

ETIOLOGICAL SPECTRUM OF ISCHEMIC STROKE IN YOUNG ADULTS AT A TERTIARY CARE CENTRE IN INDIA USING THE TOAST CLASSIFICATION

Prashant Dubey¹, Prachi Singh²

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Corresponding Author:

Dr. Prashant Dubey,

Email: drprashantdubey70@gmail.com

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¹Associate Professor Department of Medicine, Rohilkhand Medical College & Hospital, Bareilly, Uttar Pradesh, India

²Department of Obs & Gynae, Rohilkhand Medical College & Hospital, Bareilly, Uttar Pradesh, India

ABSTRACT

Background: The causes of ischemic stroke in young adults are more varied than those encountered in older patients. Their relative frequency also differs across populations because premature atherosclerosis, cardiac disease, non-atherosclerotic arteriopathy, thrombophilia, infection, pregnancy-related conditions, and inherited disorders have distinct geographic and demographic patterns. The objective is to describe the etiological distribution of imaging-confirmed ischemic stroke among patients aged 15–45 years treated at a tertiary care centre in India, using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. **Materials and Methods:** In this prospective observational study, 80 patients with arterial ischemic stroke were enrolled between July 2024 and July 2026. The standard assessment included clinical examination, cerebral and cervicocephalic vascular imaging, electrocardiography, echocardiography, Holter monitoring, and carotid Doppler ultrasonography. Autoimmune, cerebrospinal fluid, antiphospholipid antibody, thrombophilia, genetic, and catheter angiographic investigations were performed when indicated by the clinical or imaging phenotype. Stroke mechanism was assigned according to TOAST criteria. **Result:** The cohort included 48 men (60%). Other determined etiology was the largest TOAST category (28/80, 35%), followed by undetermined etiology (20/80, 25%), cardioembolism (10/80, 12.5%), large-artery atherosclerosis (9/80, 11.25%), small-vessel disease (8/80, 10%), and multiple possible etiologies (5/80, 6.25%). The other determined group comprised vasculitic and infection-associated strokes, arterial dissection, antiphospholipid antibody syndrome, systemic lupus erythematosus, malignancy, protein S deficiency, CADASIL, and moyamoya. Dyslipidemia (26/80, 32.5%), hyperhomocysteinemia (24/80, 30%), hypertension (20/80, 25%), cardiovascular disease (20/80, 25%), and diabetes (18/80, 22.5%) were common. **Conclusion:** The mechanisms of young-onset ischemic stroke in this cohort were diverse. Other determined causes accounted for more than one-third of cases, and one-quarter remained undetermined. A structured initial assessment followed by targeted vascular, cardiac, inflammatory, infectious, hematologic, and genetic testing is needed because the identified mechanism determines secondary prevention and may have implications for pregnancy counselling and family screening.

INTRODUCTION

Although stroke occurs less often in young adults than in older people, its personal and social effects can persist for decades. Survivors may experience recurrent vascular events, cognitive and psychiatric symptoms, epilepsy, long-term disability, and loss of employment. Recent analyses indicate that the worldwide number of strokes among people aged 15–49 years has increased, with a renewed rise in the age-standardized incidence of ischemic stroke in this age group.^[1,2]

Young-onset ischemic stroke has a wider differential diagnosis than stroke in later life. Hypertension, diabetes, dyslipidemia, obesity, smoking, and physical inactivity remain important, but dissection, non-atherosclerotic arteriopathy, cardiac embolism, autoimmune disease, prothrombotic states, pregnancy and puerperium, infection, malignancy, drug exposure, and monogenic disease account for a larger share of cases.^[3–6] The final etiological yield depends heavily on the scope and timing of the investigation.^[4]

In India, premature conventional vascular disease coexists with rheumatic heart disease, tuberculosis, systemic inflammation, and infection-related arteriopathy. Prospective Indian data that describe TOAST subtypes in young adults remain limited, and published estimates are affected by age definitions, referral patterns, access to advanced testing, and the classification method used.^[7–10] We therefore evaluated the etiological spectrum of imaging-confirmed ischemic stroke in patients aged 15–45 years, with particular attention to the composition of the other determined etiology category.

MATERIALS AND METHODS

Study design and setting: This prospective observational study was conducted in the Department of Medicine, Rohilkhand Medical College & Hospital, Bareilly, Uttar Pradesh, India, from July 2024 to July 2026.

Participants: Patients aged 18–45 years were eligible if they had an acute clinical stroke syndrome and an ischemic infarct confirmed by computed tomography or magnetic resonance imaging. Recruitment occurred through the emergency department, outpatient services, and medicine wards. We excluded patients whose neurological presentation was explained by head injury, an intracranial space-occupying lesion, subdural or epidural hematoma, demyelination, encephalopathy, or a major metabolic disturbance.

Clinical and etiological assessment: A structured history and general and neurological examination were completed for each participant. Recorded variables included conventional vascular risk factors, cardiovascular disease, previous transient ischemic attack or stroke, migraine, hormone exposure, pregnancy or puerperium, recent infection, malignancy, illicit drug use, and family history. All participants underwent baseline biochemical testing. The core investigation comprised 12-lead electrocardiography, transthoracic echocardiography, Holter monitoring, carotid Doppler ultrasonography, CT and/or MRI of the

brain, and CT or MR angiography from the aortic arch through the intracranial circulation. Further testing was guided by the clinical and radiological phenotype and included antinuclear antibodies by immunofluorescence, antineutrophil cytoplasmic antibodies, cerebrospinal fluid analysis, antiphospholipid antibodies, an extended thrombophilia panel, next-generation sequencing, and digital subtraction angiography. Etiology was classified using TOAST criteria.^[11] Undetermined cases were divided into extensive negative evaluation and incomplete evaluation; cases with more than one credible mechanism were classified separately.

Statistical analysis: Continuous data are presented as mean and standard deviation, and categorical data as number and percentage. The analysis was descriptive because of the modest cohort size.

Ethics: All participants provided written informed consent, and the institutional ethics committee approved the study.

RESULTS

Participant characteristics and vascular risk profile: The study enrolled 80 patients: 48 men (60%) and 32 women (40%), for a male-to-female ratio of 1.5:1. Twenty-eight patients (35%) were aged 15–30 years and 52 (65%) were aged 31–45 years. Motor weakness was the commonest presenting feature (54/80, 67.5%), followed by headache (24/80, 30%), cognitive symptoms (15/80, 18.8%), and seizures (8/80, 10%).

Eight patients (10%) had no recognized risk factor. Dyslipidemia was present in 26 (32.5%), hyperhomocysteinemia in 24 (30%), hypertension and cardiovascular disease in 20 (25%) each, diabetes in 18 (22.5%), cigarette smoking and obesity in 17 (21.25%) each, and heavy alcohol use in 16 (20%). Nineteen patients (23.75%) had a family history of stroke, 10 (12.5%) had a previous stroke, and nine (11.25%) had a history of transient ischemic attack. Hormonal exposure was recorded in five patients, and three were pregnant or postpartum.

Table 1: Selected demographic and vascular risk characteristics

Characteristic	n/N	Percent
Male sex	48/80	60
Age 15–30 years	28/80	35
Age 31–45 years	52/80	65
Dyslipidemia	26/80	32.5
Hyperhomocysteinemia	24/80	30
Hypertension	20/80	25
Cardiovascular disease	20/80	25
Diabetes mellitus	18/80	22.5
Cigarette smoking	17/80	21.25
Obesity	17/80	21.25
Heavy alcohol use	16/80	20
Recent infection	10/80	12.5
Prior stroke	10/80	12.5
History of transient ischemic attack	9/80	11.25
Migraine	8/80	10
Oral contraceptive or hormone exposure	5/80	6.25
Pregnant or postpartum	3/80	3.75

Etiological classification: Other determined etiology was the most frequent TOAST category (28/80, 35%). Twenty patients (25%) had an undetermined mechanism, including 17 after extensive investigation and three after an incomplete evaluation. Cardioembolism accounted for 10 cases

(12.5%), large-artery atherosclerosis for nine (11.25%), small-vessel disease for eight (10%), and multiple possible etiologies for five (6.25%). Other determined causes occurred in 12 of 28 patients aged 15–30 years and 16 of 52 patients aged 31–45 years.

Table 2: Etiology according to the TOAST framework

Etiological category	Total n (%)	Age 15–30 n	Age 31–45 n
Large-artery atherosclerosis	9 (11.25)	3	6
Cardioembolism	10 (12.5)	6	4
Small-vessel disease	8(10)	1	7
Other determined etiology	28 (35)	12	16
Multiple possible etiologies	5 (6.25)	1	4
Undetermined after extensive evaluation	17 (21.25)	3	14
Undetermined after incomplete evaluation	3 (3.75)	2	1
Total	80 (100)	28	52

TOAST, Trial of Org 10172 in Acute Stroke Treatment.

Composition of other determined etiology: The other determined etiology category included 10 vasculitic strokes (seven primary central nervous system vasculitis and three granulomatosis with polyangiitis) and eight infection-associated strokes (six tuberculous meningitis and two rhino-orbital

mucormycosis). Two cases each were attributed to cervical or intracranial artery dissection, antiphospholipid antibody syndrome, and systemic lupus erythematosus. Active ovarian malignancy, protein S deficiency, NOTCH3-positive CADASIL, and moyamoya accounted for one case each.

Table 3: Reported causes within other determined etiology

Reported cause	n	Clinical detail
Vasculitis	10	Seven primary CNS vasculitis; Three granulomatosis with polyangiitis
Infection-associated stroke	8	Six tuberculous meningitis; two rhino-orbital mucormycosis
Cervical or intracranial artery dissection	2	One vertebral; one carotid
Antiphospholipid antibody syndrome	2	Pregnancy noted in source table
Systemic lupus erythematosus	2	Young women
Active malignancy	1	Ovarian cancer
Thrombophilia	1	Protein S deficiency
Monogenic arteriopathy	1	CADASIL; NOTCH3 positive
Moyamoya	1	No additional detail reported

DISCUSSION

Principal findings: This cohort illustrates the etiological breadth of ischemic stroke between 18 and 45 years of age. Other determined causes comprised 35% of cases and included inflammatory, infectious, vascular, hematologic, malignant, and monogenic disorders. These diagnoses often require treatment beyond routine antiplatelet therapy and risk-factor modification. Conventional mechanisms nevertheless remained prominent: large-artery atherosclerosis, cardioembolism, and small-vessel disease together accounted for 33.75% of the cohort, and metabolic and behavioral risk factors were frequent. Evaluation of young stroke should therefore examine unusual causes without overlooking premature conventional vascular disease.

Comparison with other young-stroke cohorts: The reported distribution of young-stroke mechanisms varies considerably between studies. In the Helsinki Young Stroke Registry, age and the extent of diagnostic investigation influenced the etiological pattern among 1,008 patients aged 15–49 years.^[12] A prospective multicentre Asian study likewise found that conventional risk factors were frequent but that etiological proportions differed across participating

cities.^[13] In a North Indian tertiary-care series, undetermined stroke was the largest group, followed by cardioembolism and large-artery atherosclerosis.^[8] Differences in referral pathways, population characteristics, infection and rheumatic disease burden, vascular imaging, rhythm monitoring, and diagnostic thresholds probably account for much of this variation.

One-quarter of the present cohort remained etiologically undetermined: 17 patients after extensive investigation and three after an incomplete assessment. This proportion is compatible with the broad range reported in young-adult cohorts.^[3–5,12] A diagnosis of cryptogenic stroke should be distinguished from embolic stroke of undetermined source and from a case that has not been fully investigated. Selected patients may benefit from prolonged rhythm monitoring, transesophageal or contrast echocardiography, repeat vascular imaging, and reassessment of autoimmune or prothrombotic markers after the acute phase.^[4,14,15]

Other determined causes and regional relevance: Vasculitis was the largest subgroup among other determined causes, but this result warrants caution. Primary angiitis of the central nervous system is uncommon and has no single definitive non-invasive

test. Infection-related vasculopathy, reversible cerebral vasoconstriction syndrome, intracranial atherosclerosis, dissection, and systemic inflammatory disease can produce similar findings. Diagnostic confidence rests on the clinical course, cerebrospinal fluid results, vascular imaging, vessel-wall imaging where available, systemic assessment, and occasionally tissue biopsy.^[16] The cases of granulomatosis with polyangiitis also emphasize the need to distinguish primary central nervous system disease from secondary systemic vasculitis.

The infection-associated strokes reflect causes of particular relevance in India. Tuberculous meningitis can produce basal inflammatory exudates with perforator or territorial infarction. Rhino-orbital mucormycosis may reach the cavernous sinus and intracranial arteries, causing thrombosis, arteritis, or embolic infarction.^[17,18]

Two patients had arterial dissection. Cervical artery dissection is a recognized cause of ischemic stroke in younger adults; headache, neck pain, partial Horner syndrome, cranial neuropathy, or posterior circulation symptoms should prompt dedicated vascular imaging.^[19] The CADASIL and moyamoya cases demonstrate the value of targeted genetic and angiographic assessment. Migraine with aura, a compatible family history, early psychiatric or cognitive symptoms, recurrent lacunar events, and characteristic anterior temporal or external capsule MRI lesions support NOTCH3 testing, whereas progressive terminal internal carotid stenosis with basal collaterals suggests moyamoya angiopathy.^[20,21]

Cardioembolism and conventional vascular mechanisms: Cardioembolism accounted for 12.5% of cases. The underlying source dataset identifies rheumatic heart disease as an important substrate, consistent with its continuing relevance in India. Assessment in young patients should consider valvular disease, cardiomyopathy, intracardiac thrombus or tumour, endocarditis, arrhythmia, and patent foramen ovale (PFO). A PFO should not be labelled causal solely because it is present. Infarct pattern, shunt size, atrial septal aneurysm, competing mechanisms, and validated attribution tools should inform closure decisions.^[14,22]

Large-artery atherosclerosis and small-vessel disease accounted for 21.25% of the cohort. Dyslipidemia, hypertension, diabetes, smoking, obesity, and heavy alcohol use were common. Global estimates through 2021 identify high systolic blood pressure as the leading contributor to stroke-related disability in young adults, with important contributions from high body mass index, fasting glucose, and low-density lipoprotein cholesterol.^[2] A recent young-stroke review similarly describes increasing exposure to both established and emerging risk factors.^[1] Etiological investigation should therefore proceed alongside evidence-based control of blood pressure, lipids, glucose, tobacco exposure, diet, physical inactivity, and obesity.

Clinical implications: The findings support a staged diagnostic approach. Initial assessment should include brain and cervicocephalic vascular imaging, electrocardiography, appropriately selected echocardiography, and systematic measurement of conventional vascular risk. Further tests—prolonged rhythm monitoring, transesophageal echocardiography, contrast shunt studies, thrombophilia testing, autoimmune serology, cerebrospinal fluid examination, vessel-wall imaging, catheter angiography, metabolic assays, or genetic analysis—should be chosen according to the patient's age, sex, family history, infarct pattern, vascular phenotype, systemic features, pregnancy status, exposures, and initial results.^[4,6,14] Indiscriminate panels increase false-positive findings, whereas prematurely stopping the investigation may miss a treatable mechanism. Classification should be reconsidered when follow-up imaging, repeat laboratory testing, or new clinical information becomes available.

Strengths and limitations: The study benefited from prospective enrollment, inclusion of imaging-confirmed ischemic stroke, multimodal vascular and cardiac assessment, and detailed reporting of uncommon mechanisms. Its principal limitations are the small sample, single-centre tertiary referral setting, and resulting spectrum bias toward diagnostically complex inflammatory, infectious, and genetic disease. Specialized investigations were phenotype-directed rather than uniform.

CONCLUSION

Young-onset ischemic stroke in this tertiary-care cohort arose from a wide range of mechanisms. Other determined etiologies formed the largest category, while cardioembolism and premature conventional vascular disease also made substantial contributions; one-quarter of cases remained undetermined. A consistent first-line vascular and cardiac assessment, followed by targeted inflammatory, infectious, hematologic, and genetic investigation, offers the best balance between diagnostic yield and false-positive testing. Establishing the mechanism is clinically important because it guides antithrombotic therapy, immunotherapy or antimicrobial treatment, revascularization, pregnancy counselling, family screening, and long-term prevention.

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