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REVIEW ARTICLE

Vascular Risk Factors and Their Influence on Migraine Phenotype in Older Adults

Aynur Özge[1*], Reza Ghouri[1], Derya Uludüz[2,3]

[1]Department of Neurology, Mersin University School of Medicine, Mersin, Türkiye
[2]Department of Neurology, Brain 360 Integrative Center, İstanbul, Türkiye
[3]Department of Neurology, Cerrahpaşa University Medical Faculty, İstanbul, Türkiye

*aynurozge@gmail.com

ABSTRACT

This comprehensive review examines the impact of vascular risk factors on the phenotypic expression of migraine in the elderly population. Migraine, particularly migraine with aura, has been established as a risk factor for ischemic lesions of the brain, stroke, and other cardiovascular diseases. The association between migraine and specific vascular events, such as stroke, myocardial infarction, and angina pectoris, underscores the need for a comprehensive understanding of the interplay between migraine and cardiovascular diseases. The challenges in differentiating migraine from vascular insults, especially in the elderly population, highlight the need for improved diagnostic and treatment strategies to address the complexities of managing migraine in this demographic. Patient education and treatment of modifiable risk factors may decrease future vascular events, emphasizing the importance of addressing vascular risk factors in migraine management. The potential impact of prevention and treatment of unfavorable arterial hemodynamics on neurocognitive outcomes underscores the broader implications of addressing vascular risk factors in migraine management. The clinical and public health relevance of understanding the modifiability of vascular risk factors in elderly migraine patients extends to addressing challenges in cancer survivorship, radiological emergency response, and rational person behavior, emphasizing the diverse applications of addressing vascular risk factors in healthcare and public health. Ultimately, the clinical and public health relevance of understanding the impact of vascular risk factors on the phenotypic expression of elderly migraine underscores the need for continued research and clinical vigilance in addressing the complex interplay between migraine and vascular risk factors in the elderly population.

Keywords: elderly migraine, vascular risk factors, ischemic stroke, migraine phenotype, cardiovascular diseases, public health relevance.

I. Introduction

A. BACKGROUND OF MIGRAINE IN THE ELDERLY

Migraine, a complex neurological condition characterized by recurrent headaches, has been a subject of growing interest in the context of elderly individuals. The prevalence of migraine in the elderly population presents unique challenges due to age-related changes in pharmacodynamics, comorbidities, and the potential overlap with vascular insults such as transient ischemic attacks and amyloid angiopathy.[1] Furthermore, recent studies have suggested a possible link between migraine and a broader range of ischemic vascular disorders, including ischemic stroke and myocardial infarction.[2] Additionally, migraine with aura has been associated with an increased prevalence of cardiovascular risk factors, highlighting the importance of understanding the interplay between vascular risk factors and migraine in the elderly.[3] As the elderly population continues to grow, it becomes imperative to explore the age-dependent prevalence and clinical features of migraine, as well as its potential association with cerebrovascular diseases. Therefore, this scoping review aims to comprehensively examine the impact of vascular risk factors on the phenotypic expression of migraine in the elderly population, shedding light on the epidemiology, pathophysiological mechanisms, clinical considerations, and management implications.

B. SIGNIFICANCE OF UNDERSTANDING VASCULAR RISK FACTORS IN ELDERLY MIGRAINE

The significance of understanding vascular risk factors in elderly migraine is paramount, as recent studies have indicated a potential association between migraine and a broader range of ischemic vascular disorders, including ischemic stroke and myocardial infarction.[4] Furthermore, the increased risk of stroke appears to be more apparent among individuals with migraine without traditional risk factors, emphasizing the need to comprehend the interplay between vascular risk factors and migraine in the elderly.[5] Additionally, systemic endothelial dysfunction in migraineurs seems to develop independently of vascular risk factors, and the risk of cardiovascular disease in migraineurs, particularly those with migraine with aura, remains significant even after adjusting for vascular risk factors.[6] Moreover, the association between migraine and vascular events appears to be independent of common vascular risk factors, suggesting a direct relationship between migraine pathophysiology and vascular events, especially in younger individuals.[7] Therefore, exploring the interaction between endothelial dysfunction and cortical spreading depression in affecting risk is crucial in understanding the impact of vascular risk factors on the phenotypic expression of migraine in the elderly population.[8]

C. AIM AND SCOPE OF THE REVIEW

The aim of this scoping review is to comprehensively investigate the impact of vascular risk factors on the phenotypic expression of migraine in the elderly population. The scope of the review will encompass an examination of the epidemiology of migraine in the elderly, the association of migraine with vascular risk factors, and the potential gender differences in this association. Furthermore, the review

will delve into the pathophysiological mechanisms underlying the interplay between migraine and vascular risk factors, including shared genetic factors and the potential role of spreading depolarization in linking migraine and stroke. Additionally, the clinical considerations related to the impact of vascular risk factors on migraine phenotype in the elderly, including the association of migraine with specific vascular events such as stroke and ischemic attack, will be thoroughly explored. Lastly, the review will address the management implications, focusing on the assessment and treatment of vascular risk factors in the context of migraine management, as well as the modifiability of these risk factors in elderly migraine patients.

II. Epidemiology of Migraine and Vascular Risk Factors

A. PREVALENCE OF MIGRAINE IN THE ELDERLY POPULATION

The prevalence of migraine in the elderly population is a critical aspect of understanding the impact of vascular risk factors on this demographic. Studies have highlighted the challenges in differentiating migraine from vascular insults in the elderly, especially considering the presence of multiple comorbidities, polypharmacy, and age-related changes in pharmacodynamics and pharmacokinetics.[9] Furthermore, the association between migraine and vascular risk factors, such as hypertension, diabetes, and smoking, has been noted, indicating the need for a comprehensive understanding of the prevalence of migraine in the elderly population and its potential relationship with vascular risk factors.[10] Additionally, the prevalence of migraine with aura has been associated with an increased prevalence of cardiovascular risk factors, emphasizing the significance of exploring the prevalence of migraine in the context of vascular risk factors in the elderly.[11]

B. ASSOCIATION OF MIGRAINE WITH VASCULAR RISK FACTORS

The association of migraine with vascular risk factors has been a subject of extensive research. Studies have indicated that migraine, particularly migraine with aura, is associated with an increased risk of cardiovascular and cerebrovascular events, including stroke and ischemic attack.[5,12] Furthermore, an analysis of the prevalence of migraine in the elderly population has revealed an association between migraine and several vascular risk factors, such as hypertension, hypercholesterolemia, and physical inactivity, although traditional cardiovascular risk factors other than smoking did not interact with migraine to increase stroke risk.[13] Additionally, the association between migraine and the risk of stroke has been analyzed, highlighting the need to consider the life course of migraine when studying associations with the vascular system.[14] Moreover, an inverse association between hypertension and migraine in women has been observed, warranting further investigation.[15] These findings underscore the importance of understanding the association of migraine with vascular risk factors in the elderly population and its implications for cardiovascular and cerebrovascular health.

C. GENDER DIFFERENCES AND VASCULAR RISK FACTORS IN ELDERLY MIGRAINE

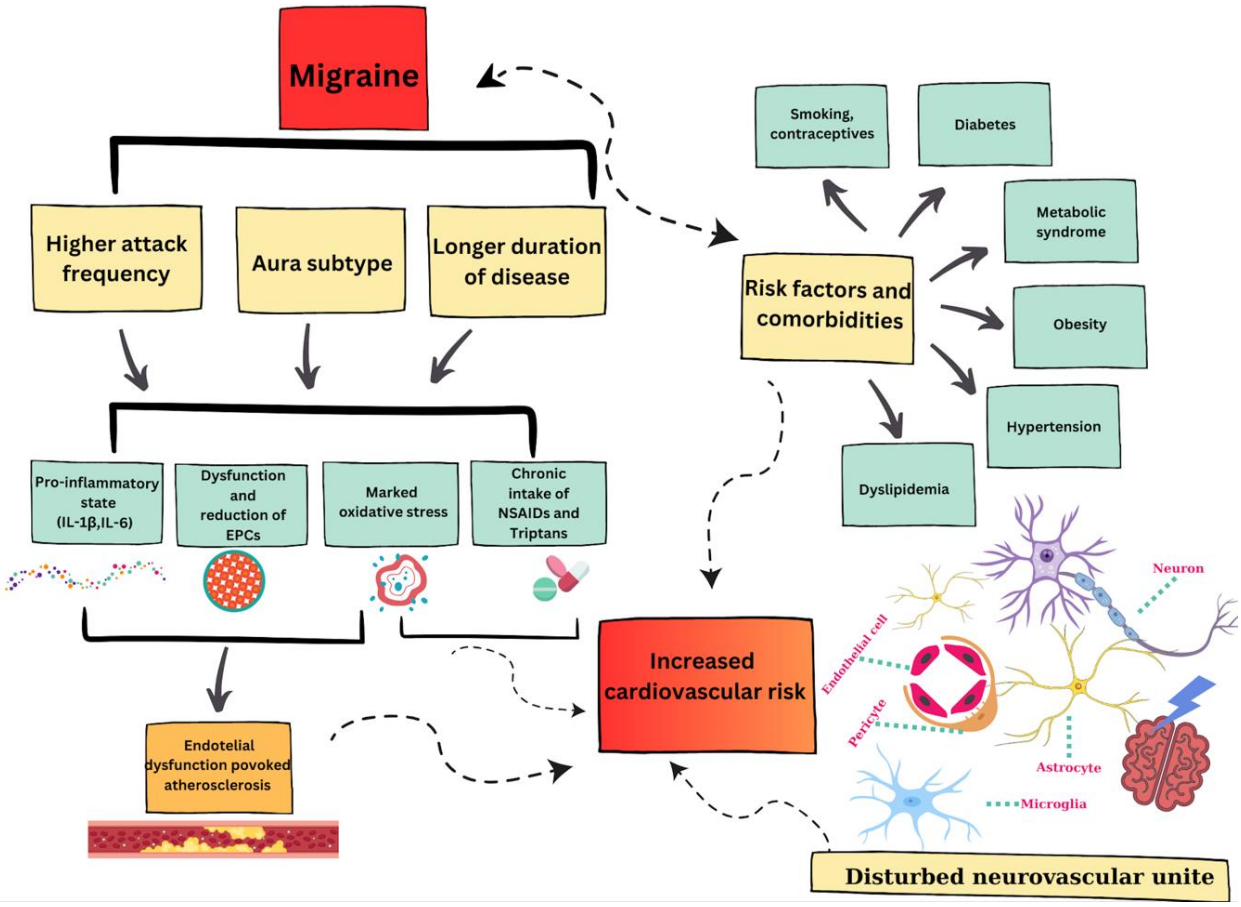
The prevalence and clinical features of migraine in the elderly population exhibit notable gender differences. Studies have indicated that headache accounts for a higher percentage of female patients visiting general practitioners compared to male patients, emphasizing the gender disparity in the prevalence of migraine in the elderly population.[1] Furthermore, the association between migraine and vascular risk factors, particularly in the context of stroke, has been found to be strongly associated with female sex, especially in individuals with migraine with aura, young age, and the use of oral contraceptives.[4] Additionally, the association between migraine with aura and cardiovascular disease has been observed to vary by vascular risk status, particularly in women, highlighting the gender-specific implications of vascular risk factors in elderly migraine patients.[5] Moreover, the prevalence of migraine in elderly individuals has been reported to be slightly higher in women than in men, suggesting a gender-specific impact of migraine in the elderly population.[16] These findings underscore the importance of considering gender differences in the association of migraine with vascular risk factors and its implications for the clinical management of elderly migraine patients.

III. Pathophysiological Mechanisms

A. SHARED PATHOPHYSIOLOGICAL PATHWAYS BETWEEN MIGRAINE AND VASCULAR DISORDERS

The pathophysiological mechanisms underlying migraine and its potential association with vascular disorders have been a subject of extensive research. Studies have indicated shared pathophysiological pathways between migraine and vascular disorders, particularly in the context of cortical spreading depression (CSD) and genetic predisposition.[17-19] CSD, a wave of neuronal and glial depolarization, has been implicated in both migraine and vascular disorders, suggesting a potential common pathophysiological mechanism. Furthermore, the genetic architecture of migraine has been found to share some commonalities with psychiatric disorders, indicating a multifactorial inheritance and potential genetic overlap with vascular and neurological conditions.[18] Additionally, the association between migraine and cluster headache has been linked to shared pathophysiological pathways, emphasizing the importance of a continued focus on understanding these shared mechanisms for future treatment avenues.[20] Moreover, advanced neuroimaging has provided insights into the pathophysiology of migraine, shedding light on the neurovascular dysfunction and cortical excitability factors that contribute to the pathophysiological mechanisms of migraine.[8,21] These findings underscore the significance of elucidating the shared pathophysiological pathways between migraine and vascular disorders, providing valuable insights into potential common mechanisms and treatment avenues.

Figure 1- Potential stakeholders of common mechanism in migraine and vascular events in elderly.



B. GENETIC FACTORS AND VASCULAR RISK IN MIGRAINE

The role of genetic factors in the association between migraine and vascular risk has been a subject of extensive investigation. Studies have indicated a higher prevalence of risk factors associated with cardiovascular disease, such as hypertension, diabetes, and hyperlipidemia, in individuals with migraine, suggesting a potential genetic predisposition to vascular risk factors in migraine patients.[22] Furthermore, plasma and genetic biomarkers for vascular diseases have been identified, indicating a potential genetic basis for the association between migraine and vascular risk factors.[23] Additionally, intricate mechanisms responsible for oxidative stress, vascular dysfunction, and vascular events in migraine have been linked to genetic and environmental factors, highlighting the multifactorial nature of the genetic influence on vascular risk in migraine.[6] Moreover, genetic analysis has revealed shared biological bases between migraine and coronary artery disease, pointing towards genetic overlap and potential shared genetic risk loci for both conditions.[24-25] These findings underscore the significance of genetic factors in understanding the association between migraine and vascular risk, providing valuable insights into potential genetic mechanisms and shared genetic risk loci.

IV. Clinical Considerations

A. IMPACT OF VASCULAR RISK FACTORS ON MIGRAINE PHENOTYPE IN THE ELDERLY

The impact of vascular risk factors on the migraine phenotype in the elderly is a complex and critical consideration in clinical practice. Recent findings have highlighted the higher genetic load, based on common polygenic variation, in familial migraine cases compared to nonfamilial cases, particularly for migraine with aura and hemiplegic migraine.[26] Additionally, epidemiological studies have indicated that the genetic contribution is highest in migraine with aura, emphasizing the paradoxical nature of this association.[27] Furthermore, the prevalence of migraine in the general population, particularly in the elderly, has been associated with an increased familial risk and evidence of genetic factors, suggesting a potential genetic predisposition to migraine.[28] Moreover, the difficulty in differentiating migraine from vascular insults in the elderly, along with the presence of multiple comorbidities, polypharmacy, and age-related changes in pharmacodynamics and pharmacokinetics, makes treatments for this cohort challenging but necessary, especially given the worldwide increase in life expectancy and the likelihood of migraine continuing to be a major personal and public health problem.[1,29] Additionally, the identification of brain-based biomarkers of pain through advances in technology and multivariate pattern analysis provides optimism for understanding the pathophysiological mechanisms of migraine and its association with vascular risk factors.[30] Careful clinical correlation and appropriate investigations are essential to exclude secondary causes, especially in the elderly population, where there is a high comorbidity of migraine and depression.[31] Furthermore, the vulnerability of the elderly population to migraine progression reflects increased biological predisposition and early life exposures, warranting a comprehensive understanding of the genetic and pathophysiological phenotypes related to migraine in this demographic.[32] Additionally, genome-wide association studies have identified numerous susceptibility variants that each result in only a small increase in overall migraine risk, highlighting the complexity of the genetic architecture of migraine.[33] Despite considerable research on the association between migraine and stroke in younger populations, a clear answer is still lacking for older individuals, emphasizing the need for further investigation in this demographic.[34] Furthermore, the presence of medical co-morbidities with specific links to bipolar disorder and anxiety disorders has been indicated in individuals with migraine, underscoring the importance of better understanding migraine-related morbidity in the elderly.[35] Lastly, the decrease in the prevalence of migraine in the elderly is partially offset by an increased prevalence of probable migraine, since attacks become shorter and less typical at older ages, highlighting the evolving nature of migraine in this population.[36-38]

B. ASSOCIATION OF MIGRAINE WITH SPECIFIC VASCULAR EVENTS

The association of migraine with specific vascular events has been a subject of extensive research, with evidence indicating a potential link between migraine and cardiovascular diseases. Recent findings have suggested that migraine, particularly migraine

with aura, is associated with an increased risk for stroke, myocardial infarction, and angina pectoris, positioning migraine as an overall risk factor for cardiovascular diseases.[39,40] Furthermore, a prospective cohort study has evaluated the association between migraine with aura and specific cardiovascular disease events, highlighting the differential impact of migraine with aura on overall and specific cardiovascular disease events based on vascular risk status.[41] Additionally, a clinic-based study has reported a growing literature on associations between migraine, especially migraine with aura, and ischemic stroke, as well as other vascular events, emphasizing the need for a comprehensive understanding of the association between migraine and cerebrovascular diseases.[22] Moreover, the association between migraine and stroke remains an open question, warranting further investigation to elucidate the potential comorbidity and causal relation between these conditions.[4]

V. Management Implications

A. ASSESSMENT AND TREATMENT OF VASCULAR RISK FACTORS IN MIGRAINE MANAGEMENT

Assessing and addressing vascular risk factors in migraine management are crucial for comprehensive patient care. Beyond the focus on pain relief, it is crucial for headache specialists to evaluate and treat concurrent vascular risk factors, especially in cases of migraine with aura, which has been associated with an increased risk for stroke, myocardial infarction, and angina pectoris[39,43]. Furthermore, a prospective cohort study has underscored the significance of investigating the connection between migraine with aura and specific cardiovascular events, emphasizing the varying impact based on vascular risk status[44]. Additionally, the role of lipid levels in association with migraine has been studied, indicating the need for further research to understand the potential implications of serum lipid levels in migraine patients[22]. Moreover, the association between migraine and stroke has been explored, with evidence suggesting a negative association between migraine and large-artery atherosclerosis, highlighting the complexity of the relationship between migraine and specific stroke subtypes[4]. These findings underscore the importance of continued research to elucidate the association between migraine and specific vascular events, providing valuable insights into potential risk factors and their implications for clinical management.

B. MODIFIABILITY OF VASCULAR RISK FACTORS IN ELDERLY MIGRAINE

The assessment and treatment of vascular risk factors in migraine management are essential components of comprehensive patient care. Recent findings have emphasized the importance of heightened vigilance for modifiable cardiovascular risk factors in migraineurs, such as obesity, hypertension, hyperlipidemia, and diabetes.[32] Furthermore, it has been suggested that in elderly cohorts, the cardiovascular burden could be too high to detect a difference in the risk of stroke according to migraine status.[2] Additionally, the pro-inflammatory role of prostaglandins in migraines has been demonstrated both in animal and human models, leading to vasodilation of intra- and extracranial vessels.[45] Moreover, the association between migraine and stroke has been explored, with evidence suggesting a negative association between migraine and large-artery atherosclerosis,

highlighting the complexity of the relationship between migraine and specific stroke subtypes.[3] These findings underscore the importance of continued research to elucidate the association between migraine and specific vascular events, providing valuable insights into potential risk factors and their implications for clinical management.

Clinical and Public Health Relevance

The clinical and public health relevance of understanding the impact of vascular risk factors on the phenotypic expression of elderly migraine is of paramount importance. The association between migraine and specific vascular events, such as stroke, myocardial infarction, and angina pectoris, underscores the need for a comprehensive understanding of the interplay between migraine and cardiovascular diseases.[49] Furthermore, the mechanisms linking migraine to ischemic vascular disease remain uncertain and are likely to be complex, necessitating further investigation.[22] The challenges in differentiating migraine from vascular insults, especially in the elderly population, highlight the need for improved diagnostic and treatment strategies to address the complexities of managing migraine in this demographic.[1] Additionally, the association between migraine and stroke, particularly in the context of genetic factors and specific stroke subtypes, warrants continued research to elucidate the potential risk factors and their implications for clinical management.[6,50] Moreover, patient education and treatment of modifiable risk factors may decrease future vascular events, emphasizing the importance of addressing vascular risk factors in migraine management.[5,51] The potential impact of prevention and treatment of unfavorable arterial hemodynamics on neurocognitive outcomes underscores the broader implications of addressing vascular risk factors in migraine management.[7,52] Furthermore, the association between migraine and specific vascular events, such as large-artery atherosclerosis, highlights the need for a comprehensive understanding of the vascular risk factors affecting individuals with migraine.[8] The clinical and public health relevance of understanding the modifiability of vascular risk factors in elderly migraine patients extends to addressing challenges in cancer survivorship, radiological emergency response, and rational person behavior, emphasizing the diverse applications of addressing vascular risk factors in healthcare and public health.[3,53] Ultimately, the clinical and public health relevance of understanding the impact of vascular risk factors on the phenotypic expression of elderly migraine underscores the need for continued research and clinical vigilance in addressing the complex interplay between migraine and vascular risk factors in the elderly population.[54,55]

VI. Conclusion

In conclusion, this comprehensive review provides valuable insights into the intricate interplay between migraine and vascular risk factors among the elderly. The prevalence of migraine in this demographic poses distinct challenges, influenced by age-related changes in pharmacodynamics, comorbidities, and potential overlap with vascular insults. Notably, the association between migraine and vascular risk factors, including gender differences, genetic predisposition, and specific vascular events, underscores the complexity of this relationship. The impact of vascular risk factors on the migraine phenotype in the

elderly underscores the importance of a holistic approach to migraine management, integrating neurological and cardiovascular considerations. The modifiability of vascular risk factors in elderly migraine patients suggests promising avenues for targeted interventions to safeguard cerebrovascular health. This review underscores the imperative for ongoing research and clinical vigilance to unravel the intricate dynamics between migraine and vascular risk factors in the elderly population.

Moving forward, the review highlights key areas for future research. First and foremost, upcoming guidelines should advocate for comprehensive support measures for migraineurs, focusing on reducing headache frequency, enhancing quality of life, and diminishing overall vascular risk. Moreover, there is a pressing need for further research to elucidate the underlying mechanisms of cardiovascular disease risk among individuals of low socioeconomic status, with a focus on identifying effective interventions for high-risk patients. Future studies should also prioritize clarifying pathogenic pathways and exploring preventive measures for dementia within headache populations. Additionally, investigations into the potential impact of preventing and treating unfavorable arterial hemodynamics on neurocognitive outcomes merit attention. Large prospective analyses are essential to deepen our understanding of the cardiovascular burden and stroke risk associated with migraine in the elderly.

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