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Propensity to the Vascular Smooth Muscle Cell Abnormality in Migraine without Aura and Vasospastic Angina along with a Genome-Wide Association Studies

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Abstract

A different genetic susceptibility contribution in migraine without aura (MWOA) and migraine with aura (MWA) has been suggested in the study using a genetic risk score (GRS). Even though epidemiologic studies reveal that comorbidity with coronary artery disease (CAD) is more common in MWA than MWOA, it has been reported that MWOA had a genetic overlap with CAD, whereas MWA did not. The author has reported that patients with MWOA in the interictal period have a selective sensitivity in dilator response to nitroglycerin (NTG) and may have systemic nitric oxide (NO) sensitivity to NTG as previously described. The result indicated a vascular smooth muscle cell (VSMC) abnormality. Meanwhile, it has been provided that migraine-associated genes were involved in both arterial and smooth muscle function in genome-wide association studies (GWAS) profiles. The author emphasizes that VSMC abnormality was detected in both vascular reactivity study and GWAS profile in migraineurs without aura. Now, vasospastic angina (VSA) is considered as a disorder of conduit arteries. It has been proposed that hypercontraction of VSMC, namely, VSMC abnormality. The author emphasizes that there is at least a common underlying mechanism of MWOA and VSA, having selective and specific response to NTG and these diseases may be linked by a propensity to VSMC abnormality. Additionally, the author also proposes that VSMC abnormality may be remarkably detected in MWOA and VSA, especially in conduit artery.

Keywords: Migraine without aura; Vasospastic angina; VSMC abnormality; Nitroglycerin-Mediated Vasodilation (NMD); Genome-Wide Association Studies (GWAS)

Introduction

Migraine without aura (MWOA) is the most common form of migraine and is characterized by recurrent severe headache attacks lasting 4-72 hours with associated gastrointestinal and autonomic symptoms [1,2]. Migraine with aura (MWA) is one-third of migraine and accompanied with transient focal neurological symptoms before or during the headache attack [1,2]. Recently, a significant relationship between several single-nucleotide polymorphisms (SNP) and migraine has been recognized [3-8]. Then, Gormley et al. clarified that the two major subtype of migraine, MWOA and MWA, have a partially shared underlying genetic susceptibility profile [8]. An association between MWOA and genetic risk score (GRS) combining multiple genetic risk variants has been indicated by Pisanu et al. But there was no association with MWA [9]. They suggested a different genetic susceptibility contribution in MWOA and MWA in their pathogenesis [9]. In epidemiological study, there is a known co-morbidity between migraine and coronary artery disease (CAD) [10,11]. Genetic analysis for a shared biological process between migraine and CAD has been studied [12,13]. Winsvold et al. indicated that shared biological processes contribute to risk of MWOA and CAD [12]. Then, flow-mediated vasodilation (FMD), an endothelium-dependent function, and nitroglycerin-mediated vasodilation (NMD), an endothelium-independent function, in the brachial artery is a potent procedure for estimating vascular endothelial and vascular smooth muscle cell (VSMC) function [14]. The author have reported that migraineurs without aura in the interictal period have a selective sensitivity in dilator response to NTG and may have systemic NO sensitivity to NTG. The data suggested VSMC abnormality in migraineurs without aura as previously described [15,16]. With respect to increased NMD, there is only one study as previously described [17.18]. Genetically, Gormley et al. identified that the 38 genomic loci associated with migraine and demonstrated the evidence that vascular and smooth muscle tissues contribute to migraine pathophysiology. It can be genetically suggested that VSMC dysfunction of the vascular have a role in migraine. The author emphasizes that VSMC abnormality was recognized in patients with MWOA in both vascular reactivity study and GWAS profile. Then, vasospastic angina (VSA) is considered as a disorder of conduit arteries [19,20]. Shimokawa has proposed that the major mechanism of the spasms in VSA is VSMC hypercontraction, namely VSMC abnormality, not endothelial dysfunction [20]. Until now, an association between migraine and some vascular disorders such as vasospastic angina and Raynaud's phenomenon has been reported [21,22]. It can be speculated that the mechanism underlying migraine may be systemic vascular tone abnormalities. The author emphasizes that there is at least a common underlying mechanism of MWOA and VSA, showing the selective and specific reaction to NTG and these diseases may be linked by a propensity to VSMC abnormality. In this article, the propensity to the VSMC abnormality in MWOA and VSA along with a genome-wide association study has been reviewed.

Literature Review

A Classification and molecular viewpoints in migraine

The classification of migraine into two main subtypes: migraine

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without aura (MWOA) and migraine with aura (MWA) were diagnosed on International Classification of Headache Disorders 3rd edition beta version (ICHD-III) [2]. Intracranial vessel dilation, specifically meningeal arteries, has been implicated in migraine [23]. Both intracranial and extracranial arteries can potentially be innervated by collaterals of the same trigeminal nerve that transverse the skull [23].

Common migraine is mostly polygenic with variants or polymorphisms in many genes contributing to susceptibility, and recent GWAS have now identified numerous gene loci to be associated with migraine [24]. Some major migraine GWAS have been reported until now. Anttila et al. firstly identified the migraine associated SNP (rs1835740) *via* a GWAS conducted in 2748 MWA cases from three European clinics with 10,747 controls [3]. A second major GWAS for migraine was performed as part of the Women's Genome Health Study and found three loci significantly associated with migraine at the genome-wide level that replicated in independent cohorts (TRPM8, LRP1, and PRDM16) [5]. A third GWAS which focused on clinic-based MWOA patients (2326 cases and 4580 controls) subsequently confirmed a role for LRP1 and TRPM8 and identified four additional novel migraine susceptibility loci (MEF2D, TGFBR2, PHACTR1, and ASTN2) [7]. PHACTR1 has both neuronal and vascular functions and has a role in endothelial cell function. It is also a susceptibility locus for coronary artery disease (CAD), myocardial infarction (MI), and other vascular diseases [25]. Gormley et al. [8] reported the analysis from 22 GWAS and revealed 44 independent SNPs that map to 38 distinct genomic loci that are significantly associated with migraine risk. They indicated that the analysis of genes linked to loci found that they were particularly enriched in those expressed in vascular tissues, as well as tissues with a smooth muscle component [8]. Subtype analysis by Gormley et al. revealed seven significantly associated genomic loci for MWOA (near TSPAN2, TRPM8, PHACTR1, FHL5, ASTN2, near FGF6, and LRP1), but none for MWA [8]. It has been reported that there are several functions and pathways of genes associated with migraine, containing vascular function, neuronal function, ion channel/homeostasis, glutamatergic transmission, nitric oxide or oxidative stress, and pain sensing [24]. They describe that the majority of genes implicated in migraine have either a vascular and neuronal function [24].

B Genome–Wide Association Study (GWAS) Profiles

A different genetic susceptibility contribution in their pathogenesis: MWOA and MWA

Several single-nucleotide polymorphisms (SNP) significantly associated with migraine have been identified [3-8]. GWAS of migraine have been successful in identifying risk loci, but most of the associations seem to be driven by migraine without aura [4,8]. A recent meta-analysis pooling data from 29 GWAS identified 12 SNPs associated with increased migraine risk and, specifically, with larger effect sizes in MWOA compared to MWA cases [4]. Gormley et al. revealed that the identified seven loci were specifically associated with MWOA in meta-analysis study. A subset analysis showed no significant association for MWA [8]. A genetic heterogeneity existence between MWOA and MWA were suggested by Gormley et al. [8] Pisanu et al. [9] investigated a genetic risk score (GRS) based on recently published, novel migraine-associated SNPs is associated with migraine prevalence, subtypes and severity in a large population-based sample. They showed that a GRS combining multiple genetic risk variants is associated with MWOA but not MWA. These results indicated that a different genetic susceptibility contribution is suggested in the two forms of migraine, MWOA and MWA in pathogenesis [8,9]. The genetic overlap between migraine and CAD [12] or ischemic stroke [26] was also studied. These results showed a much stronger overlap between cardiovascular diseases and MWOA rather than MWA [12,26].

The evidence of the migraine-associated genes are involved in both arterial and smooth muscle function

There are several identified genes that have previously been associated with vascular disease (PHACTR1, TGFBR2, LRP1, PRDM16, RNF213, JAG1 HEY2, GJA1, and ARMS2) or are involved in smooth muscle contractility and regulation of vascular tone (MRV11, GJA1, SLC24A3, and NRP1) [8]. With respect to Neuropilin 1 (NRPI), the study investigated the biological relevance of NRP 1 in smooth muscle cell *in vivo* [27]. They examined the expression of the nearest genes at migraine loci of human smooth muscle tissue. The enrichment of migraine risk variants in genes expressed in tissue with a smooth muscle component is detected in blood vessels, the stomach, or gastrointestinal tract. They assessed the distribution that it seems to be generalizable across vascular and visceral smooth muscle types [8]. It can be genetically suggested that VSMC dysfunction of the vascular have a role in migraine. The author emphasizes that VSMC abnormality was recognized in patients with MWOA in both vascular reactivity study and GWAS profile. These evidences suggest that the possibility of the main mechanism of MWOA is VSMC abnormality. In analysis for MWOA they found seven significantly associated loci (near TSPAN2, TRPM8, PHACTRI, FHL5, ASTN2, near FGF6, and LRP1). No loci were associated with MWA in the other subset analysis [8]. In the migraine subtype analysis, it was possible to identify specific loci for MWOA but not for MWA [8]. The 38 genomic loci identified suggest the evidence that factors in vascular and smooth muscle tissues contribute to migraine pathophysiology and that the two major subtypes of migraine including MWOA and MWA, have a partially shared underlying genetic susceptibility profile [8]. Additionally, they indicate that only two harbor known ion channel (KCNK5 and TRPM8), and three others (SLC24A3, near ITPK1, and near GJA1) can be linked to ion homeostasis in their study [8].

Discussion

Genetic analysis for a shared biological process between migraine and CAD

Though epidemiologic studies recognize that comorbidity with CAD is more common in MWA than MWOA, it has been reported that MWOA had a genetic overlap with CAD, whereas MWA did not [12]. Windsvold et al. suggested that genes indicated by 16 shared risk loci demonstrate mechanisms with potential roles in migraine pathogenesis and CAD [12]. Furthermore, they have also found significant enrichment of genetic variants associated with CAD as a function of their association with migraine, using two independent CAD GWAS studies [13]. With respect to PHACTR1, Patel et al. have also reported a genetic risk variant for myocardial infarction (MI) on chromosome 6p24 in PHACTR1 is associated with adverse arterial wave reflection indexes, showing central hemodynamic indicators [28].

Vascular tone disorder including migraine, vasospastic angina and, Raynaud's phenomena

VSMC abnormality in MWOA and VSA: A relationship between migraine and some vascular disorders such as vasospastic angina and Raynoud's phenomenon has been reported [21,22]. It can be suggested that the possibility of the mechanism underlying migraine may be a

systemic vascular tone abnormalities. The author have reported that migraineurs without aura in the interictal period have a selective sensitivity in dilator response to NTG and may have systemic NO sensitivity to NTG. The data suggest VSMC abnormality in migraineurs without aura [15,16] With respect to increased NMD, there is only one study in the literature [17,18]. The author has replied to the article titled "Endothlium- dependent and-independent functions in migraineurs" [16] and indicated that the main mechanism of MWOA is VSMC abnormality. Then, VSA is considered as a disorder of conduit artery [19,20], whereas microvascular angina (MVA) is a disorder of coronary microvessel [19]. It has been reported that coronary artery spasms plays significant roles in the pathogenesis of a wide range of ischaemic heart disease, especially in VSA [20]. Shimokawa has indicated that the central mechanism of spasms in VSA is VSMC hypercontraction, namely, VSMC abnormality, but not endothelial dysfunction. He also demonstrated that VSMC hypercontraction was mediated through the activation of Rho-kinase, a molecular switch of VSMC contraction [20]. Several evidences have been indicated that VSMC hypercontraction play a major role in the pathogenesis of the coronary spasm [20]. It is significant evidence that nitrates are effective to acutely abolish coronary spasm by VSMC relaxation, but have no acute beneficial effect on endothelial dysfunction [20]. Pathologically, the extensive adventitial inflammation and perivascular nerve lesions have been reported in spastic human coronary artery [29]. Experimental study also provided the evidence for the role of adventitial inflammation in the pathogenesis of coronary artery spasm [20]. It can be also plausible that VSMC abnormality through the adventitial inflammation may be pathophysiological associated with vascular tone. The author proposes that there is at least a common underlying mechanism of MWOA and VSA, showing the selectivity and specificity to NTG and these diseases may be linked by a propensity to VSMC abnormality.

A relation between migraine and Raynaud's phenomenon

There have been some reports that a relation between migraine and Raynaud's phenomenon (RP) were identified [21,22,30]. Garner et al. [30] reported that people with primary RP are four times more likely to have migraine than those without this condition. An association of RP with a polymorphism in the NOS1 gene has been reported [31].

Conclusion

Firstly, the author emphasizes the evidence that vascular smooth muscle cell abnormality as function was detected in migraineurs without aura in both vascular reactivity study and genome-wide association studies. These evidences indicate that the possibility of the main mechanism of migraine without aura is vascular smooth muscle cell abnormality. Secondly, the author suggests that there is a common underlying mechanism of migraine without aura and vasospastic angina, having selective and specific response to nitroglycerin, and these diseases may be linked by a propensity to vascular smooth muscle cell abnormality. Additionally, the author also proposes that vascular smooth muscle cell abnormality may be remarkably detected in migraine without aura and vasospastic angina, especially in conduit artery.

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References

1. Headache Classification Subcommittee of the International Headache Society (2004) The International Classification of Headache Disorders. (2nd edn). Chephalalgia 24: 9-160.
2. Headache Classification Committee of the International Headache Society (IHS) (2013) The International Classification of Headache Disorders. (3rd edn) (beta version). Chephalalgia 33: 629-808.
3. Anttila V, Stefansson H, Kallela M, Todt U, Terwindt GM, et al. (2010) Genome-wide association study of migraine implicates a common susceptibility variant on 8q22.1. Nat Genet 42: 869-873.
4. Anttila V, Winsvold BS, Gormley P, Kurth T, Bettella F, et al. (2013) Genome-wide meta-analysis identifies new susceptibility loci for migraine. Nat Genet 45: 912-917.
5. Chasman DI, Schürks M, Anttila V, de Vries B, Schminke U, et al. (2011) Genome-wide association study reveals three susceptibility loci for common migraine in the general population. Nat Genet 43: 695-698.
6. Chasman DI, Anttila V, Buring JE, Ridker PM, Schürks M, et al. (2014) Selectivity in genetic association with sub-classified migraine in women. PLoS Genet 10: e1004366.
7. Freilinger T, Anttila V, de Vries B, Malik R, Kallela M, et al. (2012) Genome-wide association analysis identifies susceptibility loci for migraine without aura. Nat Genet 44: 777-782.
8. Gormley P, Anttila V, Winsvold BS, Palta P, Esko T, et al. (2016) Meta-analysis of 375,000 individuals identifies 38 susceptibility loci for migraine. Nat Genet 48: 856-866.
9. Pisanu C, Preisig M, Castelao E, Glaus J, Pistis G, et al. (2017) A genetic risk score is differentially associated with migraine with and without aura. Hum Genet 136: 999-1008.
10. Sacco S, Omello R, Ripa P, Tiseo C, Degan D, et al. (2015) Migraine and risk of ischaemic heart disease: A systematic review and meta-analysis of observational studies. Eur J Neurol 22: 1001-1011.
11. Kurth T, Winter AC, Eliassen AH, Dushkes R, Mukamal KJ, et al. (2016) Migraine and risk of cardiovascular disease in women: A prospective cohort study. BMJ 353: i2610
12. Winsvold BS, Nelson CP, Malik R, Gormley P, Anttila V, et al. (2015) Genetic analysis for a shared biological basis between migraine and coronary artery disease. Neurol Genet 1: e10.
13. Winsvold BS, Bettella F, Witoelar A, Anttila V, Gormley P, et al. (2017) Shared genetic risk between migraine and coronary artery disease: a genome-wide analysis of common variants. PLoS One 12: e0185663.
14. Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, et al. (2002) Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol 39: 257-265.
15. Fujioka K, Oishi M, Fujioka A, Nakayama T (2018) Increased nitroglycerin-mediated vasodilation in migraineurs without aura in the interictal period. J Med Ultrason 45: 605-610.
16. Fujioka K (2019) Reply to: Endothelium-dependent and –independent functions in migraineurs. J Med Ultrason 46:169-170.
17. Yetkin E, Ozisik H, Ozcan C, Aksoy Y, Turhan H (2007) Increased dilator response to nitrate and decreased flow-mediated dilatation in migraineurs. Headache 47: 104-110.
18. Yetkin E, Öztürk S (2019) Endothelium-dependent and –independent functions in migraineurs. J Med Ultrason 46: 167-168.
19. Ford TJ, Rocchiccioli P, Good R, McEntegart M, Eteiba H, et al. (2018) Systemic microvascular dysfunction in microvascular and vasospastic angina. Eur Heart J 39: 4086-4097.
20. Shimokawa H (2014) 2014 Williams Harvey Lecture: Importance of coronary vasomotion abnormalities-from bench to bedside. Eur Heart J 35: 3180-3193.
21. Miller D, Waters DD, Warnica W, Szlachcic J, Kreeft J, et al. (1981) Is variant angina the coronary manifestation of a generalized vasospastic disorder? N Engl J Med 304: 763-766.
22. Smyth AE, Hughes AE, Bruce IN, Bell AL (1999) A case-control study of candidate vasoactive mediator genes in primary Raynaud's phenomenon. Rheumatology 38: 1094-1098.
23. Mason BN, Russo AF (2018) Vascular contributions to migraine: Time to revisit? Front. Cell. Neurosci 12: 233.

24. Sutherland HG, Griffiths LR (2017) Genetics of migraine: Insights into the molecular basis of migraine disorders. Headache 57: 537-569.

25. Deloukas P, Kanoni S, Willenborg C, Farrall M, Assimes TL, et al. (2013) Large-scale association analysis identifies new risk loci for coronary artery disease . Nat Genet 45: 25-33.

26. Malik R, Freilinger T, Winsvold BS, Anttila V, Vander Heiden J, et al. (2015) Shared genetic basis for migraine and ischemic stroke: A genome-wide analysis of common variants. Neurology 84: 2132-2145.

27. Yamaji M, Mahmoud M, Evans IM, Zachary IC (2015) Neuropilin 1 is essential for gastrointestinal smooth muscle contractility and motility in aged mice. PLoS One 10: e0115563.

28. Patel RS, Morris AA, Ahmed Y, Kavtaradze N, Sher S, et al. (2012) A genetic risk variant for myocardial infarction on chromosome 6p24 is associated with impaired central hemodynamic indexes. Am J Hypertens 25: 797-803.

29. Forman MB, Oates JA, Robertson D, Robertson RM, Roberts LJ 2nd, et al. (1985) Increased adventitial mast cells in a patient with coronary spasm. N Engl J Med 313: 1138-1141.

30. Garner R, Kumari R, Lanyon P, Doherly M, Zhang W (2015) Prevalence, risk factors and associations of primary Raynaud's phenomenon: systematic review and meta-analysis of observational studies. BMJ Open 5: e006389.

31. Munir S, Freidin MB, Brain S, Williams FMK (2018) Association of Raynaud's phenomenon with a polymorphism in the NOS1 gene. PLoS One 13: e0196279.