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Clinical evaluation of JAK2 V617F mutation in cerebrovascular accidents: a case series from a tertiary care centre

Dr Arppana Thomas[1], Dr Rajesh[2], Dr K Shaji Kumar[3], Dr Monica Moni[4], Dr Karthika Sunilkumar[5], Dr Vaishnavi Maharaj[6]

[1]*PG resident, Department of General Medicine, Travancore Medical College, Kollam, Kerala, India.*
[2]*Professor, Department of Neurology, Travancore Medical College, Kollam, Kerala, India.*
[3]*Assistant Professor, Department of General Medicine, Travancore Medical College, Kollam, Kerala, India.*
[4]*Junior Resident, Department of Neurology, Travancore Medical College, Kollam, Kerala, India.*
[5]*Junior Resident, Department of Neurology, Travancore Medical College, Kollam, Kerala, India.*
[6]*Junior Resident, Department of Cardiology, Travancore Medical College, Kollam, Kerala, India.*
Corresponding Author: Dr Rajesh

Abstract:

Background:

Ischemic stroke in young individuals and patients with recurrent stroke often remains unexplained despite comprehensive evaluation. Recent evidence suggests that Janus kinase 2 (JAK2) V617F mutation which is commonly associated with myeloproliferative neoplasms (MPNs) is known to carry a high risk of thrombotic events and has an underrecognized role in stroke pathogenesis, particularly in patients with hematological markers of hyper viscosity. Its role on association with arterial thrombosis, particularly ischemic stroke, has limited availability in literature. This study explores the clinical relevance of the JAK2 mutation in ischemic stroke patients.

Objective:

To do clinical evaluation of JAK2 V617F mutation in ischemic stroke patients with hematological indicators suggestive of myeloproliferative state and to assess its potential contribution to stroke pathogenesis without conventional causes.

Methods:

A retrospective study was conducted over a 3-year period (January 2022 -January 2025) at a tertiary care centre. Patients with ischemic stroke were screened for inclusion based on the following criteria: age <50 years (young stroke), recurrent stroke, absence of cardioembolic sources, and hematological abnormalities (Hb >16 g/dL or PCV >52%). Ninety-two patients met these criteria and underwent JAK2 V617F mutation testing by real-time PCR.

Results:

Out of 92 patients, 7 (7.6%) were found to be positive for the JAK2 V617F mutation. Out of which 5 positive cases were males and 2 were females with a mean age of 47.3 years. Recurrent stroke was seen 3 out of 7 patients and all had elevated hemoglobin and hematocrit values at the time of presentation. Splenomegaly was present in 57% patients based on imaging. None of the patients had been previously diagnosed with a hematological disorder, but the presence of JAK2 mutation suggested an underlying or evolving MPN in these cases. Stroke types involved both anterior and posterior circulations. Cytoreductive therapy (hydroxyurea, phlebotomy) was initiated in these patients following hematologic evaluation.

Conclusion:

The JAK2 mutation appears to be an under-recognized prothrombotic risk factor in ischemic stroke, especially among younger and recurrent cases with no clear etiology and with evidence of hyperviscosity. It has a potential role in recurrent stroke. Screening for JAK2 V617F mutation should be considered in patients with unexplained stroke and hematologic features suggestive of an underlying myeloproliferative disorder. Early diagnosis and targeted therapy will help to prevent recurrent thrombotic events.

Keywords: *Ischemic stroke, JAK2 V617F, Young stroke, Polycythemia, Myeloproliferative neoplasms, Recurrent stroke, Hyperviscosity syndrome.*

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I. Introduction

Ischemic stroke, remains one of the leading causes of morbidity and mortality worldwide [1]. While the majority of strokes are attributed to conventional risk factors such as hypertension, diabetes mellitus, atrial fibrillation, and atherosclerosis, a significant proportion particularly in young or recurrent cases remain unexplained after standard evaluation [2,3]. This has prompted increasing interest in determining involvement of prothrombotic and hematologic contributors to stroke pathogenesis. One such emerging factor is the Janus kinase 2 (JAK2) V617F mutation, a somatic point mutation most commonly associated with philadelphia chromosome-negative myeloproliferative neoplasms such as polycythemia vera, essential thrombocytosis, and primary myelofibrosis [4,5,6]. These haematological disorders are characterized by clonal proliferation of myeloid lineages, resulting in elevated red cell mass, leucocytosis, thrombocytosis and a tendency for thrombotic events. Its contribution to arterial thrombosis including ischemic stroke, is least explored. Emerging evidence suggests that the JAK2 V617F mutation may be found in stroke patients who have no prior history of hematological disease, especially in those presenting with elevated hemoglobin or hematocrit levels [7,8,9]. However, routine screening for JAK2 mutations in stroke patients is not currently a standard practice and the mutation often remains undetected unless clinical suspicion is high. Given these considerations, there is a growing recognition of the need to investigate JAK2 V617F mutation in patients with ischemic stroke of unknown origin, particularly in the presence of hematological abnormalities such as polycythemia or thrombocytosis. Understanding its clinical importance may lead to earlier diagnosis of MPNs and targeted management to reduce recurrence risk. This study aims to explore importance of JAK2 mutation among stroke patients who do not fit into conventional etiological categories but present with hematological signs suggestive of a hypercoagulable state. We hypothesize that JAK2 mutation is an underrecognized but important contributor to stroke pathogenesis in these individuals.

II. Materials and Methods

This is a single-centre, retrospective descriptive study conducted at a tertiary care hospital for a period of 3 years from January 2022 to December 2025.

Inclusion Criteria

Patients with ischemic stroke who met the following criteria were included:

- Age less than 50 years (young stroke)
- history of recurrent stroke
- Normal echocardiography and electrocardiography to exclude cardioembolic sources
- Hemoglobin >16 g/dL and/or PCV >52% at presentation

Exclusion Criteria

- Cardioembolic stroke confirmed by imaging or cardiac studies
- Diagnosed cerebral venous sinus thrombosis
- Patients with prothrombotic states

Data Collection

Patient demographics, clinical features, stroke subtype, imaging findings, and laboratory parameters including complete blood count, and spleen size were reviewed from medical records. Peripheral blood samples were analyzed for JAK2 V617F mutation using real-time polymerase chain reaction. All tests were conducted in an accredited molecular diagnostics laboratory.

III. Results

A total of 92 patients who fulfilled the inclusion criteria underwent JAK2 V617F testing. Of these, 7 patients (7.6%) tested positive for the mutation. Of the 7 patients, 5 were male and 2 were female, with a mean age of 47.3 years. Out of 7 patients 3 patients had recurrent ischemic strokes suggesting a strong association between JAK2 positivity and recurrence. All had elevated hemoglobin (>16.5 g/dL) and hematocrit (>52%). Four patients had splenomegaly on imaging. Clinical and Laboratory Profile of JAK2-Positive Stroke Patients are given in table 1. Stroke subtypes included Middle cerebral artery infarcts (n=2), Posterior cerebral artery infarct (n=1), brainstem stroke (n=1), Anterior cerebral artery infarct (n=1), and Transient ischemic attack (n=2). Imaging in JAK2-positive patients revealed various infarct patterns, involving MCA, PCA ACA territory (Figure 1). A comparative analysis between JAK2-positive (n=7) and JAK2-negative (n=85) patients was performed (Figure 4,5,6). Recurrent stroke was significantly more frequent in the JAK2-positive group.

Compared to the 85 JAK2-negative patients, who had a mean hemoglobin of 15.1 g/dL and PCV of 46%, the JAK2-positive group showed significantly higher hematologic values (Figure 2). Platelet counts were also higher in the JAK2-positive group, though not statistically significant. Splenomegaly was not seen in any of the JAK2-negative individuals. JAK2-positive patients also reported systemic symptoms preceding the stroke episode, including recurrent headaches, pruritus and early satiety which may serve as subtle early indicators of a myeloproliferative process. All JAK2-positive patients were initiated on secondary prevention including antiplatelets. After hematological evaluation, all were started on cytoreductive therapy (hydroxyurea or

phlebotomy), with normalization of hematologic parameters and no recurrence on short-term follow-up. None of the patients had major haemorrhagic complications during hospitalization. No further thrombotic events reported in those receiving cytoreductive therapy.

Table 1: Clinical and Laboratory Profile of JAK2-Positive Stroke Patients (n=7)

Patient number	Age (Years)	Sex	Risk Factors	Presentation	Hb(g/dl)	PCV (%)	Imaging	Diagnosis	Treatment
1	63	Male	Diabetes, Mitral stenosis, Hypertension	Dizziness	18.5	55	No acute changes	Transient ischemic attack	Hydroxyurea
2	38	Male	none	Left sided weakness	17.5	54	MCA infarct	Ischemic stroke	Hydroxyurea, Aspirin
3	45	Male	Hypertension	Blurring of vision	18	56	PCA infarct	Recurrent Stroke	Phlebotomy, Aspirin
4	37	Female	None	Recurrent TIA	17.2	52.3	MCA infarct	Recurrent Stoke	Hydroxyurea
5	48	Male	Diabetes	Slurring of speech	17.8	53.7	Brainstem infarct	Ischemic stoke	Hydroxyurea
6	43	Female	None	Right hemiparesis	18	54.2	ACA infarct	Recurrent stroke	Hydroxyurea Aspirin
7	41	Male	None	Headache, confusion	17.9	53	No acute changes	Transient ischemic attack	Hydroxyurea Aspirin

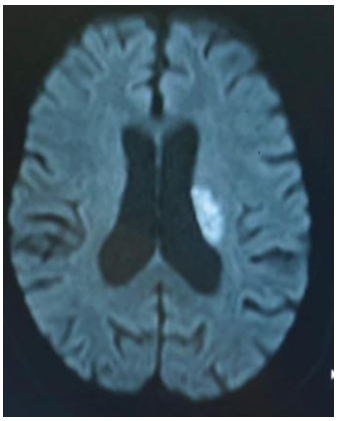

Figure 1: Cerebrovascular accident of left MCA territory

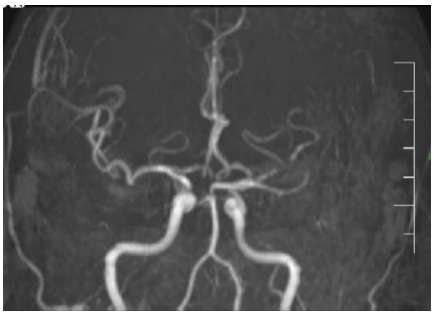

Figure 2: MRI angiogram showing occlusion of ICA

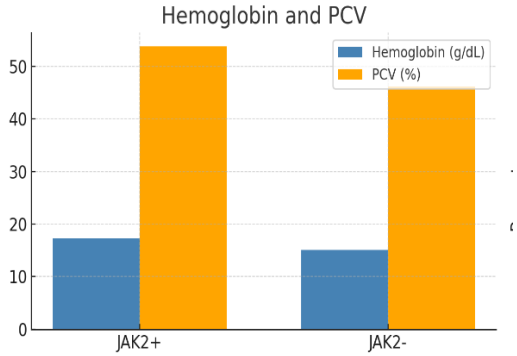

Figure 4: Comparative analysis of hemoglobin and PCV levels between JAK2-positive and JAK2-negative stroke patients.

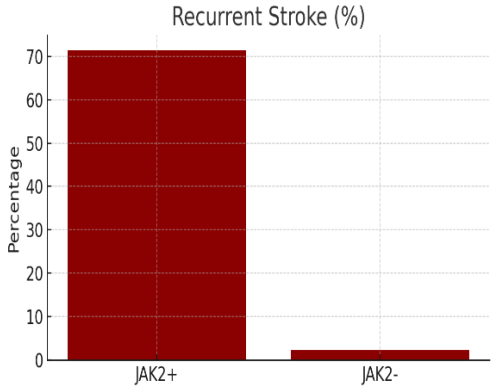

Figure 5: Comparative analysis of stroke recurrence between JAK2-positive and JAK2-negative patients.

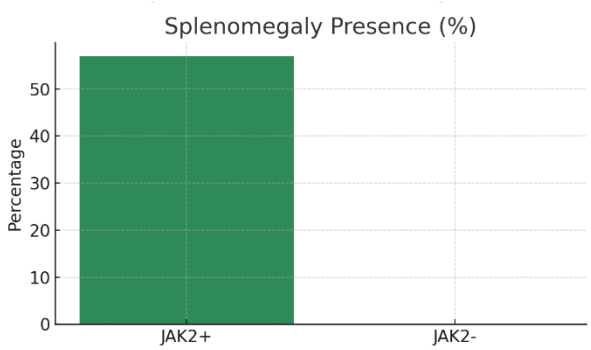

Figure 6: Comparative analysis splenomegaly between JAK2-positive and JAK2-negative stroke patients.

IV. Discussion

This case series highlights the clinical importance of screening for JAK2 V617F mutation in stroke patients of unknown etiology. 7 out of 92 patients with 7.6% mutation positivity rate in this group of stroke patients suggests a strong association with a prothrombotic myeloproliferative state. Our findings suggests that stroke may sometimes be the initial manifestation of an occult MPN. Elevated hemoglobin, PCV, and splenomegaly need evaluation of an underlying hematologic disorder, even in the absence of a MPN diagnosis. The association between JAK2 and ischemic stroke is explained by several mechanisms like increased blood viscosity, platelet, leukocyte activation and endothelial dysfunction, proinflammatory cytokines release [9,10,11]. Early identification of such patients needs hematological evaluation and need of cytoreductive therapy (hydroxyurea, phlebotomy) to reduce recurrent thrombotic risk [10,11]. Previous reports have shown similar patterns of stroke in patients later diagnosed with essential thrombocythemia or polycythemia vera [12,13,14]. These conditions may initially present with thrombotic events such as stroke, in the absence of overt hematologic symptoms [15,16]. Our findings are consistent with this observation, suggesting that routine hematological evaluation and JAK2 mutation testing in select stroke patients can uncover occult clonal disorders. Timely

identification of such patients is crucial, not only to explain the stroke etiology but also to initiate cytoreductive treatment and prevent future thrombotic events [17]. In our study, initiation of hydroxyurea and phlebotomy was associated with favourable outcomes, including stabilization of blood counts and absence of recurrent events on follow-up. Incorporating JAK2 mutation testing and basic hematologic screening can help detect underlying clonal disorders early, with significant implications for both treatment and prognosis.

Limitations

The study is limited due to its retrospective design and small sample size for mutation-positive group.

V. Conclusion

The JAK2 mutation appears to be an under-recognized prothrombotic risk factor in ischemic stroke, especially among younger and recurrent cases with no clear etiology and with evidence of hyper viscosity. It has a potential role in recurrent stroke. Screening for JAK2 V617F mutation should be considered in patients with unexplained stroke and hematologic features suggestive of an underlying myeloproliferative disorder. Early diagnosis and targeted therapy will help to prevent recurrent thrombotic events. Larger prospective studies are required to further clarify the pathophysiological and therapeutic implications.

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