent with Moya-Moya disease [Figure 2 C-F]. Moya-Moya

secondary to RA associated chronic vasculitis, was the strongest possibility in this case.

Case 4

45 year old lady presented with left half sensory symptoms and ataxia of one day duration. She had a history of hypothyroidism. Examination showed left half ataxia with motor power of 4/5 MRC grade. NIHSS was 7. MRI brain showed acute infarct in right parietal region with stenosis of right MCA M3, M4 branches and right proximal ICA narrowing suggestive of focal inflammation (Figure 3). A possibility of vasculitis was considered as rest of the stroke work up was negative. Vessel wall imaging confirmed both intracranial and extracranial vasculitis. On questioning she revealed history of constitutional symptoms suggestive of RA since 2 years. RA factor and Anti CCP antibodies were strong positive. She was initiated on parenteral steroids, along with long term disease modifying therapy with methotrexate for RA in addition to antiplatelet. She recovered completely by 3 weeks. The etiopathogenseis of stroke in this patient was attributed to RA associated vasculitis qualifying to TOAST 4.

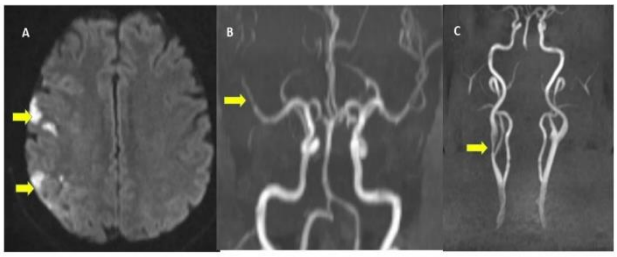

Figure 3: (Case 4) (A) showing acute infarct in right frontoparietal region in DW sequences; (B) with MRA showing intracranial vasculopathy involving right MCA M3 and M4 branches; (C) and MRA extracranial study showing right ICA narrowed suggestive of tandem lesion.

Table 1: Work up of stroke in study case series.

Cases	Age in years	Sex	Duration of rheumatoid arthritis	*DMT	Vascular risk factors	Habitual addiction	DLP	*CAD/AF (Echo)	Clinical presentation (baseline *NIHSS)	*TOAST subtypes
1	55	F	5 years	yes	Hypertension, *ILD, *OSA, Obesity	No	Yes	*AF/ RWMA/*LVEF 40%	Acute right hemiplegia with global aphasia NIHSS 19	TOAST 5 Undetermined aetiology (cardio-embolic source plus large extracranial vasculopathy)
2	48	F	8 years	No	Nil	No	No	No (normal Echo)	Left dysarthria clumsy hand syndrome NIHSS 10	TOAST 4 non atherosclerosis vasculoapthy involving intracranial vessels
3	36	M	4 years	No	Hypertension	Yes (tobacco smoking)	No	No (normal Echo)	Visual disturbances NIHSS 4	TOAST 4 Non atherosclerosis vasculopathy with secondary moya moya disease
4	45	F	Denova diagnosed constitutional symptoms since 2 years	No	Hypothyroidism	No	No	No (normal echo)	Left ataxic hemiparesis NIHSS 7	TOAST 4 Non atherosclerosis vasculopathy involving intracranial and extracranial vessel

*ILD: interstitial lung disease, OSA: obstructive sleep apnea, RWMA: regional wall movement abnormality, AF: atrial fibrillation, CAD: coronary artery disease, NIHSS: national institute of health stroke scale, DMT: disease modifying therapy, DLP: dyslipidemia, TOAST: trial of org 10172 in acute ischemic stroke treatment.

DISCUSSION

RA causes a wide range of neurologic abnormalities that includes atlantoaxial arthritis, subluxation and dislocation, acquired blocked vertebrae and cervical spine instability leading to compressive myelopathy and vertebrobasilar insufficiency.[4] Other neurological manifestation of RA are entrapment neuropathy mostly carpal tunnel syndrome (median nerve compression neuropathy), mononeuritis multiplex due to vasculitis leading to ischemia of nerve causing sensorimotor axonal neuropathy; polymyositis and rheumatoid nodules in central and peripheral nervous system, and rheumatoid meningitis.[4] Cerebral vasculitis in RA is a very rare complication.[5] Prevalence of cerebral vasculitis in RA ranges from 1% to 8%.[5] Cerebral vasculitis causes stroke and seizure.[5] Hence in addition to vasculitis in cerebral blood vessel, these patients can have cardiac manifestations of RA such as coronary vasculitis, arrhythmias, valvular heart diseases which can also lead to cardio embolic stroke.[5] This increased risk of stroke is independent of traditional risk factors such as age, sex, smoking and tobacco use, alcohol intake, hypertension, diabetes mellitus, obesity, obstructive sleep apnea, sedentary life style and dyslipidemia.[5] Pathogenesis of stroke in RA is attributed to shared inflammatory and immune mediators that affect the cerebral vasculature.[5] There is solidarity that a 1.5 multiplication factor is used when calculating cardiovascular disease risk predictor in patients with RA.[6] Hence cardio embolic stroke is one of the major risk factors of stroke in RA. In a nationwide COHORT study from Korea they found there was an increased association of ischemic stroke in patients with seropositive RA.[7] Their study suggested screening to improve outcomes in female, hypertension, non-diabetes, and non-dyslipidemia RA patients. In our case series, mean age of the cases were 46±7.87 years. Age range was between 36 years to 55 years. 75% cases were females. Among the cases included in the study, only one patient was on disease modifying therapy (methotrexate). Associated hypertension was found in two cases and dyslipidemia in one case. Mean baseline NIHSS was 10±6.4 with range of NIHSS between 4 to 19. We found that etiopathogenesis of stroke in majority of the cases was secondary to rheumatoid cerebral vasculitis (75%), rather than cardio embolic stroke. In our cases thorough evaluation including digital subtraction angiography (DSA) and vessel wall imaging (VWI) clinched the diagnosis of cerebral vasculitis in the patients with RA who presented with an ischemic stroke. Thus, in addition to conventional testing for a stroke in young, investigations viz DSA and VWI may contribute in identifying the etiopathogenesis of stroke to plan a treatment strategy. Since most of the stroke literature in RA was inclined towards cardio embolic source, this case series brought in a new dimension in the underlying etiology. Vasculitis in RA responsible for the strokes required additional disease modifying therapy in addition to antiplatelet agents and statins. Amongst the DMARDs most commonly used drug was methotrexate. DMARDs currently used for RA fall under four broad categories.[8] These include conventional synthetic DMARDs (methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine), tumor necrosis factor inhibitor biologics DMARDs (adalimumab, etanercept, infliximab, certolizumab pegol, and golimumab), non-tumor necrosis factor inhibitor biologics DMARDs (biologics targeting a different mechanism of action; abatacept, rituximab, anakinra, and tocilizumab) and targeted synthetic DMARDs (ts DMARDs) mainly the JAK inhibitors (tofacitinib, baricitinib, and upadacitinib).[8,9] In a North American clinical registry study comprising 8027 COHORTs of RA, it was observed that patients who initiated therapy with conventional synthetic DMARDs monotherapy had low disease activity when compared with those who were initiated with biologics.[10] It had been reported that patients with low disease activity had less chance of developing cerebral vasculitis. Glucocorticoids constituted an effective treatment for CNS rheumatoid vasculitis. Other treatment options such as cyclophosphamide, azathioprine, intravenous immunoglobulin, and rituximab were available for patients with corticosteroid resistant or refractory vasculitis. In our case series all our cases received parenteral glucocorticoids (30 mg/kg body weight for 5 days) along with conventional synthetic DMARDs (methotrexate). All cases responded well to parenteral steroids except one case who had cardiac risk factors and developed sepsis during the course of treatment. RA can have secondary Moya-Moya disease which had not been studied extensively. Treatment depends on type of stroke whether ischemic or hemorrhagic. In our case since it was an ischemic stroke, patient was put on aspirin 75 mg along with DMARD.

CONCLUSION

Knowledge of the etiopathogenesis of stroke in RA is very crucial for planning a treatment strategy of stroke. All RA cases with stroke need DMARDs along with standard therapy for secondary prevention of stroke with close monitoring of disease activity. Ours is the first case series which brings to light some of the fascinating observations which were never made earlier. RA vasculitis can also involve “large vessels” as described in two of our cases. Secondary Moya-Moya in RA may respond well to immunomodulatory therapy. Long term therapy depends on etiopathogenesis of stroke in these patients. Association of conventional risk factors in addition to RA have a bad prognosis compared to isolated RA. Present case series improves the understanding of etiopathogenesis of Ischemic stroke associated with RA and guides the clinicians to plan appropriate treatment strategies on a long run.

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