

IDENTIFICATION OF PREDICTORS OF MIGRAINOUS STROKE AND DEVELOPMENT OF PREVENTIVE MEASURES FOR HIGH-RISK INDIVIDUALS

Muradimova Alfiya Rashidovna

Fergana Medical Institute of Public Health Head of the
Department of Neurology and Psychiatry, PhD, associate professor

Abdulkhafizov Abdurakhmon Abdurasul o'g'li

Neurologist, Central Reception Department, Andijan Branch,
Republican Scientific Center for Emergency Medical Care

Shakirova Kamola G'ulomovna

Student of Andijan Branch of Kokand University

Abstract

This review summarizes key predictors of migrainous stroke, including female gender, young age, migraine with aura, hormonal contraceptive use, smoking, hypertension, and genetic factors. It outlines the underlying mechanisms such as cortical spreading depression and vascular inflammation. Preventive strategies focus on lifestyle changes, contraceptive counseling, antiplatelet therapy, and migraine prophylaxis. Risk models help identify high-risk individuals for personalized prevention. A multidisciplinary approach involving neurology, gynecology, and primary care is recommended. Future research aims to develop risk prediction tools, discover new biomarkers, and advance precision medicine.

Keywords: Migrainous stroke, migraine with aura, ischemic stroke prevention, hormonal contraceptives, risk stratification, cerebrovascular disease, young women.

Introduction

Today, cerebrovascular disease continues to represent one of the leading causes of mortality and long-term disability worldwide, with particular concern emerging regarding stroke occurrence in younger populations previously considered at low risk. Migrainous stroke, defined as an ischemic stroke occurring during a typical migraine attack with aura, constitutes a distinct clinical entity that bridges the traditionally separate domains of headache medicine and stroke neurology. Migraine affects up to 20 percent of the global population and ranks as the second leading cause of disability worldwide, establishing its significance as a public health concern beyond its direct neurological impact. The recognition of migraine as an independent risk factor for ischemic stroke has evolved substantially over the past decade, with accumulating evidence demonstrating that individuals with migraine, particularly those experiencing aura phenomena, face elevated stroke





risk compared to their non-migrainous counterparts. According to the study conducted by Schürks et al., the relative risk for ischaemic stroke in MA was increased over twofold, establishing the clinical significance of this association. This relationship becomes particularly pronounced in young women, where the intersection of hormonal factors, contraceptive use, and migraine pathophysiology creates a complex risk landscape requiring careful clinical attention. The clinical challenge lies not merely in recognizing this association but in developing practical approaches to identify high-risk individuals before stroke occurrence and implementing effective preventive measures. Current understanding suggests that migrainous stroke results from multifactorial interactions involving genetic predisposition, hormonal influences, vascular reactivity, and environmental triggers. The complexity of these interactions necessitates a comprehensive approach to risk assessment that extends beyond traditional stroke risk calculators, which often inadequately capture the unique risk profile of young migraineurs. Recent advances in neuroimaging, genetic testing, and biomarker development have provided new insights into the pathophysiological mechanisms underlying migrainous stroke, opening avenues for more precise risk stratification and targeted prevention strategies. Simultaneously, evolving understanding of hormonal contraceptive risks, antiplatelet therapy benefits, and lifestyle modifications has informed evidence-based approaches to stroke prevention in this population. The integration of these advances into clinical practice requires systematic evaluation of predictive factors and development of practical prevention protocols tailored to individual risk profiles.

The pathophysiology of migrainous stroke involves complex neurovascular interactions that distinguish it from conventional ischemic stroke mechanisms. Cortical spreading depression, the electrophysiological phenomenon underlying migraine aura, triggers a cascade of metabolic and inflammatory responses that may predispose to thrombotic events. This process involves transient but significant alterations in cerebral blood flow, with initial hyperperfusion followed by prolonged oligemia that may compromise vascular integrity and promote thrombogenesis. Endothelial dysfunction represents a critical mechanistic link between migraine and stroke risk. Migraineurs demonstrate elevated levels of inflammatory markers including C-reactive protein, interleukin-6, and tumor necrosis factor-alpha, indicating chronic low-grade inflammation that may contribute to accelerated atherosclerosis and increased thrombotic tendency. Additionally, altered nitric oxide metabolism in migraine patients affects vascular reactivity and may predispose to vasospasm and subsequent ischemic events. Demographic factors consistently identified as predictors of migrainous stroke include female gender, young age typically under 45 years, and specific migraine phenotypes. Women with migraine with aura demonstrate approximately two to threefold increased stroke risk compared to women without migraine, with this risk becoming particularly pronounced when additional vascular risk factors are present. The temporal relationship between estrogen fluctuations and both migraine frequency and stroke risk suggests hormonal mechanisms play a central role in this association. Among young women who have migraine with aura, some face a higher risk than others. The stroke risk increases if someone has migraine with aura and has additional risk factors for vascular disease like high blood pressure, obesity, and, in particular, smoking. Smoking appears to confer particularly high risk, with some studies suggesting multiplicative rather than additive risk effects when combined with migraine and hormonal contraceptive use. Hormonal contraceptive use represents one of the most clinically



relevant modifiable risk factors for migrainous stroke. Stroke risk in OCP users is impacted by several confounding issues, including OCP formulation, age, hypertension, smoking, and the presence of migraine with aura. The mechanism likely involves estrogen-mediated effects on coagulation factors, with increased levels of fibrinogen, factor VII, and decreased antithrombin III activity. Women with migraine using low-dose oral contraceptives had nearly 7 times the odds of ischemic stroke, and this risk increased nearly exponentially if the women were smokers. Genetic factors contribute significantly to migrainous stroke susceptibility, with several variants identified in genes regulating vascular function, coagulation, and neuronal excitability. Familial hemiplegic migraine mutations, particularly in calcium channel genes, appear to confer elevated stroke risk through mechanisms involving altered neuronal calcium handling and vascular reactivity. Additionally, polymorphisms in methylenetetrahydrofolate reductase, factor V Leiden, and prothrombin genes may interact with other risk factors to increase thrombotic tendency. Hypertension, while less prevalent in the typical young female population at risk for migrainous stroke, nonetheless represents an important modifiable risk factor that may interact synergistically with migraine pathophysiology. The combination of hypertension with migraine with aura appears to confer particularly elevated risk, possibly through mechanisms involving accelerated small vessel disease and increased susceptibility to cerebral hypoperfusion during migraine attacks.

Effective prediction of migrainous stroke requires systematic clinical assessment incorporating multiple domains including detailed migraine characterization, comprehensive cardiovascular risk evaluation, and assessment of modifiable lifestyle factors. The clinical history should focus on migraine phenotype, with particular attention to aura characteristics, attack frequency, and temporal patterns. Visual aura appears to confer higher stroke risk than other aura types, possibly reflecting involvement of posterior circulation territories more susceptible to ischemic injury. Cardiovascular risk assessment in young migraineurs requires modifications to traditional risk calculators, which often underestimate risk in this population due to young age and female predominance. Instead, clinicians should focus on migraine-specific risk factors including aura presence, attack frequency, and concurrent use of hormonal contraceptives. Additional attention should be directed toward family history of early stroke or cardiovascular disease, personal history of pregnancy complications including preeclampsia, and presence of autoimmune conditions that may increase vascular risk. Laboratory evaluation should include assessment of prothrombotic states, particularly in patients with multiple risk factors or family history of thrombotic events. Testing for factor V Leiden, prothrombin gene mutation, antiphospholipid antibodies, and protein C and S deficiency may identify individuals at particularly high risk. Additionally, assessment of inflammatory markers, lipid profiles, and hemoglobin A1c provides information about overall cardiovascular risk that may inform prevention strategies. Neuroimaging plays an increasingly important role in risk stratification, with magnetic resonance imaging revealing subclinical cerebrovascular changes in many migraineurs. White matter hyperintensities, particularly in posterior circulation territories, appear more prevalent in migraine with aura patients and may represent markers of increased stroke susceptibility. Advanced imaging techniques including arterial spin labeling and diffusion tensor imaging may provide additional insights into cerebrovascular integrity and risk stratification. Risk stratification models specifically developed for migrainous stroke incorporate multiple predictive factors into clinically useful algorithms.



Current models typically classify patients into low, moderate, and high-risk categories based on combinations of age, migraine phenotype, hormonal contraceptive use, smoking status, and additional vascular risk factors. High-risk individuals typically include women under 35 with migraine with aura who smoke and use combined hormonal contraceptives, representing the intersection of multiple synergistic risk factors. The integration of genetic testing into risk stratification remains an area of active investigation, with potential for personalized medicine approaches based on individual genetic risk profiles. Current evidence suggests that genetic factors may modify the effects of environmental and hormonal risk factors, potentially identifying individuals who may benefit from more aggressive prevention strategies or alternative contraceptive approaches.

Prevention of migrainous stroke requires a multifaceted approach addressing both migraine management and cardiovascular risk reduction. Lifestyle modifications form the foundation of prevention, with smoking cessation representing the single most important intervention for high-risk individuals. The multiplicative risk effects of smoking with migraine and hormonal contraceptives make smoking cessation absolutely essential for all migraineurs, particularly those using hormonal contraception. Combined hormonal contraceptives are contraindicated in women who have migraine with aura, in whom these drugs can increase the risk of ischemic stroke. However, contraceptive counseling must balance stroke risk against pregnancy-related risks and individual preferences, requiring individualized decision-making. For women with migraine with aura, progestin-only contraceptives, intrauterine devices, or barrier methods represent safer alternatives that avoid estrogen-mediated stroke risk elevation. For women who continue combined hormonal contraceptives despite migraine with aura, careful monitoring and additional risk reduction measures become essential. This includes optimization of blood pressure control, aggressive smoking cessation counseling, and consideration of prophylactic antiplatelet therapy in selected high-risk cases. In most cases, antiplatelet agents are used indefinitely for secondary stroke prevention in patients who have a stroke potentially related to hormonal contraception, though primary prevention applications remain more controversial. Migraine prophylaxis may provide dual benefits through reduction of attack frequency and potential modification of underlying vascular risk. Certain prophylactic medications, particularly those with cardiovascular effects such as beta-blockers and calcium channel blockers, may provide additional stroke prevention benefits beyond migraine control. Topiramate, while effective for migraine prevention, requires careful consideration in women of childbearing age due to teratogenic potential and interaction with hormonal contraceptives. Antiplatelet therapy for primary stroke prevention in high-risk migraineurs remains an area of ongoing investigation. While not routinely recommended for all migraine patients, carefully selected individuals with multiple risk factors may benefit from low-dose aspirin therapy. Decision-making should incorporate bleeding risk assessment, particularly in young women, and consider individual risk-benefit profiles. For patients with ischemic stroke secondary stroke prevention, either acetylsalicylic acid (80 mg – 325 mg daily), or clopidogrel (75 mg daily), or combined acetylsalicylic acid and extended-release dipyridamole are all appropriate treatment options.

Advances in precision medicine offer promising avenues for improved risk prediction and personalized prevention strategies in migrainous stroke. Pharmacogenomic testing may identify



individuals who metabolize medications differently or have genetic variants affecting drug efficacy, enabling tailored prophylactic regimens. Additionally, genetic risk scores incorporating multiple stroke-associated variants may provide more accurate risk stratification than current clinical models. Biomarker development represents another frontier in migrainous stroke prediction, with investigation of inflammatory markers, endothelial dysfunction markers, and neuronal injury biomarkers. Elevated levels of specific biomarkers during migraine attacks may identify individuals at highest risk for ischemic complications, enabling targeted intervention strategies. Advanced proteomic and metabolomic approaches may reveal novel biomarkers that reflect the complex pathophysiology underlying migrainous stroke. Digital health technologies including smartphone applications and wearable devices offer opportunities for real-time monitoring and prevention. These technologies may track migraine patterns, medication adherence, and physiological parameters that could predict high-risk periods. Integration with electronic health records and decision support systems may enable automated risk assessment and clinical alerts for healthcare providers. Telemedicine and remote monitoring capabilities have particular relevance for migraine management and stroke prevention, especially in underserved populations. Remote consultation enables specialist expertise to reach patients who might otherwise lack access to headache or stroke specialists, potentially improving risk identification and prevention implementation. Additionally, remote monitoring may enable early detection of concerning symptoms or medication adherence issues. Research into novel therapeutic targets continues to expand understanding of migrainous stroke pathophysiology and identify potential intervention points. Investigation of neuropeptide pathways, particularly calcitonin gene-related peptide, may reveal mechanisms relevant to both migraine pathophysiology and vascular protection. Additionally, research into neuroinflammation and neurovascular coupling may identify novel prevention strategies targeting the intersection of migraine and stroke pathophysiology.

Successful implementation of migrainous stroke prevention requires systematic approaches to identification, risk stratification, and intervention delivery. Healthcare systems must develop protocols for screening high-risk populations, particularly young women with migraine seeking contraceptive counseling or those presenting to emergency departments with severe headaches. Integration of risk assessment tools into electronic health records can facilitate systematic evaluation and ensure consistent application of evidence-based guidelines. Quality improvement initiatives should focus on standardizing care processes and measuring outcomes relevant to stroke prevention. Key performance indicators might include rates of contraceptive counseling documentation, smoking cessation intervention delivery, and blood pressure control achievement in high-risk migraineurs. Additionally, tracking of acute stroke events in previously identified high-risk individuals can provide insights into prevention strategy effectiveness. Multidisciplinary care coordination represents a critical component of effective prevention implementation. Collaboration between headache specialists, primary care providers, gynecologists, and stroke specialists ensures comprehensive risk assessment and intervention delivery. Shared care protocols and communication systems facilitate coordinated management and prevent gaps in care that might compromise prevention effectiveness. Patient education and engagement strategies must address the complex relationship between migraine and stroke risk while avoiding excessive anxiety or



fatalistic attitudes. Educational materials should provide clear, actionable information about risk factors and prevention strategies while emphasizing the relatively low absolute risk of stroke in most migraineurs. Shared decision-making approaches enable patients to make informed choices about contraception and lifestyle modifications based on their individual risk profiles and preferences.

In conclusion, migrainous stroke, especially linked to migraine with aura in young women, is a significant risk that is amplified by factors like hormonal contraceptives and smoking. Prevention requires thorough risk assessment, lifestyle changes, individualized contraceptive counseling, and selective use of antiplatelet therapy. Emerging tools such as genetic testing and digital health can improve risk prediction and personalized care. Future research should focus on validating risk algorithms and effective prevention strategies. Successful reduction of migrainous stroke depends on multidisciplinary collaboration, ongoing research, and tailored, evidence-based interventions.

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