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Journal of Neurological Disorders & Stroke

Review Article

Antiphospholipid Syndrome and Ischemic Stroke in Young Adults

Tiffany Brown and Robin L. Brey*

Department of Neurology, University of Texas Health San Antonio, USA

***Corresponding author**

Robin L. Brey, Department of Neurology, University of Texas Health San Antonio, 7703 Floyd Curl Drive Mail Code 7883, San Antonio, TX, USA, Tel: 210-450-0500; Fax: 210-562-9366; Email: brey@uthscsa.edu

Submitted: 30 September 2020

Accepted: 14 October 2020

Published: 16 October 2020

ISSN: 2334-2307

Keywords

• Stroke; Antiphospholipid Syndrome; Antiphospholipid antibodies; Secondary stroke prevention

Abstract

Ischemic stroke in young adults is a challenge globally and a potential source of major morbidity. Antiphospholipid Syndrome (APS) is a risk factor for stroke at any age, but particularly so in young adults. Young adults with APS have a higher risk for recurrent stroke and other vascular events. Here we review the current literature regarding APS and its impact on stroke in young adults. Primary and secondary stroke prevention is also discussed.

ABBREVIATIONS

APS: Antiphospholipid Syndrome; aPL: antiphospholipid antibodies; NOACS: Novel Oral Anticoagulants; INR: International Normalized Ratio

INTRODUCTION

Ischemic stroke in young adults is a challenging public and global health issue. The etiology of ischemic stroke in younger patients is often uncommon and difficult to identify. Additionally, there is a socioeconomic burden related to stroke in young adults, as it tends to result in a higher loss labor and healthcare costs. Young adults who have suffered a stroke will generally have longer life expectancies, and more years of potential disability, compared to older adults. Furthermore, medical optimization for secondary stroke prevention in young adults can be complex and uncertain. The incidence of stroke in young adults has increased worldwide in recent decades, necessitating further research in this area to prevent permanent disability in young patients [1].

Antiphospholipid syndrome (APS) is a particularly important etiology of stroke in young adults. A diagnosis of APS is made based on clinical and laboratory criteria, and mainly involves persistent antiphospholipid antibodies (aPL), including lupus anticoagulant, anticardiolipin, and anti-β2-glycoprotein I antibodies, in patients with thrombotic events and/or pregnancy loss [2]. Ischemic stroke is the most common neurological complication of APS [2]. It has been estimated that up to 20% of strokes in patients under the age of 45 years may be associated with APS. A study involving a cohort of 36 primary APS patients with new onset stroke-like symptoms found that 28% of these patients had an ischemic stroke confirmed on MRI, with a mean age of 41 years [3].

The identification of common stroke etiologies in young adults is important for secondary stroke prevention, and potentially could be useful for primary prevention of stroke in young patients when high risk individuals are identified before a cerebrovascular event occurs. APS and the presence of persistent aPL is an important risk factor for stroke in young adults, deserving of further investigation for optimal medical management and stroke prevention. Here, we review the current literature regarding APS and how it relates to stroke in young adults.

Ischemic Stroke in Young Adults

Current estimates indicate that up to 18% of all ischemic strokes occur in individuals 18-50 years old [4]. Aparicio et al., examined the Framingham Heart Study data and found that between 1962 and 2005, there was an overall decline in the incidence of stroke, with a significantly greater decline in stroke incidence in patients ≥ 55 years old when compared to patients age 35-54 years [5]. The overall incidence of ischemic stroke in young patients appears to be increasing in countries across the world. A study of patients in Dijon, France found an increased incidence of ischemic stroke in adults younger than 55 years from 1985-2011 [6]; and a study of patients in Joinville, Brazil found an increase in incidence of ischemic stroke in adults younger than 45 years from 2005-2006 to 2014-2015 [7]. There are multiple factors that may be contributing to this phenomenon, including an increased clinical suspicion for and subsequent diagnosis of stroke in the young, as well as an increase in the prevalence of common vascular risk factors in young people such as obesity, hypertension, diabetes [5,8].

Genetics likely plays a significant role in stroke in younger patients. A stronger effect of parental history of ischemic stroke on the risk of ischemic stroke in patients <65 years, when compared with parental history of ischemic stroke on stroke risk at any age, and this association was independent of traditional vascular risk factors [9].

Young adults are also at high risk of developing recurrent cerebrovascular events, as well as higher mortality, after an initial stroke. A study of first-time stroke in 1,867 young adults (age 18-45 years) in Italy found a 14% cumulative risk for recurrent brain ischemia at 10 years [10]. The 20-year cumulative mortality for

young survivors of ischemic stroke was found to be as high as 27%, up to four times higher when compared to age and sex matched individuals of the general population [8]. Vascular disease was found to be the main cause of death in young adults who died within 20 years after suffering an ischemic stroke; notably, up to half of these deaths were attributed to a vascular cause that was not stroke [8]. These findings, combined with the known risk of recurrent brain ischemia in young stroke patients, imply that young patients who develop ischemic strokes continue to be at increased risk of vascular disease in the long-term. For this reason, further research into optimal post-stroke management of this vulnerable patient population will be vital to achieving improved long-term outcomes.

Antiphospholipid antibodies and ischemic stroke

A review of published literature from 1984-2011 found that aPL was present in up to 13.5% of stroke patients [11]. One prospective study following a cohort of eighty-nine patients for one year after they had a cerebrovascular event found that 22% of these stroke patients met the criteria for APS, and APS was eventually diagnosed in 16% of "cryptogenic" stroke patients in the cohort [12]. This study also found a significant association between persistent aPL and the cerebrovascular event [12].

In a large observational study of 1000 European APS patients with a mean age of 42 years, 16.6% of the patients had a thrombotic event in the first five years of the study and 15.3% had a thrombotic event in the second five years of the study [13]. The most common thrombotic events were stroke and transient ischemic attacks [13].

Although the presence of aPL is an important stroke risk factor at any age, it is especially prevalent in the young ischemic stroke patient population. In patients younger than 50 years with cerebrovascular events, the frequency of aPL has been estimated at 17% [14]. Additionally, the presence of aPL in this younger patient population is associated with up to a fivefold increased risk of cerebrovascular events [14].

The presence of aPL appears to be a contributing factor to stroke across the globe, affecting both low- and high-income countries, and particularly involving younger patients. For instance, aPL was found to be an important stroke risk factor in sub-Saharan Africa, where there is a high stroke burden. A study involving patients in Tanzania found that lupus anticoagulant was present in 19% of stroke patients, with a higher odds ratio of lupus anticoagulant in stroke patient's ≤ 65 years of age [15].

Serum levels of aPL may also be an important prognostic factor in young patients with APS who develop an ischemic stroke. In a study from Madrid, Spain evaluating APS patients younger than 55 years with acute ischemic stroke, there was a positive correlation between serum anticardiolipin antibody level and stroke severity as measured by National Institutes of Health Stroke Scale (NIHSS) score [16]. This study also found a positive correlation between serum levels of anti-β2-glycoprotein I antibody and clinical outcomes three months after the stroke based on the modified Rankin Scale [16]. Another study found a positive correlation between serum levels of aPL (specifically anticardiolipin and antiphosphatidylserine) and higher risk of post-stroke depression in adult patients [17].

Prevention of thrombotic events in antiphospholipid syndrome

Primary prevention of thrombotic events using low-dose aspirin is encouraged in patients with aPL who are considered to be high risk. Low-dose aspirin monotherapy has been shown to have a significant effect on the prevention of arterial thrombosis, with a borderline effect on the prevention of venous thrombosis [18]. Optimal medical management of APS for secondary prevention of thrombotic events is complex and is usually done based on an individualized approach to the patient's clinical circumstances [18]. For instance, current data suggests that patients with APS who present with arterial thrombotic events may benefit from either oral anticoagulation with a higher INR goal of 3.0-4.0 or a combination approach of low dose aspirin with oral anticoagulation and an INR goal of 2.0-3.0 [18]. Alternatively, for patients with APS who present with venous thrombotic events, current data supports the use of oral anticoagulation alone with an INR goal of 2.0-3.0 [18].

A recent systematic review of multiple randomized controlled trials was done to compare the effectiveness of antiplatelet and anticoagulation agents on secondary prevention of recurrent thrombosis in APS patients. This study found that for overall secondary prevention of thrombosis in patients with APS, there was not enough evidence for or against the use of novel oral anticoagulants (NOACs) or high-dose vitamin K antagonists compared to standard dosing vitamin K antagonist therapy [19]. This study also found that there was not enough evidence for or against the use of vitamin K antagonists combined with antiplatelet therapy or dual antiplatelet therapy when compared to antiplatelet monotherapy, but did find evidence of increased bleeding events in patients on high-dose vitamin K antagonists when compared to standard doses of vitamin K antagonists. There was no evidence of additional benefit in secondary prevention of thrombotic events.

Optimal duration of treatment of APS patients with anticoagulation remains under investigation. A recent retrospective study of young APS patients (age 27-56 years) who stopped their oral anticoagulation treatment, many of whom switched to aspirin, heparin, or other agents with antithrombotic effects, showed that there was a high risk of recurrent thrombotic events, with 25% of the patients in the study experiencing a thrombotic event after anticoagulation cessation [20]. The study also found that the risk of recurrent thrombosis was high in patients who did not have persistent aPL, indicating that serum aPL levels may not be a reliable method of determining duration of anticoagulation treatment.

There is a scarcity of data regarding the primary and secondary prevention of stroke in patients with aPL or APS. Patients with APS represent a heterogenous population, varying in age, gender, comorbidities, and antibody profile, and management based on a patient-centralized approach is likely the best option while further research regarding stroke prevention in this specific patient population is on-going.

DISCUSSION & CONCLUSION

Ischemic stroke in young adults remains a challenging public and global health challenge, with high potential socioeconomic

burden. While an increase in more traditional vascular risk factors such as hypertension and diabetes continue to rise in young people, aPL remain an important risk factor in this population. Young people with stroke associated with aPL are at risk for recurrent stroke and other vascular events. This increased stroke risk is seen throughout the world and in all socioeconomic groups. Primary prevention with low-dose aspirin in high-risk people with aPL is advised. Treatment with moderate INR producing doses of vitamin K antagonists in patients with stroke in the setting of APS is advised.

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Cite this article

Brown T, Brey RL (2020) Antiphospholipid Syndrome and Ischemic Stroke in Young Adults. J Neurol Disord Stroke 7(4): 1168.