International Journal of Emergency Medicine

REVIEW

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Current understanding of stroke and stroke mimics in adolescents and young adults: a narrative review

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Abstract

Background Stroke in adolescents and young adults are uncommon, and unlike in older adults, the etiology can be a challenging puzzle to solve. Patients often lack traditional risk factors such as hypertension or may be too young for suspected atherosclerotic disease. Additionally, among this group, various stroke mimics exist that can cloud physician judgment, leading to under- or overtreatment.

Aim There is a significant gap in the current literature and clinical evidence regarding stroke in this population. This review of the literature aims to extract important information surrounding the etiology, risk factors, diagnosis, management, and complications of stroke in younger people and address stroke mimics and how they can appear similar and different from ischemic or hemorrhagic stroke. Additionally, we discuss the importance of furthering research in this specific population in all areas due to a concerning rise in stroke frequency and unique associated disabilities.

Conclusion The acute treatment of stroke in young patients is similar to older adults. While stroke mimics may complicate suspicion and cause hesitance, delays in stroke care should be avoided. There remains a need for research in the areas of diagnosis, management, and assessment of long-term care and challenges in this population of patients.

Keywords Stroke, Stroke-mimic, Adolescent stroke, Pediatric stroke, Young-adult stroke

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Introduction

Stroke in adolescents and young adults (AYA) is becoming a growing public health concern. Stroke ranks second among the most common causes of mortality worldwide, and an estimated 11 million stroke cases are diagnosed annually; among them, nearly a quarter of cases are reported to occur between the ages of 18 and 50 years [1, 2]. Recent studies have suggested an increase in stroke frequency between the ages of 15 and 39 [2]. With this, the third leading cause of increased disability-adjusted life years in 2019 will increase the burden of cost, treatment and rehabilitation in AYA to almost half of all stroke-related expenses in the U.S. by 2050 [2, 3].

Contributing factors, while many, include living in developing countries and low-resource health care systems, HIV-associated complications, and genetic predispositions such as thrombophilia, sickle cell disease and connective tissue disorders [2–4]. Due to the stark differences in etiology from adult-onset strokes, the difficulties clinicians face when approaching stroke in this population cannot be overlooked [5]. While clinical manifestations are similar, approaching the underlying cause and management demands a long-term nuanced approach.

Stroke mimics create management barriers due to the high degree of symptom similarity. Stroke mimics are defined as any such disease process that causes a focal neurological deficit without the involvement of any vascular component [5]. Most studies demonstrate that stroke mimics account for 20–30% of suspected-stroke presentations [6–8]. Given that 22% of ischemic strokes are missed in the emergency department or by neurological services (and likely higher for AYA), the early and accurate recognition of stroke and identifying its etiology, particularly in AYA, is critical due to the fatal or long-term complications, such as paralysis, depression, increased risk of recurrent strokes, thromboembolisms, and seizure disorders [9].

Strokes in AYA can be debilitating as the long-term complications extend for a greater period, compared to those who present at an older age. In addition, strokes in these populations are easily missed, as they are often confused as stroke-mimics, or sometimes strictly ruled-out early due to age. Regardless of the reason, research on strokes in this population is limited. Ethical considerations limit research for treatment consensus for adolescents, their rarity in those < 50-years old present statistical and population challenges. This review aims to compile data on stroke and present it within the context of AYA and emphasizing those that particularly address this population.

Etiology and risk factors in Acute ischemic and hemorrhagic strokes

In older adults, ischemic strokes are often the result of atherosclerosis or uncontrolled hypertension, while hemorrhagic strokes can also occur due to uncontrolled hypertension or traumatic injuries such as falls. Up 85% of strokes in younger patients < 50-years old are ischemic [10]. In AYA, strokes may be due to other unique factors such a cervical arterial dissection (CAD), arteriovenous malformations, cerebral aneurysms, cerebral venous sinus thrombosis (CVST), and reversible cerebral vasoconstriction disorder (RCVD) [11]. Risk factors include smoking and hypertension, both of which are modifiable and are the most clinically significant in all age groups, use of recreational drugs such as cocaine and methamphetamine, atrial fibrillation, patent foramen ovale (PFO), coagulability disorders, and connective tissue disorders (Table 1) [12]. The ASCOD classification system is a helpful tool that can be used to stratify typical causes of

Table 1 Risk factors contributing to stroke in adolescents and young adults

Risk Factor	Details
Autoimmune Disorders	Conditions like Systemic Lupus Erythematosus (SLE), and other systemic autoimmune diseases are linked to increased stroke risk due to chronic inflammation, vessel damage, and clotting abnormalities.
Cardiac Causes	Congenital heart defects like PFO, cardiomyopathies, infective endocarditis, and arrhythmias can contribute to stroke risk in young people.
Coagulopathies	Genetic or acquired blood clotting disorders, antiphospholipid syndrome, protein C/S deficiency, factor V Leiden mutation, or prothrombin gene mutations increase stroke risk.
Diabetes Mellitus	Young individuals with poorly controlled type 1 or type 2 diabetes are at a higher risk for stroke due to vascular complications.
Hereditary Disorders	Family history of stroke or certain genetic conditions (e.g., CADASIL) may predispose young adults to stroke.
Hyperlipidemia	Elevated cholesterol levels, particularly LDL, contribute to atherosclerosis and increase the risk of ischemic stroke in young adults.
Hypertension	Although traditionally considered a risk for older populations, elevated blood pressure in young adults can contribute to stroke by damaging blood vessels.
Obesity and Sedentary Lifestyle	Obesity and lack of physical activity increase the risk for stroke through their contribution to hypertension, diabetes, and dyslipidemia.
Smoking	Smoking is a well-known risk factor that increases the likelihood of both ischemic and hemorrhagic strokes by promoting atherosclerosis, blood clot formation, and vascular inflammation.

The risk factors illustrated in this table include several modifiable and nonmodifiable influences that increase the risk of stroke [12–18]

acute ischemic strokes as discussed, and includes atherosclerosis, small-vessel disease, cardiac pathology, other causes, and recently added, dissections [13]. Patients are graded both on the classification and on a degree of casualty, and this method aims to help physicians focus their treatment and management through prioritized lens to improve outcomes.

Ischemic strokes and hemorrhagic strokes may have similar presentations, although some are more common in one versus the other. Ischemic strokes typically develop quickly and cause sudden unilateral weakness, numbness, difficulty speaking, facial drooping, and visual deficits. Hemorrhagic strokes typically present with headache, seizure, nausea, vomiting, and altered consciousness due to acute increases in intracranial pressure [14].

A cervical arterial dissection is one of the most common causes of an ischemic stroke in AYA, accounting for as much as 25% in patients < 50-years old [15]. An extracranial carotid artery dissection is the most common type and is almost always spontaneous, accounting for 90% of carotid artery dissections [16]. However, traumatic injuries may also cause dissection and need not be major in nature, being caused by neck massages, severe cough, or exercises such as weightlifting or yoga. Dissection of the vertebral artery can also occur through similar mechanisms and cause similar complications. Connective tissue disorders can also increase the risk of dissections.

PFO is another important and common risk factor of stroke in AYA. A high prevalence, with some estimates of 2 billion people worldwide having one, PFOs are estimated to be found in 40–50% of young patients diagnosed with a cryptogenic stroke [16]. While the prevalence is high, not all PFOs are the same size and therefore do not possess the same risk of stroke as larger ones. Transesophageal echocardiogram with bubble study can help to characterize the size and risk of PFO-associated stroke [17, 18]. Transcranial Doppler has a sensitivity of 91–100% and specificity of 78–100% when compared to TEE in the diagnosis of PFO-associated embolic stroke [19].

CVST is an important but rare cause of acute ischemic stroke in adolescents and young adults. In a recent study, CVST had an incidence of 0.37 to 0.38 per 100,000 adolescents per year, compared to 1.3–1.5 per 100,000 adults [20]. CVST are also greatly misdiagnosed, with an estimated 57.4% of patients misdiagnosed on first contact.

The use of OCPs is an important modifiable risk factor, particularly in AYA. In a dose-response meta-analysis, Li, Feng et al. found that for every 10 μg increment in estrogen dosage in oral contraceptive pills (OCPs), the risk of stroke increases by 19% [21]. Standard dose OCPs typically contains 50 μg of estrogen, however, these have since been largely phased out and replaced with lower doses (10–30 μg) due to the increased risk of thromboembolisms. With respect to progestin-only contraceptives such as IUDs, there appears to be consensus that stroke risk does not increase [22, 23].

As with adults, modifiable risk factors should be discussed with patients, regardless of age. These including cessation of smoking and drinking, implementing weight-loss regimens where appropriate, and managing diabetes, hyperlipidemia and hypertension. Nonmodifiable risk factors such as autoimmune diseases and heritable disorders should be managed by a specialist and monitored closely, especially if a family history of strokes exists.

Imaging modalities and diagnostic challenges

The diagnosis of stroke in both young and older populations initially follow similar protocols. The American Heart Association (AHA) and American Stroke Association (ASA) jointly recommend that patients with suspected stroke or transient ischemic attack (TIA) receive CT or MRI of the head, ECG, and carotid ultrasonography or CTA or MRA in specific cases [24]. Additionally, labs should be drawn to evaluate CBC, PT, aPTT, glucose, HbA1c, creatinine, and lipid profiles. These values can help to rule in or out stroke mimics such as hypoglycemia and hypercoagulable states and further prognostic and therapeutic workup.

On non-contrast CT (NCCT), cytotoxic changes associated with ischemic strokes are generally subtle or absent for the first 3–6 h [25]. For patients presenting early, regardless of age, NCCT may look normal for age. However, there may be findings of loss of grey-white matter differentiation, hypodensity, or hyperdense vessel lines representing a large vessel occlusion. The use of NCCT in the acute setting serves to rule out hemorrhagic causes of stroke and to allow for safe administration of IV thrombolytics if no other contraindications exist in patients presenting with clinical and historical supporting evidence of a stroke. NCCT is highly specific for hemorrhagic causes, where thrombolytics are contraindicated, and immediate neurosurgical intervention may be required.

Due to radiation exposure, some facilities may opt to follow the algorithm set forth by Boston Children's Hospital which uses MR modalities for younger pediatric patients but may include adolescents [25]. Physicians should consider the time required for MR modalities to be used and interpreted versus radiation exposure with CT, which provides faster results, a critical component of its standard use as the initial imaging modality in suspected strokes.

MR imaging has greater sensitivity and specificity compared to NCCT in the diagnosis of ischemic strokes. Early ischemic changes can be detected in as early as 23 min after symptom onset, a superior feat compared

to NCCT, where imaging may appear normal even several hours after onset, furthering risk of misdiagnosis [26]. On diffuse-weighted imaging (DWI), hyperintense lesions are characteristic findings due to diffusion restriction caused by cytotoxic edema to the ischemic area [27]. Similar findings are seen on T2 imaging; however, DWI-MRI is more sensitive to the acute changes than T2-MRI. Fluid-attenuated inversion recovery (FLAIR) is another MRI-type modality that can be helpful in characterizing a lesion as acute or chronic. Regardless of MRI type, ischemic changes are associated with hyperintense findings, while hypointense changes are associated with hemorrhagic findings.

Other diagnostic imaging modalities include CT and MR angiography and venography (CTA, CTV, MRA, MRV). CTA can be helpful in defining the etiology of a stroke, such as aneurysms, stenosis, or dissection. CTV and MRV can be used to diagnose cerebral venous thrombosis, both with equally high sensitivity and specificity [28]. However, contrast-enhanced MRV allows for better characterization of flow gaps.

As mentioned, an important challenge physicians may face is the need to expose AYA to CT-associated radiation. Additionally, comorbidities may exist in which the use of contrast may be contraindicated. Time being of the essence, swift diagnosis along with high clinical suspicion is important, especially if nearing the maximum window for thrombolytic use. The use of supplementary diagnostic tools such as echocardiogram, ECG, and coagulation panels can help to quickly increase clinical suspicion and shift the priority from diagnosis to acute treatment.

Stroke management and treatment approaches

Acute stroke management is critical for preventing permanent and severe damage and disability. The rate of reperfusion is an important factor that directly correlates with reduced risk of disability and a decreased rate of mortality. Several therapies exist and have proven to be successful and definitive treatments for stroke patients of all ages.

Acute ischemic stroke

In adults age 18 and over, early treatment with rt-PAs such as IV Alteplase, has been a standard form of therapy for ischemic stroke. According to joint guidelines from the AHA/ASA, IV Alteplase is recommended for ischemic strokes diagnosed by neuroimaging within 4.5 h of symptom onset [29]. Given the strict timeline restrictions for administration, IV alteplase should be administered if a stroke is suspected, NCCT shows no bleed, clinical presentation and history does not indicate high probably of a bleed, and no other contraindications are obvious. In adolescents, and pediatric populations in general, the only attempt at a randomized controlled trial on the use of IV alteplase was the thrombolysis in pediatric strokes (TIPS) trial, which failed to be completed due to recruitment problems that ended their funding. However, case reports and data from established TIPS sites continue to use IV alteplase for patients ages 2–17 who are diagnosed with a stroke, using the three-dose tier of 0.75, 0.9, 1.0 mg/kg at a maximum dose at 90 kg [30, 31].

Alternatively, mechanical thrombectomy can be used to treat patients with an acute ischemic stroke. The following criteria should be met for eligibility: "(1) prestroke mRS score of 0 to 1; (2) causative occlusion of the internal carotid artery or MCA segment 1 (M1); (3) age ≥ 18 years; (4) NIHSS score of ≥ 6; (5) ASPECTS of ≥ 6; and (6) treatment can be initiated (groin puncture) within 6 hours of symptom onset" [29]. Primarily, mechanical thrombectomy addresses large vessel occlusions (LVO). In adolescents, and pediatric population in general, the use of mechanical thrombectomy is not well studied, having no randomized controlled trials being conducted on its use [32]. Evidence of its successes relies on meta-analyses and case-reports or series. In a systemic review and meta-analysis, it was found that 88.5% of patients < 18-years old had successful revascularization and on average a National Institutes of Health Stroke Scale score reduction (NIHSS) of 7.37 [32]. They also demonstrated better neurological outcomes, fewer periprocedural complications, and decreased mortality, compared to adults who underwent mechanical thrombectomy.

Hemorrhagic stroke

Patients diagnosed with hemorrhagic stroke face different challenges in acute management. AYA patients may be at increased risk for traumatic causes of hemorrhagic strokes due to increased mobility and fewer risk limitations. Regardless of cause, the immediate goal is to stop the bleeding. In patients with hypertension-induced bleeding, the AHA/ASA recommends a titrated approach to lowering blood pressure, where a cited study showed that a reduction of ≥ 20 mmHg over the course of 1 h and then maintained over a 7-day period had the best outcomes, but is still requires a nuanced approach [33].

Additionally, slow titration of blood pressure has been shown to reduce the risk of cerebral vasospasms, which can worsen patient outcomes. In patients with anticoagulation-induced bleeding, rapid reversal is critical, and appropriate reversal agents for the drug in question should be used [33]. Vitamin K, protamine sulfate, Andexanet alfa, Idarucizumab, prothrombin concentrate, and fresh frozen plasma are important reversal agents that can be used in this subgroup of patients. For adults with spontaneous cervical dissection, the use of aspirin is often recommended [33, 34].

Ultimately, regardless of age, the treatment of a hemorrhagic stroke will depend on the cause of the bleed and its

severity. For example, an AVM may require endovascular embolization or stereotactic radiosurgery, or endovascular coiling or direct surgical clipping of an intra-arterial aneurysm [35, 36].

In addition to definitive treatment, such as those established above, general management is necessary and protective. These include providing supportive airway management, correcting blood pressure, assessing blood glucose, and evaluating any electrolyte disturbances [29]. After acute management, long-term management should be discussed, including recommending appropriate follow-up outpatient care. These may include removing, substituting, or adding new medications and lifestyle modification.

Long-term outcomes and quality of life after stroke

Strokes that affect pediatric and young adult populations can carry lifelong ailments that significantly impact an individual's quality of life. However, compared to those in elderly populations, the neuroplasticity and age of stroke onset are significantly different. In younger patients, the developmental neuroplasticity of the brain is believed to be at its maximum, potentially offering greater chances of neuronal recovery poststroke [37–39]. However, a paradox exists, while neuroplasticity may be greatest at younger ages, neuronal disruption of the developing brain is also greatest and can potentially predict worse outcomes in this vulnerable patient population [39]. Despite this controversy of benefit or detriment, stroke patients of all ages demonstrate real clinical consequences, some temporary and reversible, and others permanent.

Adolescents and young adults who suffer from stroke can exhibit cognitive deficits. Weterings and colleagues reported that almost half of young adults suffer cognitive impairment [40]. These include language and visual processing dysfunction, memory delays, and attention loss. Importantly, these cognitive deficits were demonstrated within the first few hours of stroke onset and for some patients, extended more than a decade after. Consequently, young patients, particularly those still in school, can suffer from new onset learning disabilities that can impact grade and graduation. This can cause lifetime and generational socioeconomic disadvantages for patients and their families.

The psychosocial effects of stroke are equally important to the various cognitive deficits this population faces poststroke. For adolescents, these deficits can create difficult school environments for them to navigate. For young adults, getting back to work is often of greatest importance as the need for independence and family growth and care increase. Separately, Hackette et al. and Gurková et al. both demonstrated significant increases in anxiety, depression, and fatigue among young stroke survivors compared to older individuals [41, 42]. Many of these patients subsequently require the use of antidepressants and anxiolytics.

In addition to survivors' cognitive and psychosocial impacts, physical impairments are also an important part of understanding long-term complications poststroke. In a first-of-its-kind study, Jarvis and colleagues reported that 44% of young adults less than age 65 could not return to work; factors such as speed, metabolic expenditure, oxygen consumption and others were used to quantify the data [43]. A critical movement value of 0.93 m/s was found to be a predictive indicator of return to work. They also found that almost all stroke patients developed a wide stride, a potential biomechanical compensation to improve balance but which consequently slows the speed of walking. It has also been shown that AYAs can face similar disabling physical impairments that their elderly counterparts suffer from, including paralysis, weakness, contractures, and spasticity [43].

Due to the nature of strokes affecting elderly individuals more commonly, the literature describing these impacts is copious for older adults, but scarce in younger populations. There is a great need for additional research in this area.

Rehabilitation and recovery strategies poststroke

Stroke rehabilitation often involves the use of a multispecialty team to improve short- and long-term outcomes to meet individualized goals. These teams should include, at minimum, an occupational therapist, physical therapist, speech-language pathologist, neurologist, and social worker. Rehabilitation and recovery strategies have been widely discussed in the literature; however, these strategies mainly focus on adults and their needs poststroke, are nonspecific, or only presents data for medical management [43, 44]. As discussed previously, the needs of AYA poststroke differ from those of their older counterparts. Importantly, these patients may still be in school, are beginning their path to independence, are starting a family, and are seeking stable careers for long-term financial stability. These needs can also greatly change over time, emphasizing the need for long-term patient care.

For adolescents and young adults, physical, cognitive, and psychosocial competencies are still developing. Consequently, some aspects of rehabilitation and recovery can be difficult, as certain skills and aptitudes have not yet matured, if at all have begun to mature, depending on patient age and baseline [45]. Matkosky et al. described several evidence-based research deficits in cognitive and psychosocial techniques for caring for pediatric stroke survivors, including adolescents [46]. However, they stress the need for care that encompasses the patients' realties of community, family, and culture and care that is longitudinal to assess ever-changing needs in a

population whose development is still maturing. For example, they suggest neuropsychological assessments in these populations every 2 years and/or during significant academic transitions, such as moving to middle school, high school, or college [46]. Repetitive evaluations can help essential support teams monitor key developmental milestones and goals, assess chronic complications, and advise on need-based challenges that arise as new situations unfold in growing adolescents and young adults.

The American Academy of Physical Medicine and Rehabilitation established physical rehabilitation guidelines based on a combination of evidence and recommendations from the AHA, the Canadian Stroke Best Practice Recommendations, and the Australian Childhood Stroke Consensus Rehabilitation Guideline, and provided Constraint-Induced Movement Therapy for upper limb impairment an "A," in line with other research-based analyses of recommended therapies [46–48]. This type of therapy aims to encourage reorganization of the lesion-affected areas of the brain to promote recovery. Other types of techniques that have shown marked improvement in functionality include "forced use therapy, repetitive transcranial magnetic stimulation, functional electrical stimulation, and robotics" and implanted brain-computer interface technologies [47]. While these guidelines exist, as mentioned before, their application is limited, and evidence is scarce in many aspects. This is largely due to underfunding and under-research in this niche area. Nevertheless, strokes in AYAs are particularly concerning due to the unique problems their complications cause and their increasing frequency.

Psychosocial impact of stroke

Strokes have a profound psychological impact on AYAs, frequently leading to mental health disorders such as PTSD, depression, and anxiety. Psychosocial issues can have a substantially negative influence on quality of life and long-term functioning, lessen the benefits of rehabilitation programs, and increase death rates [49–52].

Young individuals who have experienced a stroke are more susceptible to mood disorders because they face unique challenges such as job loss, childcare issues, and decreased life satisfaction [53]. In the initial months following a stroke, there is an increase in mental anguish, which can persist for several years and possibly worsen over time [54, 55].

Opportunities for psychologically focused counseling and support should be made available to young survivors whose well-being is impacted by a sense of discontinuity and identity changes [49]. Counseling supports better adjustment to life after a stroke and helps individuals with social obstacles, including returning to school or work, controlling emotions, and addressing these issues.

Future direction of stroke care and research priorities

Adolescents and young adults face a myriad of problems in care, from recognition, diagnosis, treatment, and long-term care and management. Yet, little research is being done to discover ways to resolve these issues.

The principles of recognition, diagnosis, treatment, and long-term care

First, early recognition of stroke in AYA is key to prevent the additional burdens. Stroke is largely considered a disease of the elderly, but as demonstrated, a great population is being underserved by lack of awareness. Programs such as YoungStroke, Inc. works as a national patient advocacy organization to improve the perspective of the general population about strokes, and its effect on younger populations [56, 57].

Second, stroke diagnosis should be rapid and without hesitation, especially if age is the top factor contributing to hesitancy. As described, strokes can occur at any age and for any number of reasons. Delays in diagnosis not only delays critical treatment but can also worsen long-term outcomes and increase risk of mortality. Additionally, in one study, it is estimated that 15,000-165,000 strokes are misdiagnosed in the US [58]. Of those who were most likely to be misdiagnosed were young non-white women presenting atypically with headache or dizziness. Therefore, NCCT, a relatively cost-friendly, quick, typically readily available, and non-invasive method to aid in the diagnosis of acute strokes should be considered even in patients who do not present with the classic findings.

Third, an unfortunate reality of clinical research is that patients under 18 are typically excluded from drug trials. As mentioned, current recommendations for the treatment of strokes in those age 18 and under stem from adult guidelines. However, for example, alteplase has not been officially tested for its safety nor efficacy in this population. Nevertheless, its off-label use continues to persist as a standard treatment for pediatric ischemic strokes. The TIPS trial is the closest to a randomized clinical trial that was developed, and there is a great need for the restart of similar trials to be done [31].

Fourth, long-term care for adolescents and young adults can look a bit different than their elder counterparts. Currently, descriptive studies are being performed to assess the functional, medical, and psychological outcomes of young stroke survivors; the impact of the care they receive; and their incorporation into society as functioning individuals. Old scales, such as the *Diener Satisfaction with Life Scale* and *Vineland Adaptive Behavior Scale*, have been modified [59]. These modifications can help providers understand their patients' needs and goals

and adapt better to new research models and evidence being established.

While some of the pillars remain similar between young and older patients recovering from a stroke, other approaches are more nuanced depending on age and severity. For example, pursuing intimate relationships, continuing education, returning to work, and managing young children, are less likely to be issues that require immediate or near-immediate attention. As such, greater research is needed in this field to appropriately and further identify existing gaps, create targeted resources for AYA recovering from a stroke, and develop a plan to address the immediate needs of this population.

COVID-19

As incidence of COVID-19 rise, so has stroke incidence, particularly in healthy younger populations. Compared to a previous study on large vessel occlusion, which found an incidence of 3.3–5.5% in those age < 50 pre-COVID-19, current research found an incidence of 16–19% in the setting of COVID-19 [60]. In another study, 27% of patients with either ischemic or hemorrhagic stroke also had COVID-19 [61, 53]. As such, further research needs to be conducted to address both prevention and treatment of COVID-19-associated strokes.

Use of artificial intelligence

Artificial intelligence (AI) has been employed in identifying new approaches for addressing rehabilitation by considering the demographic and clinical data of poststroke patients. Moreover, AI offers significant potential for precision medicine by analyzing large data pools to predict outcomes and tailor treatments more accurately [62]. Recent AI advancements, including machine learning and deep learning, have improved pattern recognition and prediction capabilities. AI tools, such as supervised learning algorithms, can help in predicting recovery outcomes and personalizing treatment plans. Overall, the integration of precision medicine and AI could lead to more individualized and effective stroke care.

Identifying genetic components for precision medicine

New research is focusing on genes related to stroke and stroke mimics. Recent large-scale genome-wide association studies (GWAS) related to ischemic stroke have highlighted the challenges in identifying genetic factors due to stroke heterogeneity [63]. The 4q25 locus is linked to atrial fibrillation, the 12q24 locus (ADAMTS7) is associated with arterial remodeling, the 9p21 locus (CDKN2A/B) is involved in cellular aging, and the 2q36 locus (LPA) is associated with elevated lipoprotein levels [63].

Stroke biomarker trials

Stroke biomarker trials have the potential to improve diagnostic and prognostic precision, can even select patients for clinical trials, and can help identify novel therapeutic targets. In brief, these methods allow clinical phenotyping and can advance the therapeutic field toward more individualized care approaches in the future [64].

Stroke mimics: common conditions in adolescents and young adults

Stroke mimics are illnesses that present with symptoms like those of a stroke. These factors may increase the difficulty of correctly diagnosing and treating a stroke. Consequently, proper management of stroke may be lapsed. Seizures, migraines with aura, functional neurological disorder, hypoglycemia, electrolyte imbalances, acute vestibular syndrome are the most prevalent stroke mimics in this age group [21]. MELAS and multiple sclerosis are important stroke mimics but are less prevalent. Understanding shared clinical features and their key differences can help physicians distinguish a stroke from a mimic (Table 2).

Seizures: Following a seizure, postictal paralysis, also referred to as Todd's paralysis, may lead to clinical diagnostic challenges. However, the history of seizure activity, presence of postictal disorientation, and the transitory nature of the symptoms that resolves go away in within 24–48 h less than a day, allow for its differentiation from stroke [65, 66]. Post ictal aphasia are transient whereas aphasia in stroke are not and require specialized interventions via speech therapy to improve.

Migraine with aura: The aura phase of a migraine closely resembles a stroke or transient ischemic attack (TIA). The symptoms of a migraine follow an aura, with headache that worsens over a few minutes [67]. The duration of migraines with aura can last from 15 min to 1 h, though the sensory or visual problems can persist longer. Symptoms of migraine usually resolve spontaneously, whereas the symptoms of stroke persist > 24 h and will not resolve without intervention. We can distinguish it from a stroke in this way. Migraines are an independent risk factor for ischemic strokes and are associated with migrainous infarction. Migrainous infarctions is thought to be caused by prolonged vasospasm associated with migraine, thereby restricting blood flow and promoting thrombus formation [68].

Functional neurological disorder (FND): Patients with FND exhibit abrupt onset of neurological symptoms such as paralysis and trouble speaking in the absence of a true neurological disorder. FND can be further distinguished from a stroke by the presence of psychosocial or stress elements, lack of objective findings on clinical exam such as abnormalities in reflexes and tone per localization

Table 2 Common stroke mimics in adolescents and young adults

Condition	Clinical features	Key distinguishing features
Seizures (Post ictal state/ Todd's Paralysis)	Sudden onset of unilateral weakness or focal neurological impairment following a seizure activity.	Transient in nature (usually resolved within 24–48 h), history of seizure activity, postictal disorientation.
Migraine with Aura	Visual disruptions, verbal difficulties, sensory abnormality.	Gradual onset and the symptoms are accompanied by unilateral headache. Resolves spontaneously.
Functional neurological disease (FND)	Abrupt onset of neurological symptoms include weakness, paralysis, trouble speaking.	Clinical findings lack in appropriate localization. Typically, with a history of psychological stressors or disorder.
Hypoglycemia	Focal neurological impairments, weakness, difficulty in speaking, and disorientation.	There can be the presence of sympathetic activity symptoms such as palpitations and sweating. Rapid administration of glucose results in quick recovery.
Electrolyte imbalance	Weakness and muscle cramps	Negative neuroimaging. Weakness doesn't fit the pattern of a stroke. Typically, hypokalemia-associated. Resolution by normalizing electrolytes
Bell's Palsy	Unilateral facial weakness involving the forehead also	Gradual onset, absence of other neurological symptoms.
Acute Vestibular Syndromes	Vertigo, gait disturbances, nausea, vomiting	Positive head-impulse test (a rapid corrective movement of the eyes when the head is turned), nystagmus. Absence of weakness and other neurological features.

Summary of stroke mimics and their clinical and diagnostic findings [65, 67, 69, 71–74]

Table 3 Diagnostic approach to distinguish between stroke and stroke mimics

Criteria	Stroke	Stroke Mimics
Onset and Course of Symptoms	Sudden onset, reaching peak symptoms early	Gradual, sporadic onset and worsening (e.g., migraine with aura, conversion disorder)
Associated Symptoms	Neurological deficits without specific associated symptoms.	Presence of headache (migraine), palpitations, sweating (hypoglycemia), post-seizure activity
Symptom Pattern	Follows a vascular distribution (specific areas of weakness/ deficit)	Generalized weakness not aligned with any specific vascular distribution (e.g., FNDs)
Neuroimaging Results	MRI shows diffusion limitation in ischemic stroke	CT/MRI are often normal, or may show etiological abnormality and not signs of a stroke
Response to Treatment	Requires close medical monitoring, sometimes surgery	Rapid improvement with glucose (hypoglycemia) or psychological interventions (FNDs)

Summary table of stroke and stroke mimics and their diagnostic criteria or symptom patterns for differentiation [65, 69, 71, 76, 77]

[69]. FND usually presents with unilateral limb weakness, a global pattern where both flexor and extensor group of muscles are involved, which is very unlikely in strokes. Functional tremors are variable in frequency and change in response to external cues. The presentation of functional dystonia is associated with pain and disability, whereas other dystonia's are generally mobile and more variable in posture [70].

Hypoglycemia: Low serum glucose can result in focal neurological impairments and occurs acutely. Point-of-care glucose checks can be used to quickly diagnose this condition, and recovery following glucose administration can be used to distinguish between hypoglycemia and stroke [71].

Electrolyte imbalance: Electrolyte imbalances, such as hypokalemia, can present as weakness, but the weakness pattern does not correlate well with a cerebral lesion as it can be a diffuse presentation versus unilateral [72].

Bell's palsy: Bell's palsy typically presents with unilateral weakness of facial muscle. It sometimes mimics stroke as it resembles the facial weakness seen with lesions of some vascular territories. However, it has gradual onset, facial weakness that includes the muscle of forehead, and absence of associated neurological symptoms like limb weakness and headache [73].

Acute Vestibular Syndromes (AVS): Inflammation of vestibular nerve can present with sudden and intense vertigo, balance disturbances, nausea, and vomiting. It closely mimics stroke of the posterior circulation. But vestibular neuritis presents with isolated vertigo that worsens with head movement [74]. Physical exam findings may include facial drooping, aphasia, or changes in visions, typically not seen in AVS. Additionally, HINTS, or head impulse test, nystagmus test, and test of skew, is widely accepted as an appropriate screening tool to differentiate stroke vs. AVS at the bedside [75].

Clinical characteristics to separate strokes from Mimics

It is critical to distinguish between stroke mimics and real strokes to guarantee timely and effective treatment. Several clinical traits and diagnostic instruments can be useful for differentiation.

Onset and course of symptoms: Stroke symptoms typically start suddenly and reach their peak early. However,

mimics such as migraine with aura for example, appear and worsen gradually and sporadically, and will typically resolve without immediate intervention [76].

Symptom pattern: Stroke manifestations typically correspond with vascular distribution, while mimics do not.

Neuroimaging: MRI and CT scans are helpful in differentiating strokes from mimics. Diffusion restrictions observed on MRI in patients with ischemic stroke do not appear in patients with migraine, seizures, or hypoglycemia [77]. In migraine with aura, perfusion MRI studies may show white matter hyperintensities and changes in cerebral circulation associated with hypoperfusion [78, 79]. In patients with seizures, CT scans are not very sensitive, but MRI are both highly sensitive and specific, detecting common epileptogenic lesions such as small tumors and microtrauma common in adults, or tissue malformations common in adolescents and young adults [80].

Response to treatment: Glucose administration quickly relieves hypoglycemia. However, a stroke necessitates close medical monitoring, and surgical intervention might be necessary in certain circumstances.

Resisting treatment of a stroke due to uncertainty can be fatal and lead to serious consequential neurological and physical deficits. One in four stroke admittances were found to be a stroke mimic, and more than one in three of those patients underwent thrombolysis therapy without complications and experienced a positive outcome [7]. This emphasizes the need for stroke management specialists to be involved early and provides critical support for the early treatment of stroke while further diagnostic workup is pending (Table 3). In fact, according to AHA/ASA guidelines, "The risk of symptomatic intracranial hemorrhage in the stroke mimic population is quite low; thus, starting IV alteplase is probably recommended in preference over delaying treatment to pursue additional diagnostic studies" [29]. A complete clinical history, careful examination, and proper diagnostic measures should be implemented early on by a skilled physician with experience both in stroke treatment and stroke mimics to allow for greater success in management and prevention of acute and chronic complications.

Conclusion

Strokes in adolescents and young adults can occur for or due to several reasons or risk factors, but commonly involves cervical arterial dissection or presence of a PFO, amongst others. Treatment, particularly in hemorrhagic stroke where pharmacological or surgical intervention can vary greatly. In AYA presenting with an ischemic stroke, IV thrombolytics remain the standard therapy, even in adolescents. Endovascular interventions like thrombectomy is also a safe alternative. Stroke mimics can add a layer of hesitancy in the management of young patients presenting with stroke-like symptoms, such as migraines with aura or Todd's paralysis. Distinguishing these early on through key clinical findings but remaining vigilant of classic or atypical features of stroke in AYA is critical. A missed stroke can lead to delays in treatment, result in detrimental life-long consequences for young patients and can even be fatal. The path to recovery can be different from that of elderly individuals and can be quite dynamic for the developing brain. There is a great need for research on both acute and chronic management of young stroke patients and their need for rehabilitation. We hope that as stroke treatment continues to improve, younger patients can benefit from the traction earlier rather than later.

Acknowledgements
Not applicable.

Author contributions
AS was responsible for the conception of the work, authored sections on "Long-Term Outcomes and Quality of Life After Stroke" and "Rehabilitation and Recovery Strategies Poststroke," and made substantial revisions to the manuscript. YMS authored "Introduction," co-authored "Imaging Modalities and Diagnostic Challenges, " created Table 1, and made substantial revisions to the manuscript. MB co-authored "Etiology and Risk Factors in Acute Ischemic and Hemorrhagic Strokes" and authored "Stroke Mimics: Common Conditions in Adolescents and Young Adults," created Tables 2 and 3, and made substantial revisions to the manuscript. JK authored "Future Direction of Stroke Care and Research Priorities." WAA authored co-authored "Etiology and Risk Factors in Acute Ischemic and Hemorrhagic Strokes" and made substantial revisions to the manuscript.MSA authored " Psychosocial Impact of Stroke on Adolescents and Young Adults" and co-authored " Stroke Management and Treatment Approaches"AHT Co-authored " Imaging Modalities and Diagnostic Challenges" made substantial revisions to the manuscript. MM contributed substantial guidance in pathway from conception to submission and in the organization of the manuscript and made continuous revisions throughout the writing process.Although authorship is given to particular persons for specific sections, each author contributed meaningful in aspects throughout the paper.

Funding
Not applicable.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 12 October 2024 / Accepted: 17 November 2024
Published online: 27 November 2024

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