Stroke in young adults

Five new things

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Abstract

Purpose of review

The incidence of stroke in young adults is increasing, mainly driven by an increasing incidence of ischemic stroke in this population. We provide new information that has been recently presented regarding the risk factor prevalence, some specific etiologic causes, and management strategies in ischemic stroke in this population.

Recent findings

Recent studies indicate a rapid increase in traditional risk factors in young adults. New information regarding the management of patent foramen ovale in cryptogenic stroke and cervical artery dissection is available.

Summary

Stroke in young adults is a rapidly growing problem with deep public health implications. There are many areas in this field, which require further research.

The incidence of stroke in the United States among patients aged >65 years has decreased over the past couple of decades.¹ However, population-based studies have shown an increasing incidence of ischemic strokes in young adults.² Similarly, studies based on national inpatient sample data showed a rapid increase in the rates of ischemic stroke hospitalizations among individuals aged 25–44 years as opposed to a declining rate for that in older patients.^{3,4} This increase has mainly been attributed to the increase in the incidence of ischemic stroke, in contrast to a stable incidence of intracerebral hemorrhage and subarachnoid hemorrhage. Stroke in young adults comprises approximately 10%–12% of total stroke patients.⁵

In a multicenter European study, women outnumbered men in the age group <35 years, whereas men outnumbered women in the age group between 35 and 50 years.⁶ The Greater Cincinnati/Northern Kentucky stroke study showed a relative risk of 5 for all strokes reported in blacks as compared to whites within the 35–44-year age group and RR of 2.2 for in <34-year age group.² This review will highlight recent insights into changes in stroke incidence and outcomes, along with management of specific etiologies of stroke in young adults.

Risk factors

Several studies have documented an alarming increase in both risk factors and stroke rates in young adults. George et al.⁷ used the Nationwide Inpatient Sample from 2003 through 2012 to identify the prevalence of cardiovascular risk factors among adults aged 18–64 years hospitalized with diagnosis of acute stroke. This study reported an increasing prevalence of

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traditional cardiovascular risk factors across all age groups and both sexes through the studied period. Moreover, the prevalence of 3 or more traditional risk factors nearly doubled among young adults, more so as compared to the older population with stroke. Rates of prevalence of some of these risk factors are shown in table 1.

Other modifiable risk factors

Substance abuse, particularly cocaine abuse is an important risk factor in stroke in young adults. In a large population-based study, cocaine use was independently associated with a 5.7-fold increase in the odds of having an ischemic stroke in the young adults.⁸ Furthermore, de los Rios et al.⁹ found an increasing incidence of cocaine abuse as a cause of stroke among the 35–54-year-old patients with stroke. These observations make a strong case for aggressive community-based counseling regarding increasing cocaine abuse and the risk of stroke.

In one of the earliest studies reflecting the cardiovascular effects exerted by cannabis, Mittleman et al.¹⁰ reported a nearly 5-fold increased risk of myocardial infarction within an hour of consuming cannabis. Several mechanisms by which cannabis exerts its negative cardiovascular effects have been hypothesized in case reports.¹¹ These include orthostatic hypotension, cardiac arrhythmias, and intimal

hyperplasia. In addition, a prospective study of 48 young patients with ischemic stroke showed a strong temporal association of cannabis consumption and reversible cerebral vasoconstriction syndrome.¹² An Australian cohort of young patients with stroke showed that the cannabis users had 2.3-fold higher risk of developing ischemic stroke even when adjusted for all other covariates including tobacco use.¹³ Similarly, a population-based study used the US nationwide inpatient sample and demonstrated that smoking cannabis was independently associated with the occurrence of stroke. The mean age at stroke was 33.1 years.¹⁴ In contrast, a Swedish study failed to identify this independent relationship among young adults.¹⁵ With the societal drift for increased cannabis legalization for medical and recreational use, its use may not be as harmless as otherwise thought of, and more research is needed to explore the potential relationship between cannabis use and stroke.

Patent foramen ovale and cryptogenic stroke in the young

Patent foramen ovale (PFO) is observed in approximately 25% of population. In 1988, Lechat et al.¹⁶ called attention to the association of PFO with stroke. Evidence from earlier studies comparing closure of PFO with medical therapy failed to show reduction in recurrent stroke. Some of the criticisms of these studies were inappropriate selection of patients including the ones who probably did not have a stroke secondary to a paradoxical embolism and type and morphology of the PFO itself causing an insignificant right-to-left shunt. Kent et al.¹⁷ designed a score that can predict the likelihood of a cryptogenic stroke related to a paradoxical embolism (risk of paradoxical embolism score). Recently

Table 1 Rates of prevalence of vascular risk factors, (%)

Demographic	Age 18–34 y		Age 35–44 y		Age 45–54 y	
	2003–2004	2011–2012	2003–2004	2011–2012	2003–2004	2011–2012
Male						
HTN	34	41.3	54.5	65.9	69.7	76.3
HLD	14.6	29.1	29	47.8	34.6	54.7
Tobacco use	23.1	35.7	31.3	41.7	32.5	47.3
Obesity	6.8	13.3	7.7	15.2	6.1	11.7
Female						
HTN	26.1	30.7	50.1	57.3	69.8	73.7
HLD	9.6	21.7	20.8	37.8	32.4	50.9
Tobacco use	21.1	26.5	26.9	35.8	27.4	43.5
Obesity	9.1	15.7	10.9	21	9.9	17

Abbreviations: HLD = hyperlipidemia; HTN = hypertension.

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published randomized clinical trials point to a modest benefit of closing PFO in preventing recurrent stroke.^{18–20} A summary of key features of these trials is shown in table 2.

To summarize, the results of these trials are in keeping with the previous meta-analysis that showed that the rate of recurrent cryptogenic stroke from a paradoxical embolism via a PFO was as low as ~1% a year.²¹ Percutaneous closure in addition to medical therapy in very carefully selected patients (risk of paradoxical embolism score >7) with distinctive

morphological features of the PFO (large interatrial shunt and/or the presence of atrial septal aneurysm) reduces this risk to a modest degree. Recently, a randomized clinical trial conducted at 2 Korean centers was published. In this study, the investigators randomized patients with a history of stroke and a high risk of PFO based on the size and presence of atrial septal aneurysm into medical therapy or medical therapy in addition to catheter-based PFO closure. Patients in the closure group had better outcomes than those in the medically treated group.²² Nonetheless, the number of procedures required to prevent 1 stroke is relatively high. In addition, the published trials do not provide sufficient information to determine whether an alternate cause of stroke (e.g., atrial fibrillation) was the likely etiology of recurrent events. These trials suggest that compared with other available devices, the Amplatzer device is a safer closure device mainly in terms of periprocedural atrial fibrillation. More research is required to answer this question.

Table 2 Key features of recently published randomized controlled trials on management of cryptogenic stroke due to a PFO

	Close—PFO	Reduce	Respect
Inclusion criteria	a. Age 16–60 y b. Cryptogenic stroke within 6 mo with specific characteristics as below	a. Age 18–59 y b. Cryptogenic stroke within 6 mo	a. Age 18–60 y b. Cryptogenic stroke within 270 d
Identification of cryptogenic stroke	Standard stroke workup including a negative 24-h Holter monitoring	Standard stroke workup, 24-h Holter monitoring not required.	Standard stroke workup, 24-h Holter monitoring not required.
Morphologic characteristics of PFO	One of the following criteria should be met: a. Presence of a large shunt (>30 microbubbles) b. Presence of an ASA	Shunt size characterized as follows: a. Small: 1–5 microbubbles b. Moderate: 6–25 microbubbles c. Large: >25 microbubbles	Shunt size characterized as follows: a. Grade 1: 1–9 microbubbles b. Grade 2: 10–20 microbubbles c. Grade 3: >20 microbubbles
Mean RoPE score	>7 across all groups	Not available	Not available
Presence of a large shunt in closure group	66%	42.8%	49.5%
Presence of an ASA in the closure group	33%	20%	36%
Follow-up	Mean 5.3 ± 2 y	Median 3.2 y	Median 5.9 y
Primary outcome	Recurrent ischemic stroke	a. Freedom from recurrent ischemic stroke through at least 24 mo b. Presence of a new ischemic stroke including silent brain infarctions.	Composite end point of the following: a. Recurrent ischemic stroke b. Early death
Type of device used	Several devices used, more than half were Amplatzer device	Helex Septal Occluder or Cardioform Septal Occluder	Only Amplatzer septal occluder used
Main results	20 patients need to be treated to prevent 1 stroke over 5 y	28 patients need to be treated to prevent 1 stroke over 2 y	42 patients need to be treated to prevent 1 stroke over 5 y
Rate of atrial fibrillation in the treatment group	4.6%	6.6%	0.2%

Abbreviations: ASA = Atrial septal aneurysm; PFO = patent foramen ovale; RoPE = Risk of Paradoxical Embolism.

Cervical artery dissection

Cervical artery dissection (CAD) is an important etiology of stroke in young adults. For the purposes of this review, we will limit our discussion to spontaneous CAD (sCAD) and exclude traumatic causes.

The incidence of sCAD in Northern American population-based studies has been estimated to be around 2.6 (95% CI 1.9–3.3) per 100,000 inhabitants per year. Although it is a less common cause of stroke, in general, comprising approximately 2% of all cases, sCAD remains a leading factor in ischemic strokes in the young adult population.²³

Intimal tear can lead to a thrombus formation, which can potentially lead up to an artery-to-artery embolism. This phenomenon has been proposed in a large retrospective imaging-based study and forms the mechanistic basis for the theoretical benefit of early anticoagulation in CAD.²⁴ However, observational studies about the efficacy of anticoagulation have yielded conflicting results.²⁵ A meta-analysis of studies testing anticoagulation vs antiplatelet therapy did not show any difference in the rate of stroke recurrence between the 2 treatments,²⁶ and the American Heart Association/American Stroke Association (AHA/ASA) guidelines do not recommend the use of one over the other.²⁷

The Cervical Artery Dissection in Stroke Study²⁸ was a pragmatic multicenter randomized pilot trial that aimed at comparing the efficacy of anticoagulation with antiplatelet therapy in extracranial CAD. It was mainly meant to accurately characterize the incidence of recurrent stroke in this disease. This trial showed that the risk of recurrence of stroke after extracranial CAD, although small (~1%), was the highest in the first 10 days of event. Moreover, there remains a considerable amount of diagnostic challenge in detecting a CAD with approximately 20% of the patients found not to have CAD during the central imaging review. One of the criticisms of this trial is that because it enrolled patients up to 1 week of their initial stroke, some of these patients who had a recurrent stroke within this period may have been missed in the analysis of the primary outcome. Nonetheless, this trial had very slow recruitment and indicated that nearly 10,000 patients needed to be studied to detect a ~1% difference between the 2 treatment modalities. Because this remains the only randomized controlled trial testing antiplatelet therapy vs anticoagulation for CAD, the AHA/ASA guidelines cite their results to recommend a short-term therapy with either anticoagulation or antiplatelet therapy as a reasonable approach in these patients.²⁹ Thus, there is no high-quality data to support the use of anticoagulants in patients with cervical dissection.

Genetic causes of stroke

Several monogenic disorders increasing the risk of stroke in the young have been identified. A prospective screening study of 721 young patients with cryptogenic strokes

reported that 4.9% of males and 2.9% of females had Fabry disease. Based on this information, the investigators concluded that approximately 1.2% of all stroke patients in this age group may have Fabry disease and that it should be considered in all young stroke patients with an unexplained stroke.³⁰ North American population-based studies have also shown a similar rate of prevalence of Fabry disease.³¹ Furthermore, the strokes associated with Fabry disease have been shown to have low severity and low rate of recurrence in these studies.

Lombardia GENS was a multicenter prospective study aimed at diagnosing 5 monogenic disorders associated with stroke (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; Fabry disease; mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; hereditary cerebral amyloid angiopathy; and Marfan syndrome).³² Although this study included a large number of patients of all ages, it provides some vital information about the importance of considering phenotypic variations when evaluating genetic causes of stroke. Of more than 11,000 patients with stroke, this study included the patients who had a high probability of having a monogenic disorder based on clinical features such as age <55 years at onset, presence of <3 cardiovascular risk factors, family history, or at least 2 neurologic or systemic features of a genetic disorder in the absence of any other known specific causes according to the TOAST criteria. Among these patients, algorithms for the 5 monogenic diseases were applied and those fulfilling the criteria for that disease (suspected) were tested for that specific disease. With the use of this phenotype-based algorithm, their study diagnosed these genetic conditions in ~7% of patients. They also found that the algorithm had the highest efficacy in diagnosing patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Furthermore, the presence of family history was a key feature in predicting the presence of an underlying monogenic disorder when stroke in the absence of cardiovascular disease was not.³² Thus, this study calls for a narrower phenotype-based preclinical genetic screening strategy in the diagnosis of cryptogenic stroke in the young.

To summarize, although several monogenic factors that increase the risk of stroke in the young have been identified, screening for these conditions on a routine basis has been found to be low yield. The AHA/ASA guidelines do not recommend screening for genetic risk factors on a routine basis.³³

Long-term risks after stroke in the young

A Dutch study showed that the risk of mortality is 4-fold higher in younger patients who have stroke compared with matched patients who did not have a stroke. The cumulative risk of mortality at 10 years in young adults with strokes is approximately 10 times higher than the individuals of the same age in the general population.³⁴ The rate of mortality is

STROKE IN YOUNG ADULTS: 5 NEW THINGS

1. The incidence of stroke in young adults is on the rise. This is mainly driven by the increasing rate of incidence of ischemic stroke (IS) in this population. An alarming increase in traditional risk factors and substance abuse among young population contributes to the increasing incidence of IS in the young.
2. Patent foramen ovale contributes to a small number of cryptogenic strokes in young adults and is associated with a low risk of recurrence (1%). Careful selection of these patients for closure therapy may modestly reduce this risk.
3. Cervical artery dissection is an important etiology of IS in young adults associated with a low risk of recurrence, mainly early in the course. Short-term therapy with antiplatelets or anticoagulants is reasonable; however, there is no high-quality data to justify the use of anticoagulants over antiplatelet therapy.
4. The presence of family history of strokes should prompt a screening for genetic diseases in young patients with stroke.
5. Stroke in young adults is associated with a high mortality and deep public health implications due to a considerable loss of productive years of life.

even higher in young adults who have had recurrent strokes.³⁵

A large Italian cohort study found that the risk of recurrence of vascular events among young survivors of stroke is closely associated with age-specific modifiable risk factors such as migraine with aura, presence of antiphospholipid antibody, discontinuation of 1 medication at discharge after stroke, and presence of 1 vascular risk factor.³⁶ Cardiovascular disease is the main cause of this excess mortality and so strict control of secondary risk factors in these patients is critical.

Furthermore, a large retrospective response-based study showed that more than half the patients are unable to return to work after a stroke.³⁷ Because most of the young patients are of vocational age, inability to return to employment constitutes serious disability.

The risk of post-stroke depression is the highest in the first few months after stroke.³⁸ Although most of the population-based studies have described a higher risk of post-stroke depression in the elderly, it remains an important problem that can remain under-recognized in young stroke survivors and has long-term implications. Results of a European cohort

study showed that depression may be related to mortality in young adults with stroke.³⁹ Other factors that may go unrecognized and further contribute to poor outcome are sexual dysfunction, fatigue, post-stroke pain, and cognitive deficits and should be adequately addressed. Thus, stroke in the young is a growing problem with deep public health implications.

Author contributions

N. Bhatt: drafting/revising the manuscript. A.M. Malik: drafting/revising the manuscript and study supervision. S. Chaturvedi: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, and study supervision.

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